ANESTHETIC AND CRITICAL CARE AMID THE COVID-19 PANDEMIC

EDITED BY: Ru-Ping Dai, Xiangdong Chen, Xiangming Fang, Jiapeng Huang and Eric Azabou

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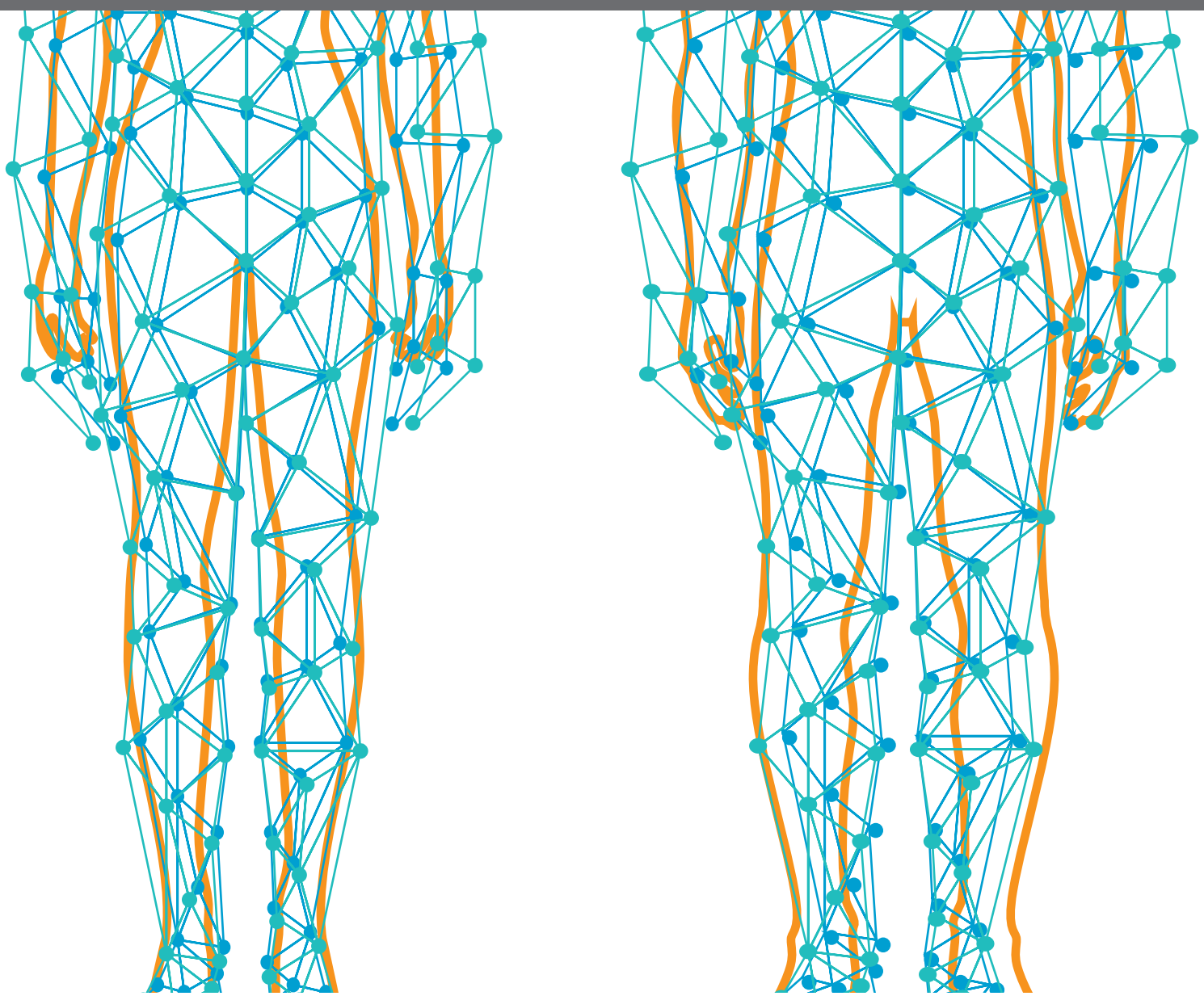

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ANESTHETIC AND CRITICAL CARE AMID THE COVID-19 PANDEMIC

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Randomized Controlled Study Evaluating Efficiency of Low Intensity Transcranial Direct Current Stimulation (tDCS) for Dyspnea Relief in Mechanically Ventilated COVID-19 Patients in ICU: The tDCS-DYSP-COVID Protocol

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The severe respiratory distress syndrome linked to the new coronavirus disease (COVID-19) includes unbearable dyspneic suffering which contributes to the deterioration of the prognosis of patients in intensive care unit (ICU). Patients are put on mechanical ventilation to reduce respiratory suffering and preserve life. Despite this mechanical ventilation, most patients continue to suffer from dyspnea. Dyspnea is a major source of suffering in intensive care and one of the main factors that affect the prognosis of patients. The development of innovative methods for its management, especially non-drug management is more than necessary. In recent years, numerous studies have shown that transcranial direct current stimulation (tDCS) could modulate the perception of acute or chronic pain. In the other hand, it has been shown that the brain zones activated during pain and dyspnea are close and/or superimposed, suggesting that brain structures involved in the integration of aversive emotional component are shared by these two complex sensory experiences. Therefore, it can be hypothesized that stimulation by tDCS with regard to the areas which, in the case of pain have activated one or more of these brain structures, may also have an effect on dyspnea. In addition, our team recently demonstrated that the application of tDCS on the primary cortical motor area can modulate the excitability of the respiratory neurological pathways. Indeed,

tDCS in anodal or cathodal modality reduced the excitability of the diaphragmatic cortico-spinal pathways in healthy subjects. We therefore hypothesized that tDCS could relieve dyspnea in COVID-19 patients under mechanical ventilation in ICU. This study was designed to evaluate effects of two modalities of tDCS (anodal and cathodal) vs. placebo, on the relief of dyspnea in COVID-19 patients requiring mechanical ventilation in ICU.

Trial Registration: This protocol is derived from the tDCS-DYSP-REA project registered on ClinicalTrials.gov NCT03640455. It will however be registered under its own NCT number.

Keywords: COVID-19, acute respiratory distress syndrome (ARDS), tDCS, dyspnea relief, brain, neuromodulation, mechanical ventilation, ICU

INTRODUCTION

Dyspnea is a "symptom" common to various ailments and pathologies such as sepsis, asthma attack, intoxication, severe metabolic disorders known for their association with acute respiratory distress syndrome (ARDS) (1–3). More than half of patients admitted to intensive care for septic shock have an ARDS (4). Coronavirus disease 19 (COVID-19) caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) presents in its severe forms a severe respiratory distress syndrome requiring patients to be put on mechanical ventilation in intensive care (5–8). This respiratory suffering has a dyspneic component, which often reaches unbearable limits and constitutes a major factor in altering the clinical state and the prognosis of patients (6, 9). Dyspnea usually persists despite adequate treatment of the underlying pathology, or sometimes worsens after it has normalized (10–13). This phenomenon of perceptual dysfunction (exaggerated, persistent perception) is linked to changes in cortical excitability due to neuronal plasticity (14). The pathophysiologic mechanisms of dyspnea are quite complex, but are beginning to be better understood (15). The dysfunctions can occur around the thoracic mechanics, the respiratory muscles and blood gases. They may also occur within the neurological and neurobiological structures ensuring the central integration. In particular there are afferents to the cortex which are compared with the motor pathways via corollary discharge (16, 17). Poor adaptation of the ventilator is also a main cause of dyspnea (3). Dyspnea appears when the respiratory work becomes excessive, in particular when the abnormalities of the respiratory mechanics increases the respiratory work, or when the capacities of ventilation are lower than the needs for the organization (18–21). The length-tension ratio of the respiratory muscle fibers, the numerous neurochemical receptors located in the chest wall, the lungs, the airways, the vascular walls, and also in the cerebral centers of respiration are all actors involved in these mechanisms. The brain correlates of respiratory discomfort have been described by several recent works (2, 22, 23). Analogies are drawn between the pathophysiology of dyspnea sensations and that of pain (14, 24, 25). It is a multidimensional experience resulting from a complex central integration of the interaction between multiple factors, physiological, social, and environmental (26). However, despite the appropriate treatment of the recognized or suspected underlying cause and normalization of the blood gazes, dyspnea is often insufficiently relieved and therefore requires—as with pain—specific treatments for this symptom (1). This applies particularly to the hyperventilation syndrome which often persists after the normalization of the underlying functional impairment, and even more so to "medically unexplained" or "psychogenic" dyspnea (11, 17). Recent years, numerous studies have shown that transcranial direct current stimulation tDCS was able to modulate, the perception of acute (27–29) or chronic pain (30–32) which raised hopes of being able to use this technique in the treatment of refractory pain by conventional therapeutic means. Studies in functional brain imaging have been able to show that the effects of this cortical stimulation—in terms of brain activity—were not limited to the cortical zone next to the stimulation electrode (33) but involved a whole set of brain structures (some of which are quite far from the stimulation site) including the anterior cingulum gyrus, the prefrontal cortex, the thalamus, the brainstem, and even the spinal cord (34, 35). While the role of some of these structures in the central integration of pain is currently well-established, they are likely to be also involved in the central integration of dyspnea. Indeed, functional imaging studies on dyspnea (36), in particular one which jointly assessed pain and dyspnea (37) have highlighted activation zones that are close or even superimposed for pain and dyspnea, probably corresponding to brain structures involved in the integration of the aversive emotional component shared by these two complex sensory experiences. Therefore, it can be hypothesized that stimulation by tDCS with regard to the areas which, in the case of pain activated one or more of these cerebral structures could also have an effect on dyspnea. In addition, our team recently demonstrated that the application of tDCS on the primary cortical motor area can modulate the excitability of the respiratory neurological pathways. Indeed, tDCS in anodal or cathodal modality allowed a reduction in the excitability of the diaphragmatic cortico- spinal pathways in healthy subjects (38).

We hypothesized that tDCS could relieve dyspnea in COVID-19 patient requiring mechanical ventilation in ICU (39, 40). We designed this project to assess the effectiveness of tDCS on the relief of dyspnea in COVID-19 patients requiring mechanical ventilation in ICU.

MATERIALS AND METHODS

Study Population

This study will enroll 63 (3 groups of 21) COVID-19 patients, admitted in ICU with ARDS requiring mechanical ventilator for at least 24 h, and having significant dyspnea (dyspnea level ≥4 on the A1 subscale of the Multidimensional Dyspnea Profile) (1, 41).

Inclusion Criteria

- Adult patient, hospitalized in intensive care for COVID-19, having required mechanical ventilation for at least 24 h.
- Not sedated or having a good awakening (Richmond Agitation Score- Sedation Scale (RASS)> −3 at the time of inclusion (42) within 48 h of stopping sedation.
- Able to answer yes or no to simple questions.
- Having significant dyspnea (level≥ 4) on the A1 scale of the Multidimensional Profile of Dyspnea (MPD-A1≥ 4) (1, 41).
- Signature of informed consent by the patient or his family member.

Exclusion Criteria

- Patient under guardianship,
- Wake up delay, coma (GCS≤ 8), or severe agitation.
- Chronic respiratory pathology.
- Medical history of respiratory, neuromuscular, or neuro-sensorial handicap (auditory or visual) pathology.
- Language barrier, refusal to participate in the study or to sign the informed consent,
- Pregnant or lactating woman,
- No affiliation to a social security scheme.

Objectives

Main Objective

The main objective of this study was to determine whether tDCS allowed a significant reduction in dyspnea, measured by the A1 subscale of the multidimensional profile of dyspnea (MPD-A1), in patients admitted to intensive care for COVID-19 placed on mechanical ventilation and suffering dyspnea.

Secondary Objectives

- To evaluate the effect of tDCS on the different components of dyspnea using the other subscales of the multidimensional profile of dyspnea "MPD": sensory (MPD-QS) and emotional (MPD-A2) subscales.
- To determine if tDCS also allowed a significant reduction in dyspnea measured by the IC-RDOS scale (intensive care respiratory distress observation scale) (43).
- To investigate the presence of pre-inspiratory potentials (PPI) on the EEG in this patient population and determine the effect of tDCS on these PPIs in patients who may have them.
- To evaluate the effect of tDCS on respiratory parameters: mouth pressure (amplitude of variation), PetCO2, tidal volume (VT), and respiratory rate (F) as well as ventilation/minute (calculated from VT and F).
- To evaluate the impact of the possible relief of dyspnea by tDCS on the patient's close outcome during the 28 days following inclusion: mortality in intensive care, in hospital on D28, the cumulative incidence of delirium and its duration until D28, the cumulative incidence of mechanical ventilation, the failure to wean from mechanical ventilation on D28, and the length of stay in intensive care.

Evaluation Criteria

Primary Endpoint

- Measurement of the differential of the score on the A1 subscale of the Multidimensional Dyspnea Profile (MPD-A1) (from 0 to 10): between before and after the use of tDCS. This primary judgment criterion will be assessed by an independent, blind observer. The differential will be measured between 30 min before the procedure and 30 min after.

Secondary Endpoints

- Differentials of the MDP-QS and MDP-A2 subscales of the Multidimensional Profile of Dyspnea measured between before and after tDCS: in order to assess the effect of tDCS on the different components of dyspnea: sensory (MPD-QS) and emotional qualifiers (MPD-A2 subscales).
- Differential in the IC-RDOS (intensive care respiratory distress observation scale) scale between before and after the use of tDCS. A significant reduction in this score after the use of tDCS will translate into a reduction in respiratory discomfort, especially dyspnea.
- Pre-inspiratory potentials (PPI) assessment: the possible presence of PPI on the EEG in this patient population could be a marker of respiratory suffering, and a possible disappearance of PPI after the use of tDCS could be interpreted as a relieving effect on breathing difficulty.
- The respiratory parameters measurement: mouth pressure (amplitude of variation), PetCO2, tidal volume (VT), and respiratory rate (F) as well as ventilation/minute (calculated from VT and F), between before and after use of tDCS.
- Evaluation of the impact of tDCS on the outcome of patients during the 28 days following inclusion:
  (a) Death by D28 in intensive care and in the hospital,
  (b) Cumulative incidence of delirium and its duration (CAM-ICU scale) (44).
  (c) Proportion of patients with mechanical ventilator dependance beyond D28.
  (d) Cumulative incidence of mechanical ventilation on D28,
  (e) The duration of the resuscitation stay.

Description of the Evaluation Parameters and Measurement Techniques

The Multidimensional Dyspnea Profile (MPD)

The A1 subscale of the multidimensional profile of dyspnea allows to diagnose dyspnea and to rate its intensity. This score is the equivalent of the visual analog scale. A score of four is considered the lower limit for moderate dyspnea (3). The QS (sensory qualifiers) and A2 (emotional) subscales allow better specifying and defining the type of components that characterize each patient's dyspnea (1, 41). These different subscales of the multidimensional profile of dyspnea will be performed before the start of tDCS, then after the end of tDCS for each patient.

The IC-RDOS (Intensive Care Respiratory Distress Observation Scale) Score

The IC-RDOS scale is derived from the respiratory distress observation scale (RDOS). It is composed of the five items (heart rate, use of the neck muscles during inspiration, paradoxical abdominal movement, facial expression of fear, and additional oxygen) and is validated to serve as tools for objective and reliable evaluation of dyspnea in resuscitation patients (43) and could therefore be used as an alternative to psychometric scales to assess dyspnea in patients who are unable to communicate verbally.

The Pre-inspiratory Evoked Potentials (PPI)

PPIs are slow brain waves generated during the milliseconds preceding the start of inspiration in healthy subjects in a situation of voluntary or forced breathing, and in patients suffering from respiratory discomfort: COPD, asthma, respiratory distress, Ondine (45–50). These potentials are absent in the case of spontaneous breathing in healthy subjects and disappear in patients as soon as the respiratory discomfort is removed. EEG signal was synchronously recorded with the respiratory flow and pressure signals using a Nihon Kohden France manufactured EEG-9100J/K, digital EEG system. Scalp electrodes were placed according to the conventional "10–20" topographic system, via a 19-electrodes cap installed after rubbing and cleaning with alcohol and application of a conductive gel. The ground electrode was positioned at Fpz. The EEG traces are then divided into 3 s sections centered on the start of inspiration (from 2.5 s before the start of inspiration until 0.5 s after the start of inspiration). At least 40–50 EEG samples are required. These 40–50 EEG samples thus cut are then averaged to objectify the PPI. This step of analysis and processing of signals (sampling and averaging) is done automatically using EEG software. The presence or not of the PPI recorded during the 30 min preceding the start of stimulation with tDCS will be recorded, as well as during the 30 min following the cessation of tDCS.

The Respiratory Parameters

The subject being connected to the ventilator, by measuring devices corresponding to a series connection which comprises—downstream of the subject—a device equipped with a CO2 sensor and a pneumotachograph, the pressure sensor of which also makes it possible to measure the mouth pressure (Pm) (NICO2 sensor combined CO2 adult flow Novametrix Nico).

The oxygen saturation will be determined with your finger using a pulse oximeter (Novametrix Oxymeter). The acquisition of all of these respiratory signals (Pm, instantaneous flow rate, expired CO2 and SatO2) is carried out during a period of 15 min before the introduction of tDCS, then again for 15 min after the end of tDCS.

The following respiratory parameters will be precisely measured and calculated:

- The pressure measured at the mouth (Pm), the amplitude of variation of which (aPm), gives an indirect but fairly practical reflection of the additional respiratory effort, which, in the case of dyspnea linked to laden breathing is one of the parameters that is best correlated with its intensity.
- PETCO2: the partial pressure of CO2 at the end of expiration: by being (in the ideal case), a reflection of capnia, the increase of this being another mechanism inducing dyspnea with a strong unpleasant connotation (air hunger) especially in a context where ventilation is forced to a level lower than that which would have been chosen spontaneously. Thus, the measurement of aPm and PetCO2 will allow us to assess an equivalent of physical stimulus for each of the two types of dyspnea and to assess the relationship of these with the intensity of the dyspnea. In addition, in the case of aPm, it will provide an index of the motor response to the loads.
- Tidal volume and respiratory rate as well as ventilation/minute (calculated from the instantaneous flow signal) will provide us with an interesting insight into the adaptation of breathing to the physiological mechanisms underlying dyspnea.

The CAM-ICU Scale

The confusion assessment method for the intensive care unit (CAM-ICU) will be used for detection and monitoring of delirium during the 28 days of follow-up after inclusion (44).

Experimental Design

Randomization

After verification of the inclusion and exclusion criteria, the patients will be prospectively and randomly included in three groups of 21 patients, depending on the type of tDCS treatment received: anodal tDCS group, cathodal tDCS group, and placebo tDCS group. The tDCS will be applied up on the cortical representation zone of the primary motor and left pre-motor cortex for 30 min; intensity 2 mA (in anodal, cathodal, or placebo modality). The patient will be blinded from the randomization arm. Randomization will be performed on a dedicated and secure specific website (Cleanweb). Randomization will be carried out in a 1: 1: 1 ratio with permutation blocks of size unknown to the investigators.

Description of the Acts Performed and Devices Used

This is a clinical, interventional, bi-centric, randomized, single-blind, 3-arm trial, including a placebo-controlled arm, and 2 experimental arms, evaluating the effectiveness of a medical device for therapeutic purposes (tDCS) with 63 (3 groups of 21) patients on mechanical ventilation in intensive care with dyspnea. The primary endpoint will be assessed by an independent, blind observer. Transcranial stimulation will be delivered using a medical certified "Starstim 8" brain stimulator controlled via Bluetooth using a laptop computer (Neuroelectrics, Barcelona, Spain), Stimulation will delivered through traditional 5×7 cm rectangular sponge electrodes, with a contact area of 35 cm^2 (Sponstim, Neuroelectrics, Barcelona, Spain). The tDCS will be applied upon the left hemisphere because of the functional dominance of this hemisphere in humans and in accordance with previous studies having evaluated the effect of tDCS on pain and the respiratory tract (27, 28, 32, 38, 51). As described in our previous work (38), two identical, rectangular, saline-soaked electrodes, each 7 cm long and 5 cm wide (35 cm^2), were secured to the scalp. For anodal tDCS, the anode will be placed over the left diaphragmatic

primary motor cortex (4 cm lateral to the midline and 1 cm anterior to the binaural line) and the cathode will be placed above the right orbit. These positions will be switched to obtain cathodal tDCS. For both anodal and cathodal tDCS, intensity will be 2 mA and the duration 30 min. The current density used will be 0.057 mA/cm^2, which has been proven to be safe (52–55). For the sham condition (placebo tDCS), intensity was also 2 mA but duration was only 2 min. Nitsche and Paulus reported in 2000 that at least 3 min of tDCS was necessary to induce after-effects (31).

Measurements of the Parameters Evaluated

The parameters studied (in particular those used to calculate the main judgment criterion) will be measured during the 30 min preceding (pre) and the 30 min following (post) the use of tDCS in each of the three different experimental conditions (anodal tDCS, cathodal tDCS, and placebo tDCS). The placebo tDCS condition constitutes the control condition (fictitious stimulation: absence of delivered current (sham), therefore acting as placebo. The **Figure 1** represents a diagram of the course of the experimental procedure.

Side-Effects and Adverse Effects Assessment

Side-effects and adverse effects associated with the tDCS during the course of the trial will be assessed using the adverse effects questionnaire proposed by Brunoni et al. for tDCS studies in order to improve systematic reporting of tDCS-related adverse effects (56).

Research Calendar

The total duration planned for the study is 12 months. The total duration of participation for each patient is 28 days; because each patient will be followed up for a period of 28 days after inclusion in order to collect the evolution data. The **Table 1** summarizes the research chronology.

Selection and Inclusion Visit

Inclusion will be made when all the inclusion and non-inclusion criteria are verified and the patient has given informed consent to participate in the study. During inclusion and before the start of the single session of the protocol, the following clinical, drug, and other co- variable data will be collected. These data are in principle systematically measured in intensive care patients.

Demographic data (age and sex), the reason for admission; medical history (neurological, respiratory, cardiological) initial severity by the SAPS-II score (57), the number of organ failures by the SOFA score (58), neurological assessment scores (Glasgow, FOUR score) (59); CAM-ICU (44) and the RASS score (to assess depth of sedation (42). The determinants of secondary cerebral aggression of systemic origin: body temperature, blood pressure, PaO2, PaCO2, natremia, glycemia. The neurological examination which includes: examination of the cranial pairs (spontaneous eye movements, pupil size, photo-motor reflex, oculo-cephalogyr reflex, corneal reflex, reaction to Pierre Marie-Foix's maneuver, cough reflex), the search for archaic reflexes (corneo- mandibular, palmo- mental, yawning, chewing, grasping), osteo-tendinous, and plantar skin reflexes.

The practical implementation of the protocol will consist of a single session of ∼1 h 30 m and will include the three stages described in **Figure 1**. After inclusion and randomization, the set of parameters studied will be measured for each patient, for 30 min before using tDCS, then for 30 min after stopping tDCS. The tDCS will be applied for 30 min to the cortical representation area of the primary motor area and the supplementary left motor area.

Research Follow-Up Visits

The patients will then be followed for a period of 28 days after inclusion in order to collect the evolution data including: Death, measurement of delirium (CAM-ICU scale) until D28; ventilation status (spontaneous or mechanical) and withdrawal (in progress, successful, failure) until D28, the cumulative incidence of mechanical ventilation, and the length of stay in intensive care.

End of Research Visit

The last visit made on D28 for patients for patients who survived to this date, will be identical to previous visits.

Statistical Analysis

Descriptive Analysis

A descriptive analysis of inclusions and monitoring of the protocol will be carried out. The main analysis will be carried out according to the intention to treat principle. Only patients who have withdrawn their consent can be excluded from the analysis. Patients who have decided to discontinue the management planned for the trial, lost to follow-up, or discontinued the trial will be included in the analysis. In general, the quantitative variables will be described by their median and their first and their third quartiles and the qualitative variables will be described by the frequencies of the modalities and the associated percentages. The epidemiological and clinical characteristics of the patients at inclusion will be described by group, without statistical tests being carried out. The protocol violations, the causes of abandonment and loss of sight and the characteristics of these patients will be detailed.

Primary Judgment Criterion

The studied parameters will be measured during the 30 min before (pre) and 30 min following (post) the use of tDCS in all three conditions (tDCS anodal, tDCS cathodal, and tDCS placebo). The placebo tDCS condition is the control condition (fictitious stimulation). The different measures of the judgment criteria will be carried out by one of the investigating doctors blinded in the randomization arm. In order to test the effect of tDCS, the judgment criteria will be compared according to the different experimental conditions (anodal tDCS, vs. cathodal, vs. placebo tDCS). Each experimental arm will be compared to the placebo group at risk 0.025 using Students *t*-test and applying Bonferroni correction if needed.

Secondary Judgment Criteria

- Differentials of the MDP-QS and MDP- A2 subscales of the Multidimensional Profile of Dyspnea measured between before and after tDCS, in order to assess the effect of tDCS on

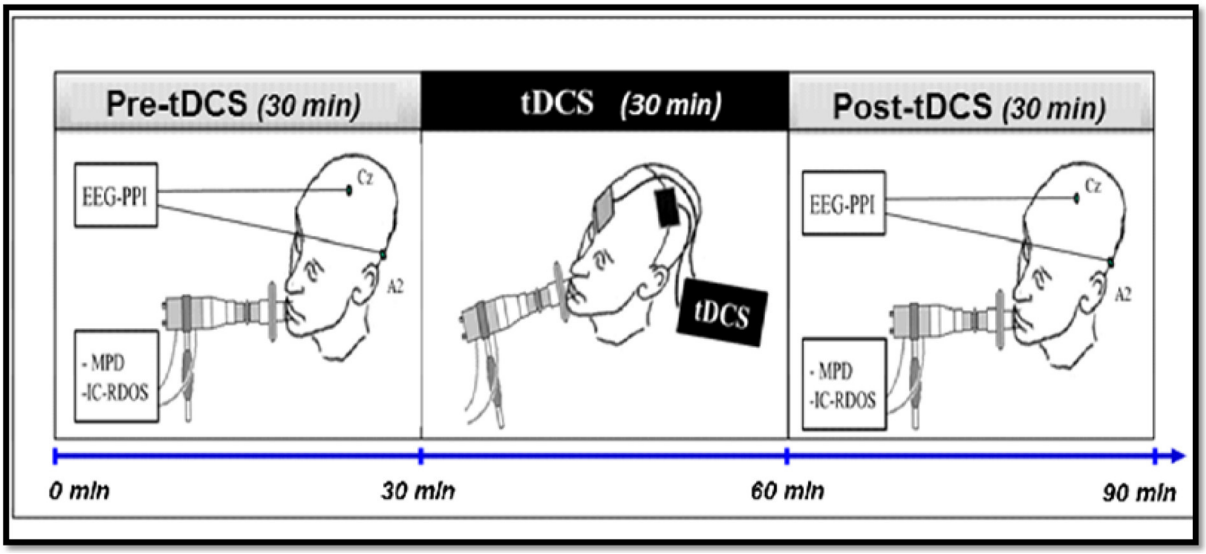

FIGURE 1 | Diagram of the experimental procedure. The practical implementation of the protocol consists of a single session of ∼1 h 30 min and will include the three stages. After inclusion and randomization, the set of parameters studied will be measured for each patient, for 30 min before using tDCS, then for 30 min after stopping tDCS. The tDCS will be applied for 30 min to the cortical representation area of the primary motor area and the supplementary left motor area. tDCS, Transcranial stimulation with 2 mA intensity current in anodal, cathodal or placebo polarity, applied to the cortical representation area of the left primary and pre-motor areas; EEG-PPI, EEG to measure the Pre-Inspiratory Potentials; MPD, Scales of the Multidimensional Profile of Dyspnea; IC-RDOS, Scales of the Intensive Care Respiratory Distress Observation Scale.

TABLE 1 | Summary of the research chronology.

Actions	Day 0 (inclusion, before tDCS)	Day 0 (after tDCS)	Day 1 to Day 27	Day 28 (after tDCS)
information	X			
Informed written consent	X			
Background	X			
SAPS-II score	X			
SOFA score	X			
Clinical and neurological examination	X	X	X	X
Glasgow score	X	X	X	X
RASS score	X	X	X	X
FOUR score	X	X	X	X
CAM-ICU score	X	X	X	X
Ventilation status	X	X	X	X
Ventilation weaning status (in progress, successful, failed)			X	X
Multidimensional dyspnea profile	X	X		X
IC-RDOS scale	X	X		X
EEG for PPI assessment	X	X		X
Respiratory Function Evaluation: PaO2, PaCO2, Mouth pressure, PetCO2, Tidal volume (VT), Respiratory frequency (F), Ventilation/minute (calculated from VT and F)	X	X		X

the different components of dyspnea: sensory (MPD-QS) and emotional qualifiers (MPD-A2 subscales). Each experimental arm will be compared to the placebo group at risk 0.05 using a Student test. If the two experimental arms are greater than the placebo arm, they will be compared to each other at risk 0.05.

- Differential in the IC-RDOS (intensive care respiratory distress observation scale) scale: between before and after the use of tDCS. A significant reduction in this score after the use of tDCS will translate into a reduction in respiratory discomfort, especially dyspnea. Each experimental arm will be compared to the placebo group at risk 0.05 using a Student test. If the two experimental arms are greater than the placebo arm, they will be compared to each other at risk 0.05.

- Pre-inspiratory potentials (PPI): the possible presence of PPI on the EEG in this patients population could be a marker of respiratory suffering, and a possible disappearance of PPI after the use of tDCS could be interpreted as a relieving effect on breathing difficulty. Each experimental arm will be compared to the placebo group at 0.05 risk using a Fisher test. If the two experimental arms are greater than the placebo arm, they will be compared to each other at risk 0.05.
- The respiratory parameters: mouth pressure (amplitude of variation), PetCO2, tidal volume (VT), and respiratory rate (F) as well as ventilation/minute (calculated from VT and F). The comparisons of each of these parameters will be carried out. Each experimental arm will be compared to the placebo group at risk 0.05 using a Student test. If the two experimental arms are greater than the placebo arm, they will be compared to each other at risk 0.05.
- Evaluation of the impact of tDCS on the patient's future outcome during the 28 days following inclusion:

  (a) Death on D28 in intensive care and in the hospital: Each experimental arm will be compared to the placebo group at 0.05 risk using a Fisher test. If the two experimental arms are greater than the placebo arm, they will be compared to each other at risk 0.05. Kaplan-Meir curves for death.
  (b) Cumulative incidence of delirium and its duration (CAM-ICU scale): The cumulative incidence estimates will be made using the gray method and compared according to the previous procedure using a gray test.
  (c) Proportion of patients who failed to withdraw from mechanical ventilation on D28: Each experimental arm will be compared to the placebo group at 0.05 risk using a Fisher test. If the two experimental arms are greater than the placebo arm, they will be compared to each other at risk 0.05.
  (d) Cumulative incidence of mechanical ventilation on D28: The cumulative incidence estimates will be made using the gray method and compared according to the previous procedure using a gray test.
  (e) The duration of the resuscitation stay: Estimates of the median length of stay in intensive care will be made from an inverted Kaplan Meier estimator and compared according to the previous procedure using a log rank test.

Calculation Hypotheses for the Number of Subjects Required and Result

The MDP-A1 subscale of the Multidimensional Dyspnea Profile is the main evaluation criterion of this study. This subscale is similar to the visual analog scale. Assuming a difference of 1 (on the primary efficacy endpoint, superiority study) between one of the 2 experimental groups and the placebo group and a standard deviation of 1, with a first species risk (alpha risk) of 2.5% (to take into account the 2 comparisons of each experimental group with placebo) and a power of 80% (beta risk at 20%), it will be necessary to include 21 patients per group or 63 patients in total. This number is consistent with that of other studies in tDCS (29, 60, 61).

The main analysis will be carried out according to the intention to treat principle. Only patients who have withdrawn their consent can be excluded from the analysis. If the period of inclusion in the research is still active, patients who have withdrawn their consent will be replaced. Patients who have decided to discontinue treatment planned in the trial, lost to follow-up or discontinued from the trial will be replaced, as will patients for whom there have been technical problems. Analyzes will be carried out with the intention of treating. Regarding missing data issue, in case of patient drop-out, in order to clearly understanding of the effectiveness of the therapy, we will first report results based on the completed cases, then secondarily with mixed-model or similar approaches which take into account partially available data, and finally with multiple imputation techniques.

ETHICAL AND LEGAL ASPECTS

This study was approved by our legal ethical committee: Comité de Protection des Personnes Ouest III, Université de Poitiers; CPP number 170946 and renewed on april 28th 2020. Informed consent should be obtained from each patient or family member before inclusion in the study.

CONCLUSIONS

Dyspnea is a painful suffering that often reaches unbearable limits. Unfortunately, it is very frequent in intensive care and constitutes a major factor affecting the prognosis of intensive care patients, and more particularly patients under mechanical ventilation. Many COVID-19 patients continue to suffer from it, despite being put on mechanical ventilation and the use of relaxing and analgesic drugs (40). The effectiveness of the treatments currently available therefore remains very limited and there is a pressing need to develop other innovative treatments, including non- medicinal ones, in order to combat this scourge even more effectively and reduce the suffering of patients (39). The tDCS has demonstrated efficacy in pain relief, which shares the same neural substrates as dyspnea. It is a painless, easy to use and non-invasive technique. The originality and the innovative character of this study reside in the development of an effective method of treatment by neuro-modulation non-invasive and easy to use to combat this respiratory suffering in COVID-19 patient. Effective relief of dyspnea with tDCS would also have a significant impact on the prognosis of these patients. Finally, one may argue that it could have been better to conduct a multisession tDCS study, however this study is a pilot, designed to assess whether a single 30 min tDCS session could be beneficial for dyspnea relief in this specific patients' population. According to the

findings of the present study we will conceive and assess outcome of other tDCS treatment strategies and designs including multisession ones.

AUTHOR CONTRIBUTIONS

EA, FL, DA, and TS developed the study concept. All authors wrote and drafted the manuscript, read, and approved the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Clinical Characteristics of Adult Fevered COVID-19 Patients and Predictors for Developing Severe Events

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Aim: Clinical findings indicated that a fraction of coronavirus disease 2019 (COVID-19) patients did not show fever. However, the difference between the clinical characteristics of fevered and non-fevered patients is still unclear. The aim of the present study was to describe the clinical characteristics of these patients and analyze the predictors for severe events of adult fevered COVID-19 patients.

Methods: Clinical and laboratory data of fevered and non-fevered COVID-19 patients in Changsha, China, were collected and analyzed. Logistic regression analysis and Receiver Operating Characteristic Curve (ROC Curve) analysis were adopted to analyze risk factors and evaluate the effectiveness of the predictors for severe events in adult fevered COVID-19 patients.

Results: Of the 230 adult COVD-19 patients in this study, 175 patients (76.1%) had fever and 55 patients (23.9%) did not have fever. Compared with non-fevered patients, the fevered patients showed a lower lymphocyte proportion ($P = 0.000$) and lymphocyte count ($P = 0.000$) as well as higher levels of C-reactive protein (CRP) ($P = 0.000$) and erythrocyte sedimentation rate ($P = 0.000$). The proportion of severe cases was significantly elevated in adult fevered patients ($P = 0.000$). Compared to non-severe fevered patients, severe fevered patients showed a lower lymphocyte count ($P = 0.000$), a lower lymphocyte proportion ($P = 0.000$), and higher levels of CRP ($P = 0.000$). As determined by the multivariate analysis, CRP (OR 1.026, $P = 0.018$) and lymphocyte proportion (OR 0.924, $P = 0.009$) were significantly associated with the risk of developing severe events in fevered adult COVID-19 patients. Furthermore, ROC Curve analysis revealed that the area under the curve (AUC) for CRP combined with lymphocyte proportion to diagnose severe events in fevered adult COVID-19 patients was 0.874 (95% CI 0.820–0.927).

Conclusions: Adult fevered COVID-19 patients were more likely to progress into severe cases, while CRP and lymphocyte proportion were effective predictors for developing severe events in these patients.

Keywords: COVID-19, adult, fever, C-reactive protein, lymphocytes

INTRODUCTION

The emergence of coronavirus disease 2019 (COVID-19), which was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in China in late 2019 (1–5) and has quickly led to outbreaks in other countries, such as Italy, Iran, and South Korea (6–8). As of April 12, 2020, more than 1.6 million people worldwide have been diagnosed with COVID-19, and about 100,000 people have died (9). How to block transmission of SARS-CoV-2, early screening of severe cases, and find effective treatments are urgent issues for scientists worldwide.

As the most common symptom and sign of infection, fever is generally initiated by a pyrogen, which causes a rise in temperature setting point and increases body heat production (10, 11). Body temperature screening is widely used as a screening tool for patients with COVID-19 in many places, such as communities and airports (12). The latest report found that fever was the most common symptom of COVID-19 patients, but more than 10% of patients with COVID-19 did not develop fever (4, 13). However, differences in clinical characteristics and prognosis between fevered and non-fevered COVID-19 patients remain unclear. In this study, we presented the clinical characteristics of these patients and analyzed predictors for developing severe events through Logistic regression analysis.

MATERIALS AND METHODS

Participants

Inclusion criteria: all laboratory-confirmed adult COVID-19 patients admitted to Public Health Treatment Center of Changsha, China, on admission from January 17 to March 15, 2020, were enrolled.

Two of our team carefully collected and reviewed the medical records of patients, individually. The detailed information on demographic data, underlying comorbidities, symptoms before and during admission, first laboratory and chest computed tomographic (CT) scans results after admission were recorded.

The temperature and symptoms before admission were based on the patient's description. After admission, all patients were monitored for axillary temperature more than once a day using mercury thermometers for 10 min each time, which were evaluated by professional nursing staff finally. Fever was defined as axillary temperature $\geq$37.3°C (14, 15).

Definition and Study Endpoints

We used one of the following criterial to determine the severe cases of COVID-19: (1) respiratory rate $\geq$ 30 /min; (2) oxygen saturation <93%; (3) $PaO_2/FiO_2 \leq 300$ mmHg; (4) lung lesion progression > 50% within 24–48 h; (5) mechanical ventilation was implemented; (6) shock; and (7) intensive care unit admission (16). SARS-CoV-2 nucleic acid tests were performed at least two times consecutively after remission of symptom (sampling time interval is at least 1 day). Two consecutive negative results are considered negative for the virus (16); virus shedding duration was defined as the time between symptom onset (the day of diagnosis for asymptomatic patients) and the first negative samples without any positive sample thereafter. Respiratory symptoms were defined as cough, expectoration, hemoptysis, and dyspnea, while digestive symptoms were defined as anorexia, nausea, vomiting, abdominal pain, and diarrhea.

Statistical Analysis

We used median with range and Mann-Whitney test to depict and analyze all continuous variables because of non-normal distribution. The χ^2 test and or Fisher's exact test was utilized to compare the differences of the categorical variables. Logistic regression analysis and Receiver Operating Characteristic Curve (ROC curve) analysis were adopted to analyze predictors and evaluate the effectiveness of the predictors for severe events in fevered COVID-19 patients. All analyses were performed using IBM SPSS version 26 software.

TABLE 1 | Baseline characteristics of fevered and non-fevered COVID-19 patients.

	No fever (n = 55)	Fever (n = 175)	*P*-value
Sex (male/female)	25/30	90/85	0.440
Age, median (range), y	41 (19–81)	46 (21–84)	0.353
Tobacco (*n*, %)	7 (12.7)	12 (6.9)	0.272
Alcohol (*n*, %)	3 (5.5)	7 (4.0)	0.934
Comorbidities			
Hypertension (*n*, %)	8 (14.5)	28 (16.0)	0.796
Cardiovascular disease (*n*, %)	2 (3.6)	7 (4.0)	1.000
Diabetes (*n*, %)	4 (7.3)	11 (6.3)	1.000
COPD (*n*, %)	0 (0.0)	1 (0.6)	1.000
Cerebrovascular disease (*n*, %)	0 (0.0)	6 (3.4)	0.340
Chronic liver disease (*n*, %)	2 (3.6)	10 (5.7)	0.797
Malignancy (*n*, %)	2 (3.6)	0 (0.0)	0.056
Symptoms			
Respiratory symptoms (*n*, %)	36 (65.5)	155 (88.6)	**0.000**
Digestive symptoms (*n*, %)	31 (56.4)	119 (68.0)	0.114
Chest CT positive rate (*n*, %)	50 (90.9)	170 (97.1)	0.110
Chest CT with ground-glass change	23 (41.8)	86 (49.1)	0.343
Respiratory support			
Non-invasive ventilation (*n*, %)	0 (0.0)	4 (2.3)	0.057
High-flow oxygen therapy (*n*, %)	0 (0.0)	13 (7.4)	0.081
Invasive ventilation (*n*, %)	0 (0.0)	4 (2.3)	0.575
ECMO (*n*, %)	0 (0.0)	3 (1.7)	1.000
Prognostic indicators			
Severe cases (*n*, %)	0 (0.0)	45 (25.7)	**0.000**
Length of hospital stay, median (range), days	15 (5–34)	16 (5–41)	0.424
Virus shedding duration, median (range), days	18 (3–46)	18 (6–59)	0.563
Mortality (*n*, %)	0 (0.0)	2 (1.1)	1.000

P < 0.05 was considered statistically significant (marked in bold). Continuous variables were described as median with range and analyzed by Mann-Whitney test. Categorical variables were described as percentages and analyzed by the χ^2 test or Fisher's exact test.

Abbreviations: COVID-19, coronavirus disease 2019; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation.

RESULTS

Characteristics of Fevered Patients

All 230 adult patients diagnosed as COVID-19 by March 15, 2020, were included in this study; of these, 175 patients (76.1%) had fever and 55 patients (23.9%) did not have fever.

The clinical characteristics of the non-fevered and fevered patients were summarized in **Table 1**. There was no significant difference in age ($P = 0.353$) and gender ($P = 0.440$) between fevered and non-fevered COVID-19 patients as well as common underlying diseases, such as hypertension ($P = 0.796$), diabetes ($P = 1.000$), and cardiovascular disease ($P = 1.000$). Compared with non-fevered patients, the fevered patients showed higher ratios of respiratory symptoms (88.6 vs. 65.5%, $P = 0.000$; **Table 1**).

The fevered COVID-19 patients had a lower lymphocyte proportion (median, 25.0 vs. 31.7%, $P = 0.000$), lower lymphocyte counts (median, 1.0 vs. 1.5 $\times$ 10^9/L, $P = 0.000$), higher levels of C-reactive protein (CRP) (median, 20.2 vs. 3.8 mg/L, $P = 0.000$), higher erythrocyte sedimentation rate (ESR) levels (median, 48.0 vs. 27.0 U/L, $P = 0.000$), and a higher proportion of elevated procalcitonin (30.9 vs. 16.4%, $P = 0.036$; **Table 2**).

Although all patients on ventilator had fever, there was no significant difference in the proportion of receiving different respiratory support between the fevered and non-fevered COVID-19 patients. In terms of prognosis indicators, there were no obvious differences in mortality ($P = 1.000$), length of hospital stay ($P = 0.424$) and virus shedding duration ($P = 0.563$) between fevered and non-fevered patients. However, fevered patients showed significantly increased proportion of severe cases (25.7 vs. 0.0%, $P = 0.000$) compared to non-fevered COVID-19 patients (**Table 1**).

Characteristics of Severe Fevered Patients

Because of the significant increased probability of severe events in fevered COVID-19 patients, we further performed a subgroup analysis of fevered patients based on the disease severity. Compared to non-severe fevered patients, severe fevered patients were older (median, 57 vs. 42 years, $P = 0.000$) and had a higher proportion of underlying diseases, including hypertension (33.3 vs. 10.0%, $P = 0.000$) and cardiovascular disease (11.1 vs. 1.5%, $P = 0.017$). More severe fevered patients had respiratory symptoms (100.0 vs. 84.6%, $P = 0.005$) and ground-glass change in chest CT (68.9 vs. 42.3%, $P = 0.002$; **Table 3**). Severe patients also showed a lower lymphocyte count (median, 0.7 vs. 1.1 $\times$ 10^9/L, $P = 0.000$), lower lymphocyte proportion (median, 18.6 vs. 27.5 $\times$ 10^9/L, $P = 0.000$), and higher levels of CRP (median, 40.8 vs. 16.0 mg/L, $P = 0.000$; **Table 4**).

Moreover, significantly more severe fevered patients received mechanical ventilation (non-invasive:8.9 vs. 0%, $P = 0.004$; high-flow oxygen therapy: 28.9 vs. 0%, $P = 0.000$; invasive: 8.9 vs. 0%, $P = 0.001$) and extracorporeal membrane oxygenation (ECMO) (6.7 vs. 0%, $P = 0.016$) as compared with non-severe cases. Length of hospital stay and virus shedding duration were both prolonged in severe fevered patients (**Table 3**).

Analysis of Relative Factors for Severe Events

The associations between severe events of adult fevered COVID-19 patients and related factors were presented in **Table 5**. As determined by the multivariate analysis, CRP (OR 1.026, 95% CI 1.004–1.048, $P = 0.018$) and lymphocyte proportion (OR 0.924, 95% CI 0.871–0.980, $P = 0.009$) were significantly associated with the risk of developing severe events in fevered adult COVID-19 patients (**Table 5**).

Predictive Factor Analysis

ROC Curve analysis revealed that the areas under the curve (AUCs) for CRP and lymphocyte proportion to diagnose severe events in fevered adult COVID 19 patients were 0.759 (95% CI 0.675–0.843) and 0.767 (95% CI 0.691–0.843), respectively, while the AUC increased to 0.874 (95% CI 0.820–0.927) when CRP combined with lymphocyte proportion (**Figure 1**).

TABLE 2 | Laboratory findings of fevered and non-fevered COVID-19 patients.

	Normal range	No fever ($n = 55$)	Fever ($n = 175$)	*P*-value
White blood cell count, $\times 10^9$/L, median (range)	4-10	5.0 (2.4-9.9)	4.5 (0.8-13.4)	0.136
Lymphocyte count, $\times 10^9$/L, median (range)	0.8-4.0	1.5 (0.4-3.7)	1.0 (0.1-3.2)	**0.000**
Lymphocyte %, median (range)	20-40	31.7 (8.6-61.1)	25.0 (2.1-54.1)	**0.000**
Alanine aminotransferase, U/L, median (range)	0-42	16.9 (2.6-87.7)	20.3 (4.9-93.7)	0.058
Aspartate aminotransferase, U/L, median (range)	0-37	22.3 (11.5-78.8)	24.8 (2.0-82.1)	**0.008**
Total bilirubin, μmol/L, median (range)	3.4-20.5	10.6 (5.7-38.2)	11.0 (4.0-162.1)	0.767
C reactive protein, mg/L, median (range)	0-8	3.8 (0.2-62.1)	20.2 (0.1-101.9)	**0.000**
Erythrocyte sedimentation rate, mm/h, median (range)	0-15	27.0 (1.0-121.0)	48.0 (5.0-143.0)	**0.000**
Procalcitonin, ≥0.05 ng/ml, No. (%)	< 0.05	9 (16.4)	54 (30.9)	**0.036**
Creatinine, μmol/L, median (range)	21.5-104	53.3 (25.5-124.1)	51.6 (20.6-255.7)	0.242
Creatine kinase, U/L, median (range)	10-190	68.2 (23.0-235.0)	76.5 (11.3-986.4)	0.066
Creatine kinase-MB, U/L, median (range)	0-24	9.5 (0.7-19.9)	9.6 (0.3-221.7)	0.976

$P < 0.05$ was considered statistically significant (marked in bold). Continuous variables were described as median with range and analyzed by Mann-Whitney test. Categorical variables were described as percentages and analyzed by the χ^2 test or Fisher's exact test.
Abbreviations: COVID-19, coronavirus disease 2019.

TABLE 3 | Baseline characteristics of fevered COVID-19 patients with different severity.

	Non-severe (*n* = 130)	Severe (*n* = 45)	*P*-value
Sex (male/female)	64/66	26/19	0.323
Age, median (range), y	42 (21–84)	57 (25–75)	**0.000**
Tobacco (*n*, %)	10 (7.7)	2 (4.4)	0.689
Alcohol (*n*, %)	4 (3.1)	3 (6.7)	0.537
Comorbidities			
Hypertension (*n*, %)	13 (10.0)	15 (33.3)	**0.000**
Cardiovascular disease (*n*, %)	2 (1.5)	5 (11.1)	**0.017**
Diabetes (*n*, %)	7 (5.4)	4 (8.9)	0.632
COPD, (*n*, %)	0 (0.0)	1 (2.2)	0.257
Cerebrovascular disease (*n*, %)	4 (3.1)	2 (4.4)	0.648
Chronic liver disease (*n*, %)	7 (5.4)	3 (6.7)	1.000
Malignancy (*n*, %)	0 (0.0)	0 (0.0)	NA
Symptoms			
Respiratory symptom (*n*, %)	110 (84.6)	45 (100.0)	**0.005**
Digestive symptom (*n*, %)	86 (66.2)	33 (73.3)	0.374
Chest CT positive rate (*n*, %)	125 (96.2)	45 (100.0)	0.330
Chest CT with ground-glass change	55 (42.3)	31 (68.9)	**0.002**
Respiratory support			
Non-invasive ventilation (*n*, %)	0 (0.0)	4 (8.9)	**0.004**
High-flow oxygen therapy (*n*, %)	0 (0.0)	13 (28.9)	**0.000**
Invasive ventilation (*n*, %)	0 (0.0)	4 (8.9)	**0.004**
ECMO (*n*, %)	0 (0.0)	3 (6.7)	**0.016**
Prognostic indicators			
Length of hospital stay, median (range), days	15.5 (5.0-41.0)	21.0 (8.0–41.0)	**0.007**
Virus shedding duration, median (range), days	16.5 (6.0-53.0)	21.0 (12.0–59.0)	**0.002**
Mortality (*n*, %)	0 (0.0)	2 (4.4)	0.065

P < 0.05 was considered statistically significant (marked in bold). Continuous variables were described as median with range and analyzed by Mann-Whitney test. Categorical variables were described as percentages and analyzed by the χ^2 test or Fisher's exact test.
Abbreviations: COVID-19, coronavirus disease 2019; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation. NA, not applicable.

TABLE 4 | Laboratory findings of fevered COVID-19 patients with different severity.

	Normal range	Non-severe (*n* = 130)	Severe (*n* = 45)	*P*-value
White blood cell count, $\times 10^9$/L, median (range)	4-10	4.5 (1.9-13.4)	4.6 (0.8-10.4)	0.604
Lymphocyte count, $\times 10^9$/L, median (range)	0.8-4.0	1.1 (0.4-3.2)	0.7 (0.1-1.9)	**0.000**
Lymphocyte %, median (range)	20-40	27.5 (6.8-54.1)	18.6 (2.1-34.2)	**0.000**
Alanine aminotransferase, U/L, median (range)	0-42	19.7 (4.9-58.4)	23.9 (8.2-93.7)	**0.010**
Aspartate aminotransferase, U/L, median (range)	0-37	23.3 (2.0-59.5)	30.6 (16.9-82.1)	**0.000**
Total bilirubin, μmol/L, median (range)	3.4-20.5	10.9 (4.0-31.6)	11.8 (4.7-162.1)	0.805
C reactive protein, mg/L, median (range)	0-8	16.0 (0.1-91.4)	40.8 (2.7-101.9)	**0.000**
Erythrocyte sedimentation rate, mm/h, median (range)	0-15	46.0 (5.0-143.0)	51.5 (9.0-129.0)	0.208
Procalcitonin, ≥0.05 ng/ml, No. (%)	<0.05	38 (29.2)	16 (35.6)	0.429
Creatinine, μmol/L, median (range)	21.5-104	51.3 (20.6-105.1)	53.4 (21.9-255.7)	0.720
Creatine kinase, U/L, median (range)	10-190	69.2 (11.3-365.3)	92.0 (17.4-986.4)	**0.014**
Creatine kinase-MB, U/L, median (range)	0-24	9.3 (0.3-221.7)	11.2 (1.1-35.2)	**0.049**

P < 0.05 was considered statistically significant (marked in bold). Continuous variables were described as median with range and analyzed by Mann-Whitney test. Categorical variables were described as percentages and analyzed by the χ^2 test or Fisher's exact test.
Abbreviations: COVID-19, coronavirus disease 2019.

TABLE 5 | Logistic regression analysis for severe events of fevered COVID-19 patients.

Variables	Univariate		Multivariate	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Age	1.046 (1.021-1.073)	**0.000**	1.002 (0.965-1.040)	0.921
Gender	1.411 (0.712-2.797)	0.324	1.082 (0.421-2.780)	0.870
Hypertension	4.500 (1.935-10.466)	**0.000**	2.420 (0.761-7.700)	0.135
Cardiovascular disease	8.000 (1.494-42.831)	**0.015**	2.899 (0.267-31.439)	0.381
Lymphocyte %	0.878 (0.834-0.924)	**0.000**	0.924 (0.871-0.980)	**0.009**
Creactive protein	1.042 (1.025-1.058)	**0.000**	1.026 (1.004-1.048)	**0.018**
Alanine aminotransferase	1.045 (1.015-1.076)	**0.003**	1.000 (0.953-1.050)	0.990
Aspartate aminotransferase	1.079 (1.043-1.117)	**0.000**	1.018 (0.966-1.074)	0.498
Creatine kinase	1.006 (1.003-1.010)	**0.000**	1.004 (1.000-1.008)	0.053

P < 0.05 was considered statistically significant (marked in bold). COVID-19, coronavirus disease 2019.

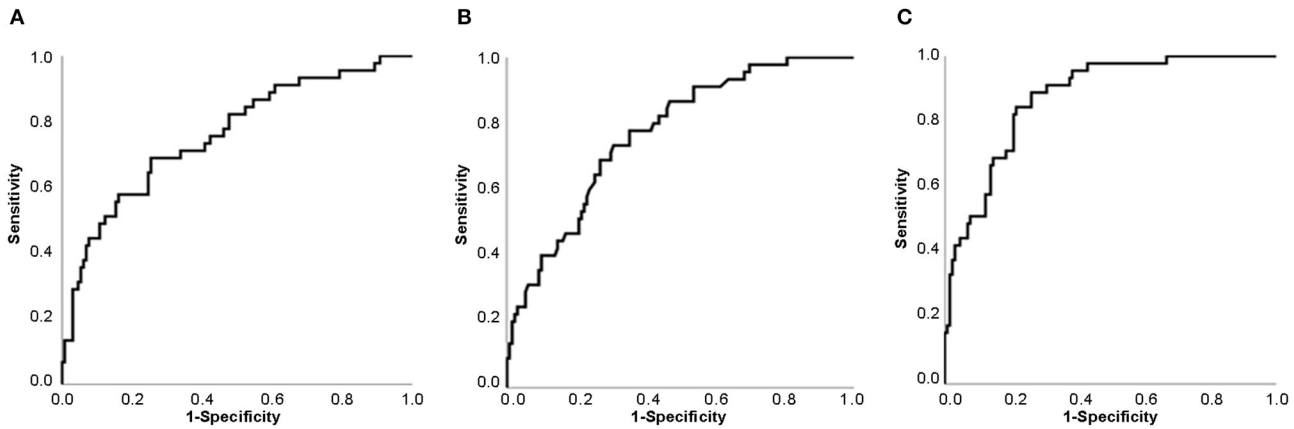

FIGURE 1 | Receiver Operating Characteristic Curve (ROC Curve) for predicting the possibility of severe events in adult fevered COVID-19 patients. **(A)** ROC Curve of CRP. **(B)** ROC Curve of lymphocyte proportion. **(C)** ROC Curve of CRP combined with lymphocyte proportion. Abbreviations: CRP, C-reactive protein; COVID-19, coronavirus disease 2019.

DISCUSSION

In this study, we first presented the clinical characteristics of fevered and non-fevered patients, and found that adult fevered COVID-19 patients were more likely to develop into severe cases, while CRP and lymphocyte proportion were effective predictors for developing severe events in these patients.

Although fever is the most common symptom of COVID-19 patients (5, 17–19), the proportion of fever is significantly lower compared to Middle East respiratory syndrome (MERS) and the severe acute respiratory syndrome (SARS) (20, 21). The proportion of fever varied in different studies, but a latest meta-analysis of 19 articles reported that about 88.7% COVID-19 patients had fever, which indicated that more than 10% patients had a normal temperature. In this study, we presented a slightly lower proportion of fever (76.1%) in COVID-19 patients, which may be related to the inclusion of some asymptomatic infections in this study. In general, a small number of COVID-19 patients do not show symptoms of fever, which suggests that using body temperature to screen COVID-19 patients may lead to some missed diagnosis. Nucleic acid testing now used in many places may be a more effective way to screen SAR-CoV-2 infection than body temperature testing.

Previous studies found that the elderly patients and old animal models showed an impaired fever response to infection or inflammatory factors (22–25). However, in this study, we found there was no significant difference in gender, age, and basic diseases between COVID-19 patients with fever and without fever, which suggested that the basic status may not be a major factor for fever response in COVID-19 patients.

Several studies showed the incidence of fever was significant higher in severe COVID-19 patients (26–28). In this study, we found that the proportion of severe cases was significantly higher in fevered COVID-19 patients compared to non-fevered patients, which indicated that fevered patients were more likely to progress into severe cases. Moreover, it seemed that all severe cases appeared in fevered COVID-19 patients in this study, while those non-fevered patients rarely developed into severe cases, and Huang et al. also showed none of non-fevered COVID-19 patients in their study progressed into severe cases (28), which

suggested normal body temperature may be a valuable indicator to rule out severe COVID-19 patients.

Currently, hyperinflammation is considered to be an important cause of organ damage and even death in COVID-19 patients (29–32). Patients with severe or fatal COVID-19 showed significantly higher levels of inflammatory factors, such as CRP, interleukin-6 (IL-6), interleukin-2 (IL-2) and interleukin-7 (IL-7) (3, 33). In this study, fevered COVID-19 patients had a stronger inflammatory response than non-fevered patients, manifested by significantly increased erythrocyte sedimentation rate and CRP, which may be the reason for the higher proportion of severe patients in fevered COVID-19 patients.

Although the proportion of severe cases of fevered COVID-19 patients in this study increased significantly, some fevered patients did not develop severe cases. Therefore, we compared the clinical characteristics of non-severe and severe fevered patients to try to find the risk factors for severe events of fevered patients. Through logistic regression analysis, CRP and lymphocyte proportion were considered to be effective predictive factors for severe cases.

This study presented several limitations. First, few cases were included in this study, and the conclusion of the study may need to be verified by studies with larger sample size. Second, the body temperature was not measured regularly before admission, which may result in some fevers not being detected. Third, we have not obtained screening data on bacterial infection and drug treatment data after admission. Therefore, it is still unclear whether the fever after admission was caused by secondary infection, drug fever, or factors other than SAR-CoV-2 infection, and this still needs to be further studied and followed up on. Additionally, although the two died patients were both with fever, there was no statistical difference in mortality between patients with fever and those without fever, which may be relate to the low overall mortality rate and small sample size.

CONCLUSIONS

In summary, we presented for the first time the clinical features of COVID-19 patients with or without fever. In this study, a few adult COVID-19 patients showed no fever. Adult fevered COVID-19 patients presented a higher risk of developing severe events compared to non-fevered patients, while CRP and lymphocyte proportion may be effective predictive factors.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the data used in this paper are from public health treatment center, which can only be obtained with the approval of relevant institutions. Requests to access the datasets should be directed to Yanjun Zhong, zhongyanjun@csu.edu.cn.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional ethics board of the Second Xiangya Hospital of Central South University (No. 2020001). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

GWa and QZ were involved in study design, interpreting data, statistical analysis, creating tables and figures, and writing of the manuscript. YZ was involved in interpreting data, statistical analysis, designed the research, and supervised the work. CW, FW, BY, JL, GWu, and SZ were all involved in data collection, data interpretation, and critical revisions of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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OPINION
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Impact of Coronavirus and Covid-19 on Present and Future Anesthesiology Practices

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INTRODUCTION

The Covid-19 pandemic has swept the world in fewer than 3 months, and there remains no end in sight. Approximately 6.1% of Covid-19 cases were classified as critical—defined as respiratory failure, shock, and multiple organ dysfunction or failure (1). Among the critically ill Covid-19 patients, ∼6–47% of them were intubated in China (2–7), 71–75% were intubated in the United States (8, 9), and 88% were intubated in Italy (10). The sheer volume of patients who require invasive mechanical ventilation support entails that anesthesia professionals have been put under significant pressure during this pandemic. This pressure is exacerbated by the fact that many urgent and emergent surgeries must proceed, even in situations in which patients have confirmed or suspected Covid-19. Clearly, anesthesia providers are playing a fundamental role in the frontline efforts to fight against this formidable pandemic. This paper discusses the impact Covid-19 is having on contemporary anesthesia practice through different phases and highlights some of the lessons we can learn to inform future practice (**Figure 1**).

THE PANDEMIC PHASE

Role Changes and Issues Identified

Be it as a measure of precaution, resource-saving, better manpower allocation, or ensuring availability of hospital beds, many hospitals throughout the world have canceled or postponed elective and semi-elective surgeries amid the current pandemic. While the reduction in the volume of surgical procedures being performed varies across different hospitals, it can be as high as 70–90%. This move suddenly relieves most anesthesia providers from perioperative care, with only a small portion being deployed to provide anesthesia for urgent or emergent surgeries. At the same time, as a result of the rapidly expanding number of patients admitted to hospitals and intensive care units (ICUs), anesthesiologists are being mobilized and re-deployed to serve outside the perioperative setting.

During this pandemic, anesthesia providers are typically being asked to provide the following services: (1) to intubate critically ill patients who require invasive mechanical ventilatory support; (2) to work in the ICU in the roles of intensivists, respiratory therapists, or nurses; (3) to place intra-arterial catheters and peripheral or central intravenous catheters; and (4) to work in the emergency departments or fever clinics to ensure the gaps in resources created by the sudden increase in symptomatic patients are filled (11). This is the overall global picture; however, the type and load of the work assigned to anesthesia providers outside the perioperative environment primarily depend on the number of cases encountered by individual hospitals and vary by country.

Various issues that directly impact anesthesia providers have arisen in the midst of providing care to critically ill Covid-19 patients. These issues are related to self-protection, best practices of intubation and ventilation, and professional liability in delivering care to patients outside any specialist scope of practice.

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Issue 1: What Are the Most Appropriate Self-Protection Measures?

In mid-March 2020, an article was published documenting the intubation and ventilation experiences in one of the epicenters—Wuhan, China (11). In this paper, the authors described the personal protective equipment (PPE) used by the Chinese healthcare workers. Of note, when performing invasive procedures in Covid-19 patients, including intubation and ventilation, all healthcare workers in China were required to follow Level III protective measures. Put simply, this mandates coverage of the entire body (11). This practice has caused a wide-range discussion outside China. In comparison, in the United States, standard protective practice does not involve covering the neck or leg below the knee. Although we agree that neither under-protection nor over-protection are warranted, the most ideal approach to self-protection is unclear. We hope this information will come to light with future analyses of worldwide practice data.

Issue 2: How Do We Deal With the Shortage of Personal Protective Equipment?

Regardless of what level of protection is most efficient, the shortage of PPE has caused some significant concerns. Especially at the early stage of the pandemic, there is a global shortage of almost every piece of PPE that is deemed necessary when performing invasive procedures in Covid-19 patients. Many medical practitioners are scrambling to identify methods of sterilizing and reusing N95 masks and/or making their own face shields. Reports of doctors and nurses using unconventional self-protection innovations, such as transparent plastic bags to cover the head and neck, have flooded social media and newspapers. The shortage of PPE and the difference in the availability of self-protection resources across different hospitals, regions, and countries have caused concern and confusion, and this has even resulted in some providers refraining from attending work (12). Moving forward, ensuring adequate PPE supply at all times with a robust production and supply chain capability is a priority.

Issue 3: What Are the Best Practices for Intubation and Ventilation?

In regards to the best practice when intubating and ventilating Covid-19 patients, there is no universal agreement, but the experiences of different countries should be considered (11, 13–16). Most anesthesia providers typically perform the following steps during intubation: (1) maintain the oxygenation and ventilatory support that has already been used in the patient; (2) avoid bag-mask ventilation if possible; (3) use 100% oxygen for 5 min during pre-oxygenation; (4) cover the patient's nose, mouth, and face; (5) perform rapid sequence induction; (6) aim for complete muscle relaxation; (7) avoid coughing and bucking; (8) perform video laryngoscope guided intubation;

Abbreviations: Covid-19, coronavirus disease 2019; ICU, intensive care unit; PPE, personal protective equipment.

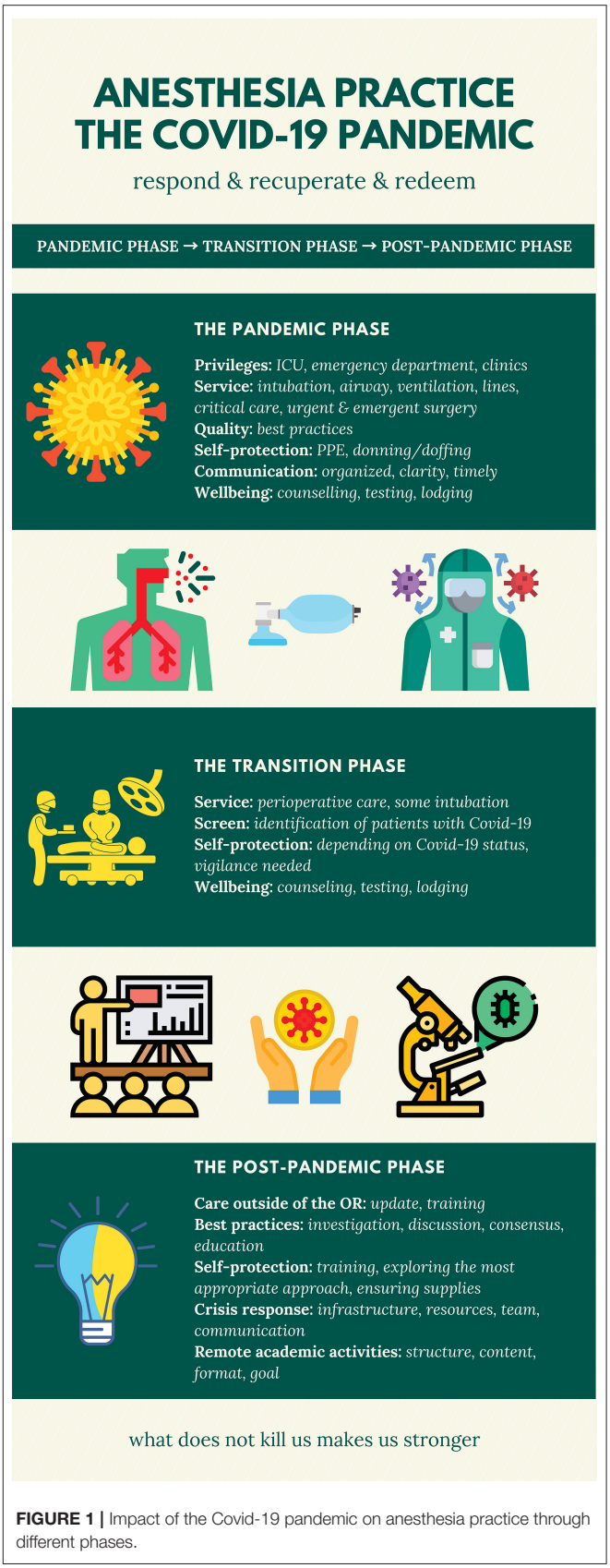

FIGURE 1 | Impact of the Covid-19 pandemic on anesthesia practice through different phases.

and (9) avoid chest auscultation. When delivering ventilatory support, most providers adhere to the following processes. They should avoid non-invasive ventilation, including continuous positive airway pressure and bilevel positive airway pressure, if there are enough ventilators and manpower for invasive mechanical ventilation. This is supported by reports from Lombardy region, Italy, where 11% of cases received non-invasive ventilation and 88% invasive mechanical ventilation during the first 24 h of ICU admission;(10) and in California, United States, 4% of ICU cases received high-flow nasal cannula, 1% non-invasive ventilation, and 91% invasive mechanical ventilation (17). They should adopt lung-protective ventilation strategies; set an ideal oxygenation goal; deliver early prone position ventilation; ensure adequate sedation and analgesia; and provide muscle relaxation when needed (11, 18). Lastly, the best approach to extubation is equally important as it may generate infectious aerosols as a result of patient coughing, and agitation (11).

Issue 4: How to Protect Anesthesiologists From Liability?

Most anesthesia providers are not credentialled to work outside the perioperative environment, especially in the United States. Although it appears that the Covid-19 crisis is a scenario in which the Good Samaritan principle would apply, there is still a requirement to rapidly authorize anesthesia providers to care for patients in the ICUs, emergency departments, and clinics. Depending on the local policy and practice, credentialing committees should quickly facilitate the process to legally authorize anesthesia providers to deliver necessary services in settings outside the perioperative environment as appropriate.

Issue 5: How Do We Effectively Organize and Communicate?

The Covid-19 pandemic presents some unprecedented challenges to anesthesiology departments. The environment is sporadic, chaotic, and unpredictable, with the situation changing daily, if not hourly, especially at the early stage of the pandemic. While every effort is made to ensure all practitioners are updated on the current status via timely communications, confusion and anxiety are commonplace. While it is understandable that almost all practitioners are witnessing a crisis of this severity for the first time in their lives, it is imperative that efforts are invested in streamlining the communication process so things proceed in the most smooth and effective fashion (19).

Most anesthesiology departments have quickly established a task force that is specifically responsible for dealing with the Covid-19 crisis. Organized, centralized, clear, and timely communication is essential. The leader of this task force or the individual to whom the leader delegates responsibility needs be in charge of the departmental communication. The message needs be as clear and transparent as possible to avoid any confusion. Reports from front-line staff go to the task force, not the entire department, for collection, summary, and dissemination. Daily conference calls with clinical leadership serve to keep everyone informed and delivering a consistent message to their teams.

Issue 6: What Are the Measures to Support Anesthesia Providers?

Every effort needs be made to protect frontline providers (19). The anesthesiology department needs work aggressively with hospital partners to seek alternative sources of supplies when facing a shortage of critical PPE and medications. Counseling for mental health and wellbeing needs be provided to department members (20). Lodging can be considered for individuals who are particularly concerned about risks of contamination of their home environment. Departmental leaders are role models for the team members by offering courage, acting as a source of inspiration, and encouraging a spirit of caring for each other.

THE TRANSITION PHASE

As of mid-April 2020, the current pandemic appears starting to head into a transition phase, with the progress varying from country to country. The transition phase is characterized by a dramatic decrease, but not complete elimination, of cases and risks of infection. During this phase, regular work order is gradually resumed while continuing to care for varying numbers of Covid-19 patients.

Issue 1: How to Reopen the Operating Rooms?

During the transition phase, it may be tempting to maximize the capacity of the operating rooms to address the cases that were postponed or rescheduled at the height of the pandemic. However, it is prudent to open the operating rooms more gradually for several reasons. First, the infection risk is lower but still lingers. Infection control requires time and energy and consumes resources. The need to ensure adequate protection and maintain control over the virus should be treated as a higher priority than maximizing caseload, given the potential for severe unintended consequences. Second, perioperative personnel, including anesthesia providers, have relearned and redesigned their approach to patient care to emphasize caution over throughput. Short of a vaccine that abolishes the future risk of Covid-19, there cannot be an immediate return to business as usual. Practitioners likely cannot achieve the necessary level of caution from an infection prevention standpoint, while achieving high throughput surgical volume, without neglecting other aspects of patient care and safety. Third, as we have learned now, some critically ill patients will continue to occupy the ICU beds, even weeks into the transition phase. Therefore, if a surgical case would typically require ICU admission after surgery, there will be a need to coordinate resource management with the hospital bed flow management team. Finally, the spread of the disease (hopefully through community spread and not at-work exposure/infection) will reduce the available workforce unpredictably. Contact

tracing and temporary quarantine further reduce the numbers of available workers.

Issue 2: How Do We Prepare Patients for Surgery?

Vigilance is needed as the risk of infection still exists during the transition phase. It has been suggested that all surgical patients undergo SARS-CoV-2 nucleic acid (typically a PCR test) and antibody tests and chest x-rays or CTs even if they are clinically asymptomatic. False negative rates are non-zero but poorly defined (2–29% estimated based on current data June 2020) (21). The preoperative preparation during the transition phase requires standardized approaches and policies. At a minimum, anesthesia providers need to be cautious during preoperative patient preparation. It is prudent to do the following: (1) wear a surgical mask and eye protection (goggles or face shield) when visiting, interviewing, and examining patients; (2) wash hands before and after each visit; (3) wear gloves when touching and examining patients; (4) consider avoiding chest auscultation if not clinically indicated; (4) be vigilant for the signs of infection; (5) follow up on pertinent labs; (6) follow up on chest x-ray or computed tomography results if ordered; (7) always remember to screen the patient for a history of Covid-19 and/or close contact with confirmed cases; and (8) consider testing for Covid-19 and the presence of an antibody response. Moreover, data regarding the protection provided by an immune response to prior Covid-19 infection and the duration of immunity are desperately needed.

Issue 3: Protections in the Operating Rooms?

In the operating rooms, full self-protection including N95 masks or power air purifying respirators (PAPRs), goggles or face shields, and waterproof gowns needs be worn if the patient has confirmed or suspected Covid-19; otherwise, wearing a surgical mask with a face shield should be the minimum for patients without evidence of Covid-19. If a Covid-19 patient is undergoing surgery, the following recommendations are advised: 1) perform the surgery in a dedicated Covid-19 negative-pressure operating room; (2) follow the consensus PPE guidelines during intubation and ventilation; (3) ensure smooth emergence and extubation; (4) use filters that are capable of preventing virus transmission/contamination to the anesthesia machine; (5) try to use disposable supplies when possible; and (6) thoroughly clean/sterilize any non-disposable equipment after surgery.

THE POST-PANDEMIC PHASE

Even after the pandemic has been officially declared over, things will not go back to how they used to be (even if there is an effective vaccine). The impact of Covid-19 on anesthesia practice will be deeply embedded. As the adage goes: what does not kill us makes us stronger. The lessons that can be learned from this pandemic are summarized below.

Lesson 1: Infection Control and Prevention

The most effective methods of protecting providers against virus transmission need to be identified (22–24). Different hospitals, regions, and countries have adopted different approaches. Evidence regarding the relationship between the various self-protection mandates that are available and the risk of cross-contamination is needed; neither under-protection nor over-protection is warranted. Different viruses have different behaviors, virulence, and modes of transmission; therefore, preparedness to adjust the approach to self-protection when confronting a novel virus and a new outbreak will be needed. A related issue concerns the adequacy of PPE supplies. Regular stockpile checking needs to be mandated. Methods of sterilizing and reusing different components of PPE need to be investigated and established. The supply chain needs to be bolstered, with contacts regularly maintained. All providers should be trained on the appropriate use of PPE, including the donning and doffing processes.

Lesson 2: Best Practices of Intubation and Ventilation

The best practices regarding intubation and ventilation need to be elucidated. Although there is some consensus, most of the actions that have been taken thus far amid this pandemic are opinion-based. Evidence to support or revise these is needed. One example is the non-invasive ventilatory support in critically ill Covid-19 patients. Bilevel positive airway pressure ventilation support was popularly used in the epicenter in Wuhan, China (11). Continuous positive airway pressure ventilation support has been used in the United Kingdom (25). However, non-invasive ventilation support has not been widely recommended for use in both Italy and the United States (10, 17). The three primary factors that determine which one to choose are clinical effectiveness, risk of cross-contamination, and the availability of resources. Clearly, the best practices concerning care for critically ill patients in situations like this pandemic need to be further investigated and discussed.

Lesson 3: The Skill Set for Future Anesthesiologists

The scopes of the clinical skills that future anesthesia providers should possess need to be clarified. This crisis has taught us that, during pandemics of this nature, anesthetists are not only needed for surgical procedures and airway management but also for work in the ICUs, emergency departments, and clinics. It is plausible to quickly teach practitioners immediately before and during the required activities; however, it would be better if the potential need in any future situation similar to this Covid-19 pandemic is anticipated and our providers are proactively trained so that they possess the skills they may need in an emergency situation. The good news is that the skills required outside the perioperative environment (e.g., ventilatory support) are not something unfamiliar to anesthesia providers, as critical care training is a component of anesthesiology residency in most countries. Therefore, regularly updating knowledge and practicing essential skills can be sufficient to ensure preparedness.

Lesson 4: Effective Team Response

A mechanism is needed to rally the team when situations similar to this pandemic occur again. This mechanism includes the ability to quickly assemble a task force, identify the available resources, establish a channel for efficient and clear communication, allocate jobs based on the strength and talent of individual team members, deliver counseling to ensure mental health and well-being, and closely collaborate with colleagues from other departments. The goal of this mechanism is to help practitioners efficiently join forces during the fight against a hidden enemy. The success in this great fight against SARS-CoV-2 resides in the resilience of all professionals related to the care for the Covid-19 patients, including nurses and physicians at different levels of training and practices and across different specialties. As we applaud this unprecedented all-out effort, we should also plan further team building to better prepare for any future outbreaks or pandemics.

Lesson 5: Continuous Academic Efforts

In a crisis like the Covid-19 pandemic, the traditional conduct of education and research are not permissible due to concerns surrounding virus transmission. Many trainees and research personnel have to stay at home for weeks. Instead of staying passive, anesthesia providers should use this period of time to effectively enhance education and research. Doing so also promotes a feeling of enrichment and satisfaction, which is a positive way of promoting well-being. The widely available remote conferencing platforms revolutionize how people are connected with each other in the modern era, making virtual academic activities possible. Contemporary technologies also allow people to gather online, see each other, talk to each other, reconnect with each other, help each other, exchange information, and move forward together as a team. Finally, the coming months during which people are awaiting for a Covid-19 vaccine will hopefully see a true tipping point in the transition to distance learning, expansion of telemedicine, and remote conferencing that will replace destination continuous medical education, non-essential face-to-face patient encounters, and convention center society meetings.

SUMMARY

The impact of the Covid-19 pandemic on anesthesia practice varies dynamically with the various phases of the pandemic. As we respond, recuperate, and move forward from the Covid-19 pandemic, the impact on anesthesia practice and the lessons learned should be summarized and addressed to ensure better preparedness and results in the future. The areas in which improvements are needed center on self-protection, best practices, scope of practice, organized response, and remote education, research, and gathering. Preparedness may use certain resources and cause financial concern, especially when a crisis is not observed for many years. Therefore, it would be wise to use the process of preparedness to promote a higher quality of patient care, education, research, and culture building. Simulation and quality assurance activities will facilitate "maintenance of preparedness." *Vigilance* is the motto of the North American anesthesiology community, and it appears to be more appropriate now than ever.

AUTHOR CONTRIBUTIONS

LM helped with the concept and design, administrative and material support, data interpretation, manuscript drafting, and critical revision of the manuscript for important intellectual content. DM helped with the data interpretation and critical revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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METHODS
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Care for Critical Ill Patients With COVID-19: Establishment of a Temporary Intensive Care Unit in an Isolated Hospital

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The current global spread of COVID-19, a highly contagious disease, has challenged healthcare systems, and placed immense burdens on medical staff globally. With a sharp increase in the number of newly confirmed cases and the rapid progression of the disease into a critically ill state, overstretched critical care units have had to contend with a shortage of beds, specialist personnel, and medical resources. Temporary intensive care units (ICUs) were therefore set up in isolated hospitals to provide the required standardized care for all severe cases. The current paper describes the authors' experience of setting up and managing such an ICU in Wuhan, Hubei Province, China, from the identification of critically ill COVID-19 patients through to the arranging and equipping of the unit, providing training and protection for staff, and standardizing all aspects of care.

Keywords: COVID-19, management, severe, temporary, intensive care unit

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is highly contagious. In recognition of the global threat it poses, on March 11, 2020, the World Health Organization (WHO) declared COVID-19 to be a pandemic. By July 22, 2020, the total officially confirmed cases in China reached 86,152 with 4,653(5.4%) having died since the outbreak began in December 2019 (https://covid19.who.int/). COVID-19 has high mortality throughout the world, being especially high in Italy (n = 236,076, mortality with 32,867/236,076), Spain (n = 264,836, mortality with 28,422/264,836), Russia (n = 783,328, mortality with 12,580/783,328), Brazil (n = 2,098,389, mortality with 79,488/2,098,389), the United States (n = 3,748,248, mortality with 139,964/3,748,248), and South Africa (n = 373,628, mortality with 5,173/373,628) (https://covid19.who.int/, https://www.epicentro.iss.it/en/coronavirus/bollettino/Infografica_10giugno%20ENG.pdf). The high incidence and mortality of COVID-19 puts pressure on the need for urgent and special requirements for global medical resources and infrastructures.

PURPOSE AND SIGNIFICANCE OF A TEMPORARY COVID-19 ICU

Data provided by the Chinese Center for Disease Control and Prevention revealed a total of 44,672 confirmed COVID-19 cases in China by February 11, 2020. Of these, the majority (87%) were aged

between 30 and 79, while 3% were aged 80 or more. A total of 14% of these patients were, or had been, severely ill, and 5% required critical care (1). Data from a single-center, retrospective study of 52 critically ill COVID-19 patients showed that 61.5% died at 28 days, 71% required mechanical ventilation, and 67% had acute respiratory distress syndrome (ARDS). Patients who died from the disease were recorded longer lingering time from onset of symptoms to ICU admission than those who survived (2).

As the number of newly-confirmed and critical COVID-19 cases rose sharply from December 2019 onwards in Wuhan, isolated hospitals charged with caring for such patients had to solve immense challenges in terms of finding sufficient bed space, personnel, and resources, particularly in relation to the provision of care for the critically ill patients (3). As COVID-19 is characterized by a high rate of contagion and rapid progression coupled with a high mortality rate, especially in the case of critical patients, it was essential to identify potentially critical cases at the earliest possible stage so they could be transferred to ICU timely to achieve necessary respiratory or circulation support in order to reduce mortality rates (4).

Given the shortage of critical care facilities and resources in isolated hospitals (5), the establishment of temporary ICUs in such hospitals was an essential part of the infrastructure for providing care to critically ill COVID-19 patients. The government thus made the decision to allocate an estimated 2,500 beds in three general hospitals in the city of Wuhan as temporary isolated wards for the treatment of severely infected patients. Over 3,000 medical personnel, including up to 1,000 ICU doctors and nurses, were called together from elsewhere in China to form centralized, specialist rescue teams in each isolated hospital. Each member of the teams represented a different department; thus, uniform and normative team management and patient care were challenging. Existing medical resources were leveraged to meet the needs of these ICUs, and the training of non-ICU staff was also critically important.

Over the course of a month in Wuhan, after the temporary ICU was established, a total of 157 critically ill patients were admitted into our temporary ward; they had characteristics of a mean age at 62 years old, a mean hospital stay at 16.01 days, 14.0% requiring invasive or non-invasive mechanical ventilation, and 3.82% died at discharge. Hence, the current paper shares best practices gleaned from the establishment and management of temporary ICUs in isolated hospitals during the epidemic in Wuhan; the centralization of severe confirmed cases enabled reintegration and maximum use of existing medical resources, thus facilitating effective professional treatments for COVID-19 patients.

ESTABLISHMENT OF A TEMPORARY COVID-19 ICU

On February 7, 2020, a national medical team from Xiangya Hospital, Hunan, took over the 51-bed ophthalmic ward in the Union Hospital Tongji Medical College Huazhong University of Science and Technology, Wuhan, in response to the insufficient number of ICU beds in isolated hospitals to cope with the rapidly increasing numbers of cases presenting with COVID-19. Combining the characteristics of the ward and taking into consideration severe cases, we planned to establish a temporary ICU in the Ophthalmic Ward; however, given its previous use, not all beds were supplied with sufficient oxygen pressure to run the necessary ventilators.

Early Identification and Sorting of Critical Cases

The first stage in the care of COVID-19 patients is to identify those who are critically ill. For this purpose, we modified the National Early Warning Score (News) (6) and SOFA score and added two further predicted risk factors for severe COVID-19 infection: age $\geq$ 66 years old (2, 7, 8) and persistent lymphocytopenia (2, 8, 9) (**Figure 1**). Post-admission, critically ill patients were sorted into one of four risk categories on the basis of their scores on the severity grading scales: mild, moderate, critical, and severe critical. It was important to recognize that critically ill patients who presented with silent hypoxemia (severe hypoxemia without signs of respiratory distress), particularly older ones, required vigilant monitoring. Initially, due to the lack of severe respiratory distress symptoms at the early stage of COVID-19 in some severe confirmed patients, clinicians might delay tracheal intubation, and invasive ventilation. This postponing would bring disastrous consequences for these patients. Hence, early identification of severe critical patients was crucial in enabling personnel to offer optimized treatment within the temporary ICU in the shortest time.

Dividing the Ward Into Sectors

The ward was divided into three sectors according to the results of the severity grading scales to facilitate clinical management (**Figures 2**, **3**).

The first sector, containing 12 beds supplied with sufficient oxygen pressure to run ventilators, was designated for the management of severe critically ill patients, including those requiring invasive ventilator support or prone ventilation, exhibiting hemodynamic instability. This sector was located close to the nurses' and doctors' workstations, enabling staff to monitor patients closely and provide immediate attention. The beds were placed at least two meters apart to prevent cross-infection. **Figure 4** displays the special medical equipment required in the temporary ICU, including non-invasive and invasive ventilators, high-flow nasal cannula (HFNC), renal replacement machines, extracorporeal membrane oxygenation machines, videobronchoscopes (with external monitor), equipment to monitor central venous pressure (CVP) or invasive arterial blood pressure, ultrasound machines, videolaryngoscopes, infusion or syringe pumps, vibrating expectoration machines, and closed tracheal suction catheters.

The second sector of the temporary ICU consisted of a ring of 25 beds outside the critical care sector and was designated for the care of moderate to critical patients, typically requiring low-parameter high flow oxygen therapy with a maximum flow rate of 40 L/min and inspired oxygen (FiO2) of 50%, or mask oxygen support with a maximum flow of 5 L/min. The third part, which consisted of 14 beds around the perimeter of the ward, was for

Modified National Early Warning Score (News) in COVID-19 infection							
Parameters	**3**	**2**	**1**	**0**	**1**	**2**	**3**
Respiration rate (breaths/min)	≤8		9-11	12-20		21-24	≥25
Oxygen saturation,%	≤91	92-93	94-95	≥96			
Any supplemental O2?		Yes		No			
Temperature (°C)	≤35.0		35.1-36.0	36.1-38.0	38.1-39.0	≥39.1	
Systolic BP (mmHg)	≤90	91-100	101-110	111-219			≥220
Heart/pulse rate (beats/min)	≤40		41-50	51-90	91-110	111-130	≥131
Level of consciousness (AVPU)				A			V,P,or U
Age				<66		66-79	≥80
Lymphocytopenia, × 10^9/L	≤0.62			>0.74			

FIGURE 1 | Early classification of critically COVID-19 patients. BP, blood pressure, level of consciousness; A, Alert; V, Responds to voice; P, Responds to pain; U, Unresponsive.

the use of patients identified as moderate, or who were in the recovery stage or requiring nasal catheter oxygen.

COVID-19 Infection Special Intensive Care Teams Establish

With insufficient trained ICU personnel to meet demand, we set up a multidisciplinary intensive care team led by senior intensive care specialists, and an intensive nurse team led by experienced intensive care nurses. Our first task was to evaluate isolation conditions, after which we divided the ward into inner and outer zones to give workers a space in which they could rest safely. Since every patient under our care was suffering from the same disease, we then took steps to standardize treatments by establishing protection strategy for each healthcare operation, for example routine medical care, tracheal intubation, and percutaneous tracheotomy.

Protecting Patients and Health Workers

Preventing a nosocomial outbreak of COVID-19 through transmission from patients to healthcare workers was of vital importance. To this end, every health worker had to be equipped with the correct personal protective equipment (PPE) and given training in its use before they could start caring for patients. After donning a medical protective mask, every worker was required to ask another to check if it was sufficiently tight, and, after they took their PPE off, they used quick-drying hand sanitizer. Different levels of PPE were assigned to healthcare workers according to the severity of the patients under their care, as showed in **Figure 5**. Workers administering oxygen therapy to confirmed COVID-19 patients in the third sector wore level-II protection consisting of protective clothing, gloves, shoe covers, head covers, a N95 mask, and protective (anti-fog) glasses, and they also carried out hand hygiene measures. Personnel carrying out operations among patients that might be associated with aerosol generating procedures, like sampling or sputum suction, wore level III-1 protection consisting of all the above items plus a waterproof isolation gown, and a face shield and also carried out the hand hygiene procedures. Personnel caring for sector-two patients, suffering from severe respiratory distress but not requiring invasive ventilation treatment, were also obliged to use level III-1 PPE (8). According to recent recommendations (10, 11), the highest level of PPE, level III-2, which included an air-purifying respirators (PAPRs), was reserved for high risk operations including tracheal intubation, tracheotomy, or fiberoptic bronchoscopy.

Education and Training of Health Workers

It is estimated that a considerable proportion of healthcare workers have been infected since the COVID-19 outbreak (for example, infected rates of health workers were 28603/236076 (12.1%) in Italy (https://www.epicentro.iss.it/en/coronavirus/bollettino/Infografica_10giugno%20ENG.pdf). Minimizing the risk of nosocomial outbreak amplification and protecting healthcare workers are of critical importance (8, 12). Widespread use of recommended barrier precautions in isolated wards must be of highly priority. The temporary ICUs set up to manage the epidemic in China established protocols for both the prevention of infection and contingency management, including PPE regulations, procedures for entering and leaving quarantined zones, emergency plans to cope with occupational exposure, checks on the hygiene standards observed by healthcare workers, and management of preventive medication. It is imperative that ensuring every healthcare worker is properly trained, continually protected against droplet infection, and versed in all the necessary checks and precautions, including the use of PPE. This is vital in the battle against a highly infectious disease such as COVID-19.

MANAGEMENT

Data from a follow-up study of 99 COVID-19 cases, dated January 25, 2020, reveal that 11% died, 9% required invasive

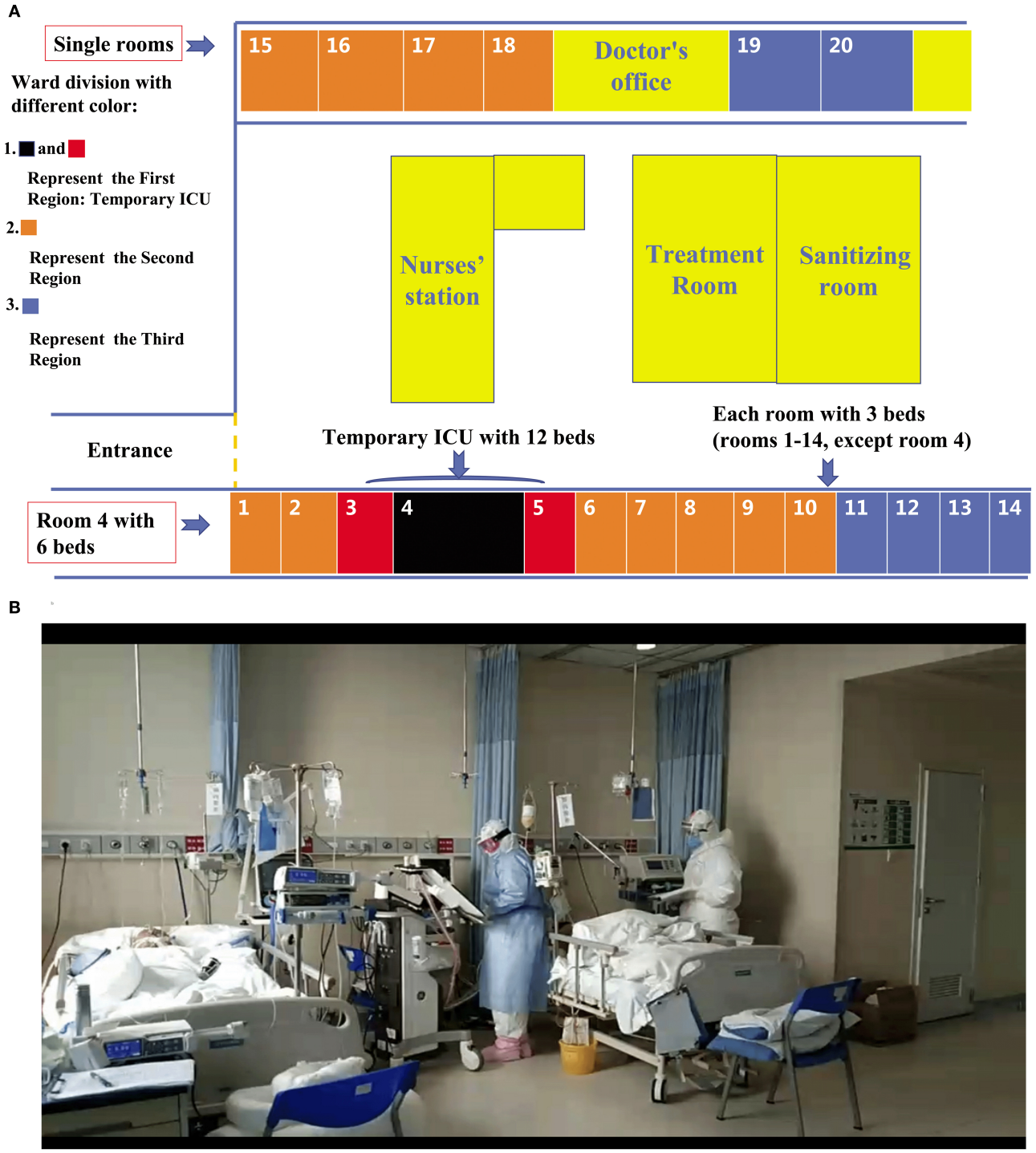

FIGURE 2 | Dividing a ward into sectors. **(A)** After the ophthalmology ward was transformed into a temporary ICU, beds were arranged as follows: the first sector, consisting of 12 beds, made up the temporary ICU (room four with six beds; room three with three beds; and room five with three beds); the rooms shown in orange indicate the second sector, comprising 25 beds; the rooms shown in blue indicate the third sector, comprising 14 beds. **(B)** A team led by specialized ICU physicians viewing critically ill COVID-19 patients in a temporary ICU.

mechanical ventilation, and 3% required extracorporeal membrane oxygenation (ECMO) (13). Among the significant findings was that before January 30, 2020, only about 25% of patients who died from COVID-19 received invasive mechanical ventilation or ECMO, and that HFNC and/or non-invasive ventilation (NIV) were used for an average

Early classifying critical cases with COVID infection							
Situation of ward	**Risk Grading**	**Score**	**Symbols**	**Nurses**	**Bed/Nurse ratio**	**Scaled of PPE**	**Level of Critical Care**
The Third region	Low	1-4	Blue	One ICU nurse leads a team of 6 trained non-ICU nurses	4:1	Level II	Usual oxygen therapy
The Second region	Moderate	5-6	Orange	One ICU nurse leads a team of 3 trained non-ICU nurses	3:1	Level III-1	Oxygen therapy with mask; Low parameter of high-flow nasal cannula
The First region of Temporary ICU	Critical	≥7	Red	One ICU nurse leads a team of 2 trained non –ICU nurses	2:1	Level III-1	High flow or non-invasive ventilation
The First region of Temporary ICU	Severe critical	≥7	Black	One ICU nurse leads 1 trained non-ICU nurse	1:1	Level III-1/ Level III-2 (special protection)	• Consideration for early invasive ventilation • Lung-protective ventilation strategies • Prone positioning • Hemodynamic monitoring

FIGURE 3 | Early sorting of critically ill COVID-19 patients according to a modified Early Warning Score in a temporary ICU.

Equipment for Usual critical care in temporary ICU				
Ward division		**The first region (Temporary ICU)**	The second region	The third region
Equipment	**Details**	Score ≥7	Score: 5-6	Score: 1-4
Ventilators	invasive ventilators	+	-	-
	no-invasive ventilators	+	+	-
	high flow nasal cannula	+	+	-
	renal replacement machines	+	+	-
	extracorporeal membrane oxygenation	+	-	-
Monitors	with CVP model	+	-	-
	with invasive arterial blood pressure model	+	-	-
Visual equipment	videolaryngoscopes	+	-	-
	videobronchoscopes	+	-	-
Ultrasound machines		+	+	-
Equipment for nursing care	infusion pumps	+	+	+
	syringe pumps	+	+	+
	vibrating expectoration machines	+	+	+
	closed tracheal suction catheters	+	+	+

FIGURE 4 | Summary of the requirements for special medical equipment in a temporary ICU caring for critically ill COVID-19 patients.

of 6 (4–8) days before intubation or death (14). It can be inferred that invasive mechanical ventilation was delayed, possibly due to a lack of the necessary equipment, specialist staff, or areas in which the procedure could be carried out or to a fear of infection during the operation of trachea intubation.

COVID-19 is an infectious disease characterized as an acute hypoxemic respiratory insufficiency or failure which requires

Different scales of Standard personal protective equipment (PPE) for Usual critical care of confirmed COVID-19 patients in temporary ICU			
	Scaled protection		
Equipment	**Level II (General Oxen therapy)**	**Level III-1 (Suction, pharyngeal swab sampling, NIV or HFNC)**	**Level III-2 (Intubation, tracheotomy, or bronchoscopy)**
Waterproof isolation gowns	±	+	+
Protective clothing	+	+	+
Gloves	**+ (one or double)**	**+ (double)**	**+ (three)**
Shoe covers	+	+	+
Head covers	+	+	+
Face screen	-	+	+
Medical protective masks	±	+	+
N95	+	+	+
Protective glasses (anti-fog)	+	+	+
Air-purifying respirator (PAPR)	-	-	+
Hand hygiene	+	+	+

+, mandatory; -, not needed; ±, decision made according to the work scenario

FIGURE 5 | Standard personal protective equipment (PPE) required for normal critical care with COVID-confirmed patients in a temporary ICU. The required standard of PPE is based on the guidelines for the prevention and control of COVID-19 infection in medical institutions laid out by the government in China. Doctors have different scales of PPE to care for severe confirmed patients in different situations. **(A)** A doctor with level-II PPE at the nurses' station; **(B)** A doctor with level III-1 PPE for ultrasonography in a temporary ICU; **(C)** Two doctors with level III-2 PPE preparing for percutaneous tracheostomy in a temporary ICU.

the use of oxygen and ventilation therapies. Most infected patients suffer mild symptoms and are self-healing; however, in severe cases, progression is rapid and can lead to ARDS, septic shock, metabolic acidosis, and coagulopathy (15), especially when combined with old age, comorbidities, or persistent lymphocytopenia, which is difficult to correct. As standardizing the management of care is a vital element in improving survival rates, the National Health Commission of the People's Republic of China (http://www.nhc.gov.cn/yzygj/s7653p/202002/d4b895337e19445f8d728fcaf1e3e13a.shtml) and the WHO (https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf) have established a

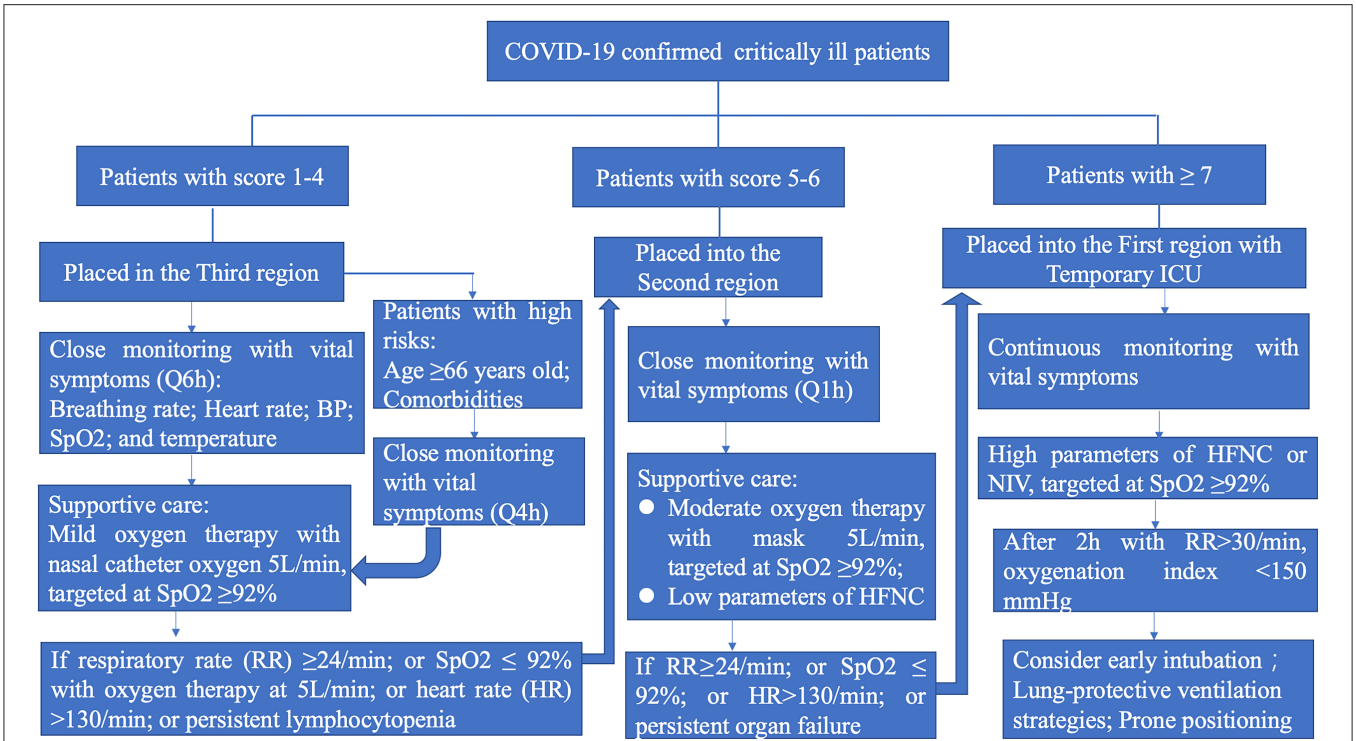

FIGURE 6 | The management algorithm based on the clinical severity of critically ill COVID-19 patients. HFNC, high flow nasal cannula; NIV, non-invasive ventilation.

protocol for the treatment of COVID-19. Timely and effective airway management and maximized first-pass success rate of airway operation for COVID-19 patients are recommended (8, 11).

For patients in the third sector of the temporary ICU (who have mild symptoms), healthcare workers must give supportive care and ensure monitoring at 6-h intervals of the vital symptoms, such as breathing rate, oxygen saturation (SpO2), and heart rate. Oxygen therapy should be initiated at 5 L/min and titrated to SpO2 ≥ 92% in COVID-19 patients. For patients with high risk factors (≥66 years old and comorbidities), nurses must ensure close monitoring of vital symptoms at 4-h intervals. In the following conditions, patients must be swiftly transferred to the second (moderate) sector, in case they need HFNC oxygenation or NIV: breathing rate ≥24/min, SpO2 <92% with oxygen therapy at 5 L/min, or heart rate >130/min, or persistent lymphocytopenia. Throughout treatment, conservative intravenous fluid strategies must be strictly implemented unless septic shock occurs.

In the case of severe patients with persistent respiratory distress, a respiratory rate >30/min, oxygenation index <150 mmHg, or showing no improvement after HFNC or NIV, continuous monitoring is necessary from an experienced ICU team. The vital symptoms must be monitored after HFNC or NIV treatment at intervals of no more than 2 h (16). If there is no improvement after 2 h, or the patient's condition worsens, the team should consider early invasive ventilation (8), followed by lung-protective ventilation strategies and early prone positioning during mechanical ventilation for more than 12 hours per day (**Figure 6**).

CONCLUSIONS

The sudden outbreak of the highly contagious disease now known as COVID-19 in China in December 2019 has impacted healthcare system and societies more widely across the world. Should another virus of this type emerge, it will be vital to first control the source of infection and second prevent transmission. Moreover, the identification, sorting, and management of infected patients in different isolated sectors according to level of severity is crucial in ensuring full use is made of the medical resources available. Public anxiety around COVID-19 centers on the large numbers of critically ill patients and high death rates. In this regard, setting up a temporary ICU in isolated hospitals, run by multidisciplinary staff under the leadership of intensive care specialists and nurses, is crucial not only in caring for critically ill patients and bringing down mortality rates, but also in allaying public fear.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

MP contributed to the literature search, figures, writing of the original draft, and project administration of the manuscript. ZQ and LZ contributed equally to the conceptualization, data and resource curation, supervision, validation, and writing, reviewing, and editing of the research. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Short-Term Outcomes of Patients With COVID-19 Undergoing Invasive Mechanical Ventilation: A Retrospective Observational Study From Wuhan, China

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Background: COVID-19 has spread rapidly worldwide. Many patients require mechanical ventilation. The goal of this study was to investigate the clinical course and outcomes of patients with COVID-19 undergoing mechanical ventilation and identify factors associated with death.

Methods: Eighty-three consecutive critically ill patients with confirmed COVID-19 undergoing invasive mechanical ventilation were included in this retrospective, single-center, observational study from January 31 to March 15, 2020. Demographic, clinical, laboratory, radiological, and mechanical ventilation data were collected and analyzed. The primary outcome was 28-day mortality after endotracheal intubation. The secondary outcomes included the incidences of SARS-CoV-2-related cardiac, liver, and kidney injury.

Results: Seventy-four out of 83 (89.2%) patients achieved oxygen saturation above 93% after intubation. Forty-nine out of 83 (59%) patients died and 34 (41%) patients survived after 28 days of observation. Multivariable regression showed increasing odds of death associated with cardiac injury (odds ratio 15.60, 95% CI 4.20–74.43), liver injury (5.40, 1.46–23.56), and kidney injury (8.39, 1.63–61.41), and decreasing odds of death associated with the higher PaO_2/FiO_2 ratio before intubation (0.97, 0.95–0.99). PaO_2/FiO_2 ratio before intubation demonstrated a positive linear correlation with platelet count ($r = 0.424$, $P = 0.001$), and negative linear correlation with troponin I ($r = -0.395$, $P = 0.008$).

Conclusions: Cardiac, liver, and kidney injury may be associated with death for critically ill patients with COVID-19 undergoing invasive mechanical ventilation. The severity of pre-intubation hypoxia may be associated with a poorer outcome of patients with COVID-19 undergoing invasive mechanical ventilation. Larger, multi-institutional, prospective studies should be conducted to confirm these preliminary results.

Keywords: COVID-19, SARS-CoV-2, invasive mechanical ventilation, critically ill patients, outcomes

INTRODUCTION

An ongoing outbreak of SARS-CoV-2 has spread rapidly worldwide (1–4). The epidemiological findings, clinical presentation, and clinical outcomes of patients with COVID-19 have been reported (2, 5–8). However, the clinical course and outcomes of patients with COVID-19 undergoing invasive mechanical ventilation is still not clear.

Confirmed COVID-19 patients with comorbidities can rapidly develop acute respiratory distress syndrome and require intensive care unit admission as well as invasive/non-invasive mechanical ventilation (6, 7, 9). The overall mortality rate exceeds nearly 60% in critically ill COVID-19 patients from the Jin Yin-tan hospital study (7). No vaccine or specific effect medicines for COVID-19 has yet been shown to be effective, so invasive mechanical ventilation via endotracheal intubation is particularly important for severe cases to slow progression and reduce mortality (6, 7, 10). As many critically ill patients require invasive mechanical ventilation, it is critical to gain a deeper understanding of the association between mechanical ventilation and its subsequent clinical outcomes. In addition, it has previously been observed that multi-organ injury, such as lung, heart, kidney, liver injury is a common condition among hospitalized patients with COVID-19, and it may associate with higher risk of in-hospital mortality (8, 11–13). However, the progression of organ injury and outcomes of critically ill patients undergoing mechanical ventilation remain poorly defined. Identifying or more promptly treating patients undergoing mechanical ventilation is crucial to decrease the mortality rate.

Therefore, in this retrospective study, we aimed to investigate the clinical course and outcomes of patients with COVID-19 undergoing mechanical ventilation and identify factors associated with death.

MATERIALS AND METHODS

Study Design and Participants

For this single-center, retrospective, and observational study, we included 83 consecutive patients with confirmed COVID-19 undergoing invasive mechanical ventilation at the West Campus of Union Hospital from January 31 to February 15, 2020. This hospital is one of the main designated tertiary care centers for severe cases of COVID-19. We retrospectively collected and analyzed the patients with laboratory-confirmed COVID-19 according to World Health Organization (WHO) interim guidance (9). No sample size calculation was performed a priori due to the exploratory nature of this study, and thus we included all possible critically ill COVID-19 patients in our investigation.

This study was approved by the institutional ethics committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (No. 20200097). Written informed consent was waived by the hospital's ethics commission. This manuscript adheres to the applicable CONSORT guidelines.

Data Collection

The clinical electronic medical records, nursing records, laboratory findings, and chest x-rays of all patients were analyzed. Clinical characteristics, laboratory findings, radiological data, as well as treatment and outcomes data were collected with standardized data collection forms (modified from the standardized International Severe Acute Respiratory and Emerging Infection Consortium case report forms) (14). Data were independently verified to ensure accuracy by two investigators. The researchers also directly communicated with involved health-care providers and patient family members to minimize data loss, and ensure the accuracy and reliability of the data. We collected data including age, sex, chronic medical histories (hypertension, cardiovascular disease, chronic pulmonary disease, chronic neurological disorder, chronic kidney disease, diabetes), vital signs (heart rate, blood pressure, SpO_2, PaO_2), laboratory findings, chest CT scans, electrocardiogram (ECG), and information on oxygenation status (PaO_2/FiO_2 ratio [P/F] and SpO_2 before and after intubation). Vital signs and laboratory parameters were collected on admission into hospital (ADM-) and continuously tracked daily from pre-intubation (PRE-) until 7 days after intubation (POST-1 to POST-7). The partial pressure of arterial oxygen (PaO_2) was measured by arterial blood gas analysis. The P/F was calculated using the formula PaO_2/FiO_2 (mmHg).

Procedures of Intubation and Mechanical Ventilation

Endotracheal intubation was performed by experienced anesthesiologists using airborne precautions according to the interim guidance recommended by the World Health Organization (WHO): patients receiving high-flow nasal oxygen should be in a monitored setting and cared for by experienced personnel capable of endotracheal intubation in case the patient acutely deteriorates or does not improve after a short trial (about 1 h) (9). All study patients were intubated orally using a video laryngoscope. Vital signs including the patient's SpO_2, blood pressure, heart rate, and breathing status were closely observed and recorded after intubation. A protective ventilation strategy with small tidal volumes (e.g., 4–6 $ml.kg^{-1}$ ideal body weight), low inspiratory pressures (Pplat < 30 cmH_2O) and optimal PEEP [by ARDSNet (15)] was used to reduce ventilator-induced lung injury. Unfortunately, the exact data on mechanical ventilation were not recorded and the compliance rate with the protective mechanical ventilation were not known.

Outcome Measures

The primary outcome was 28-day mortality after endotracheal intubation with the final date of follow-up being March 15, 2020. Secondary outcomes included the incidences of SARS-CoV-2-related cardiac, liver, and kidney injury. Cardiac injury was defined as the serum levels of troponin I (TnI) above the upper limit of the reference range (>26 $ng.L^{-1}$) or new ST segmental and T-wave changes or pathologic Q-waves found on ECG (16). Liver injury was diagnosed if the serum levels of aspartate transaminase (AST), alanine transaminase (ALT), and AST/ALT were above the upper limit of the reference range (ALT

TABLE 1 | Baseline characteristics, laboratory results, chest CT findings, and clinical outcomes of survivors and non-survivors with COVID-19.

	Total patients (*N* = 83)	Survivors (*N* = 34)	Non-survivors (*N* = 49)	*P*-value
Baseline characteristics				
Age, years				
Mean (SD)	64 (11.0)	61 (10.6)	66 (10.9)	0.039
Median (IQR)	65 (60–71)	62 (55–68.8)	68 (63–71)	
Sex, No. (%)				
Female	25 (30.1)	9 (26.5)	16 (32.7)	0.546
Male	58 (69.9)	25 (73.5)	33 (67.3)	
Chronic medical illness, No. (%)				
Hypertension	42 (50.6)	12 (35.3)	30 (61.2)	0.020
Cardiovascular disease	13 (15.7)	4 (11.8)	9 (18.4)	0.416
Chronic pulmonary disease	7 (8.4)	1 (2.9)	6 (12.2)	0.231
Chronic neurological disorder	3 (3.6)	1 (2.9)	2 (4.1)	>0.999
Chronic liver disease	5 (6.0)	1 (2.9)	4 (8.2)	0.644
Chronic kidney disease	4 (4.8)	2 (5.9)	2 (4.1)	0.706
Diabetes	30 (36.1)	10 (29.4)	20 (40.8)	0.288
Vital signs at pre-intubation, median (IQR)				
Heart rate, bpm	99 (84.3–119.3)	92 (79.3–116.8)	100 (88.3–122.3)	0.564
Systolic pressure, mmHg	132 (120.0–153.5)	128 (116.0–147.5)	137 (123–157)	0.684
Diastolic pressure, mmHg	80 (67.0–91.5)	73 (66.8–92.3)	85 (69.5–90.5)	0.979
MAP, mmHg	93 (86–115)	91 (83–102)	98 (86–113)	0.735
SpO_2	82 (71.5–89.3)	88 (78.0–92.5)	79 (66.5–84.0)	0.001
PaO_2, mmHg	53.1 (45.6–59.5)	59 (52.5–64.3)	49 (42.6–55.4)	<0.001
P/F at pre-intubation	121 (103.6–135.2)	134 (119.4–146.1)	112 (96.8–125.8)	<0.001
P/F at pre-intubation, No. (%)				
P/F >150 mmHg	10 (12.0)	7 (20.6)	3 (6.1)	0.515
100≤ P/F ≤150 mmHg	55 (66.3)	26 (76.5)	29 (59.2)	0.156
P/F <100 mmHg	18 (21.7)	1 (2.9)	17 (34.7)	<0.001
Laboratory results at pre-intubation, median (IQR)				
Leucocytes count, $\times 10^9.L^{-1}$	12.46 (9.15–16.65)	12.38 (8.68–15.36)	12.53 (9.50–17.22)	0.982
Lymphocyte count, $\times 10^9.L^{-1}$	0.54 (0.42–0.71)	0.67 (0.45–0.83)	0.49 (0.35–0.60)	0.107
Neutrophil count, $\times 10^9.L^{-1}$	9.73 (7.82–16.57)	9.60 (7.28–15.04)	9.95 (8.47–17.03)	0.362
Platelet count, $\times 10^9.L^{-1}$	147 (98–197)	134 (90.50–185)	120 (69.75–167)	0.021
ALT, $U.L^{-1}$	42 (26–68)	53 (38–93.50)	30 (20–54)	0.425
AST, $U.L^{-1}$	41 (30–68)	47 (28.50–68.50)	38 (31.25–65.50)	0.926
AST/ALT	0.99 (0.65–1.31)	0.82 (0.60–1.03)	1.14 (0.83–1.450)	0.011
BUN, $mmol.L^{-1}$	8.73 (5.78–11.51)	7.55 (4.92–8.97)	9,35 (6.68–12.50)	0.047
Creatinine, $\mu mol.L^{-1}$	65.9 (54.80–88.50)	62.9 (52.30–76.93)	69.6 (56.60–89.80)	0.338
BNP, $pg.ml^{-1}$	86.34 (48.35–138.08)	63.7 (45.2–89.23)	114.6 (64.28–185.50)	0.051
TnI, $ng.L^{-1}$	34.78 (19.96–77.68)	24.4 (16.25–51.87)	52.65 (23.48–87.93)	0.362
CRP, $mg.L^{-1}$	81.9 (54.6–131.0)	87.2 (46.5–131.0)	81.4 (61.7–130.5)	0.750
Chest CT findings, No. (%)				
Bilateral distribution of patchy shadows or ground glass opacity	83 (100)	34 (100)	49 (100)	
Duration from admission to intubation, median (IQR)	6 (4–11)	8 (4–12)	6 (3–10)	0.088
Complications, No. (%)				
Cardiac injury	37 (44.6)	8 (23.5)	29 (59.2)	0.001
Liver injury	36 (43.4)	8 (23.5)	28 (57.1)	0.002
Kidney injury	25 (30.1)	3 (8.8)	22 (44.9)	<0.001

(Continued)

TABLE 1 | Continued

	Total patients (*N* = 83)	Survivors (*N* = 34)	Non-survivors (*N* = 49)	*P*-value
SOFA score at post-intubation day 3, median (IQR)	5 (4–6)	4 (4–4.8)	6 (5–7)	<0.001
Clinical outcome, No. (%)				
Hospitalization with extubation	11 (13.3)	11 (32.4)	0	
Hospitalization with intubation	23 (27.7)	23 (67.6)	0	
Died	49 (59.0)	0	49 (59.0)	
Survival time, median (IQR)	19 (10–28)	28 (28–28)	11 (8–16)	<0.001

Data are mean (SD), median (IQR) and No. (%). P-values indicate differences between survivors and non-survivors. P < 0.05 was considered statistically significant. IQR, interquartile range; P/F, PaO_2/FiO_2 ratio; MAP, mean arterial pressure; SpO_2, oxygen saturation; PaO_2, partial pressure of oxygen; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; BNP, brain natriuretic peptide; TnI, troponin I; CRP, C reactive protein; SOFA, Sequential Organ Failure Assessment.

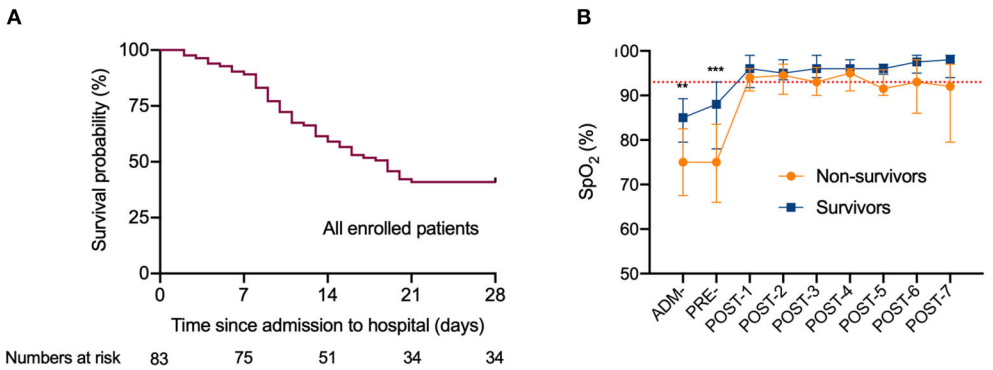

FIGURE 1 | The survival curve of critically ill patients with COVID-19 undergoing invasive mechanical ventilation, and dynamic changes of the oxygen saturation during hospitalization. **(A)** The survival curve of all enrolled patients with COVID-19 undergoing invasive mechanical ventilation. **(B)** Dynamic changes of the oxygen saturation during hospitalization. The dotted lines in red show the SpO_2 at 93%.Data are median (IQR). *Indicate difference between the survivors and non-survivors by *t*-tests or Mann-Whitney *U*-test. Significant differences are expressed as follows: * < 0.05, ** < 0.01, *** < 0.001. SpO_2, oxygen saturation; ADM-, admission to hospital; PRE-, pre-intubation; POST-1 to POST-7, post-intubation day 1 to post-intubation day 7.

> 40 U/L; AST > 40 U/L; AST/ALT > 1) (17). Kidney injury was diagnosed if the serum levels of creatinine and blood urea nitrogen (BUN) were above the upper limit of the reference range (creatinine > 133 $\mu mol.L^{-1}$; BUN > 8.2 $mmol.L^{-1}$) (18). All laboratory findings mentioned above were provided by the laboratory of West Campus of Union Hospital.

The Sequential Organ Failure Assessment (SOFA) was calculated on admission and every 24 h until the final date of follow-up. The worst values for each parameter in the 24-h period were used in scoring tabulation. The daily SOFA score was calculated for each patient on the basis of six organ systems: cardiovascular, respiratory, renal, hepatic, coagulation, and neurologic systems (scores for each system range from 0 to 4, with higher scores indicating more severe organ-system dysfunction; maximum score, 24).

Statistical Analysis

Continuous data were presented as mean (SD) or median (IQR), and categorical data were presented as number (%). Means for continuous data were compared using independent group *t*-tests when the data were normally distributed; otherwise, the Mann-Whitney *U*-test was used. Proportions for categorical variables were compared using the Chi-square (and Fisher's exact) test. Survival analysis was performed using Kaplan-Meier survival curves. Univariable and multivariable logistic regression models were used to explore the risk factors associated with death for patients with COVID-19. Considering the total number of deaths ($n = 49$) in this study and to avoid overfitting in the model, five variables (age, P/F, cardiac injury, liver injury, and kidney injury) were chosen for multivariable analysis on the basis of previous findings and clinical constraints. The correlation coefficient was calculated by Pearson's correlation analysis. A two-sided α of <0.05 was considered statistically significant. All statistical analysis was performed with GraphPad Prism version 8 (Graph-Pad Software Inc., San Diego, CA, U.S.) and SPSS software (version 25 for Mac; IBM, New York, USA).

RESULTS

We observed 83 critically ill patients with confirmed COVID-19 undergoing invasive mechanical ventilation. In the cohort of 83 consecutive patients, the median (IQR) age was 65 (60–71) years, and 58 (69.9%) patients were men (**Table 1**).

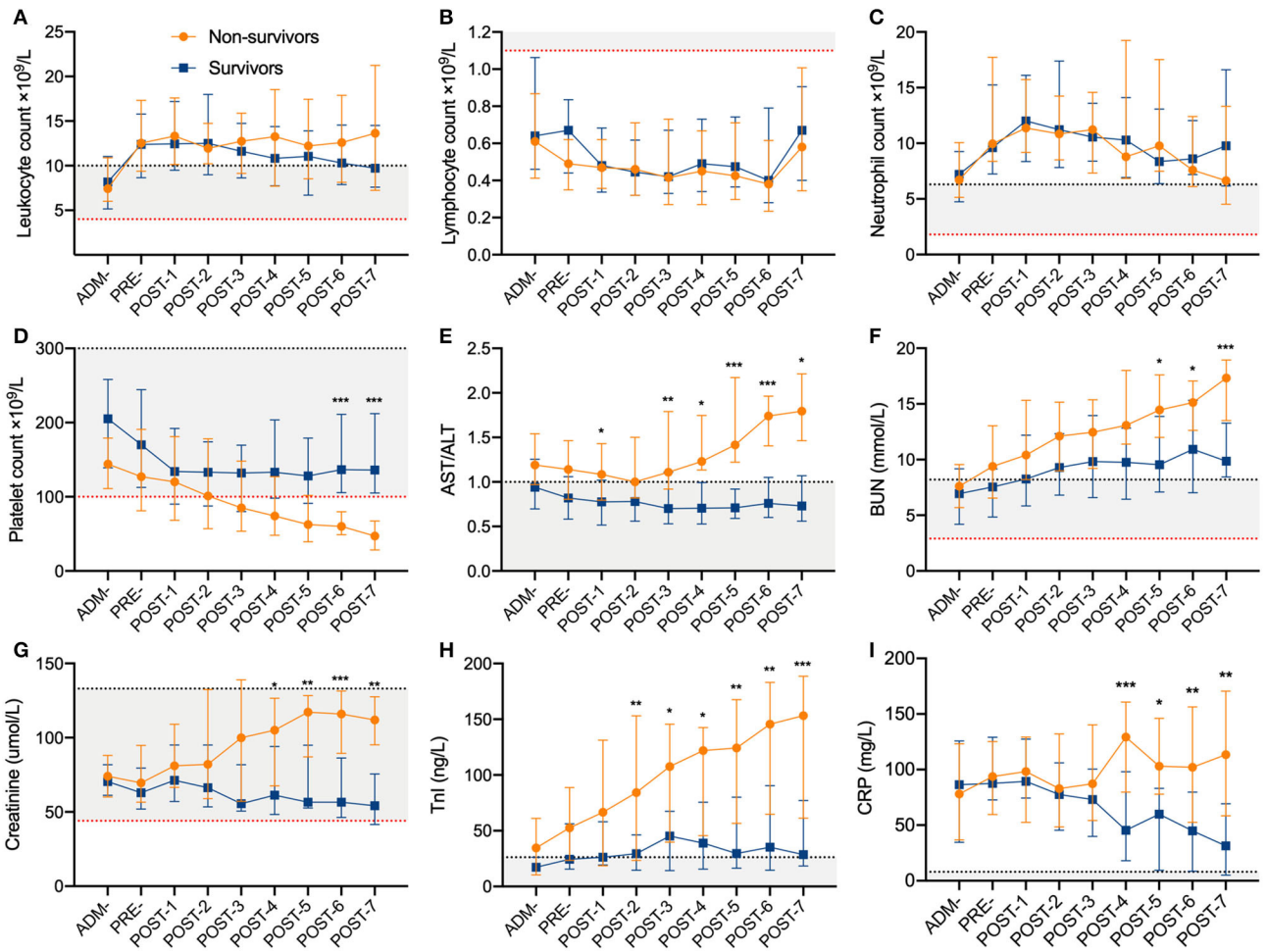

FIGURE 2 | Dynamic changes of laboratory parameters during hospitalization for survivors and non-survivors. **(A)** Leukocyte count, **(B)** Lymphocyte count, **(C)** Neutrophil count, **(D)** Platelet count, **(E)** AST/ALT, **(F)** BUN, **(G)** Creatinine, **(H)** TnI, **(I)** CRP. The dotted lines in red/black show the lower/upper normal limit of each parameter, and the shaded areas represent the normal reference range of each parameter. Data are median (IQR). *Indicate difference between the survivors and non-survivors by *t* tests or Mann-Whitney *U* test. Significant differences are expressed as follows: * < 0.05, ** < 0.01, *** < 0.001. IQR, interquartile range; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; TnI, troponin I; CRP, C reactive protein; ADM-, admission to hospital; PRE-, pre-intubation; POST-1 to POST-7, post-intubation day 1 to post-intubation day 7.

Sixty-four (46.4%) patients had one or more chronic medical illness including: hypertension (42 [50.6%]), cardiovascular disease (13 [15.7%]), chronic pulmonary disease (7 [8.4%]), chronic neurological disorder (3 [3.6%]), chronic liver disease (5 [6.0%]), chronic kidney disease (4 [4.8%]), and diabetes (30 [36.1%]) (**Table 1**). Eighty-three (100%) patients showed bilateral distribution of patchy shadows or ground glass opacity. The median (IQR) duration from admission to intubation for total patients was 6 (4–11). By March 15, 2020, 23 (27.7%) patients remained intubated in the hospital, 11 (13.3%) patients had been successfully extubated, and 49 (59.0%) patients died (**Table 1**). The median survival time of total patients was 19 (IQR 10–28) days (**Figure 1**).

We divided all patients into survivors (n = 34) and non-survivors (n = 49) (**Table 1**). Regarding the primary outcome, 49 (59.0%) of 83 patients died within 28 days of observation even though 74 (89.2%) patients achieved oxygen saturation above 93% after invasive mechanical ventilation was initiated (**Figure 1**). Prior to intubation, the median (IQR) SpO_2 with O_2 supplement were 79 (66.5–84.0) vs. 88 (78.0–92.5), P =0.001 for non-survivors vs. survivors, and the median (IQR) PaO_2/FiO_2 ratio were 112 (96.8–125.8) vs. 134 (119.4–146.1), P <0.001 for non-survivors vs. survivors. Post intubation, SpO_2 were 94 (91–96) vs. 96 (93–99), P = 0.117. The average age of the survivors was younger than the non-survivors (61 vs. 66 years old, P = 0.039). No significant difference was found in the duration from admission to intubation between the survivors and non-survivors (P = 0.088) (**Table 1**). At pre-intubation, the differences in levels of leucocytes, lymphocytes, and neutrophils between survivors and non-survivors were not statistically significant, although these values were abnormal in both groups (**Figure 2**).

TABLE 2 | Risk factors associated with death for patients with COVID-19 undergoing invasive mechanical ventilation.

	Univariable OR (95% CI)	*P*-value	Multivariable OR (95% CI)	*P*-value
Baseline characteristics				
Age, years	1.05 (1.00–1.10)	0.049	1.03 (0.97–1.09)	0.343
Male sex (vs. female)	0.74 (0.27–1.93)	0.547		
P/F pre–intubation, mmHg				
P/F	0.97 (0.95–0.99)	0.002	0.97 (0.95–0.99)	0.006
Laboratory results at post–intubation day 3, median (IQR)				
Platelet count, × 10^9.L^{-1}				
>100	0.47 (0.15–0.38)	0.175		
<100	2.13 (0.72–6.48)	0.175		
AST/ALT				
≥1	5.13 (1.80–15.83)	0.003		
<1	0.19 (0.06–0.56)	0.003		
BUN, mmol.L^{-1}				
≥8.2	2.16 (0.65–7.60)	0.215		
<8.2	0.46 (0.13–1.54)	0.215		
Creatinine, μmol.L^{-1}				
≥133	2.86 (0.73–14.29)	0.154		
<133	0.35 (0.70–1.37)	0.154		
BNP, pg.ml^{-1}				
≥100	4.00 (1.28–13.46)	0.019		
<100	0.25 (0.07–0.78)	0.019		
TnI, ng.L^{-1}				
≥26.2	11.00 (3.05–48.37)	<0.001		
<26.2	0.09 (0.02–0.33)	<0.001		
Complications				
Cardiac injury	8.04 (2.95–24.95)	<0.001	15.60 (4.20–74.43)	0.001
Liver injury	4.33 (1.69–12.04)	0.003	5.40 (1.46–23.56)	0.016
Kidney injury	8.42 (2.56–38.38)	0.002	8.39 (1.63–61.41)	0.019

Data are Odds Ratios (95% CI). P < 0.05 was considered statistically significant. P/F, PaO_2/FiO_2 ratio; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; BNP, brain natriuretic peptide; TnI, troponin I.

Compared with survivors, non-survivors developed higher incidences of SARS-CoV-2-related cardiac (29 [59.2%] vs. 8 [23.5%]; $P = 0.001$), liver (28 [57.1%] vs. 8 [23.5%]; $P = 0.002$), and kidney injury (22 [44.9%] vs. 3 [8.8%]; $P < 0.001$) (**Table 1**). It is worth noting that non-survivors showed lower blood pressure, higher level of CRP (C reactive protein), and progressive thrombocytopenia, cardiac injury, liver injury and kidney injury from about the 3rd day post intubation (**Figure 2**). Non-survivors showed a higher SOFA score (6 [IQR 5–7] vs. 4 [4–4.8]; $P < 0.001$) at post-intubation day 3 (**Table 1**).

In univariable analysis, odds ratios of death (49 non-survivors vs. 34 survivors) was higher in patients with lower P/F before intubation, AST/ALT >1, BNP ≥100 pg/ml and TnI ≥26.2 ng/L. Cardiac, liver, and kidney injury were also associated with death for critically ill patients with COVID-19 undergoing invasive mechanical ventilation (**Table 2**). When including five variables in the multivariable logistic regression model, we found that P/F pre-intubation, cardiac, liver, and kidney injury were associated with death for critically ill patients with COVID-19 undergoing invasive mechanical ventilation (**Table 2**).

In correlation analysis, P/F before intubation in patients with COVID-19 correlated significantly with platelet count ($r = 0.424$, $P = 0.001$) and TnI ($r = -0.395$, $P = 0.008$) (**Figure 3**).

DISCUSSION

In this study, we report on the clinical course and outcomes of 83 critically ill patients with confirmed COVID-19 undergoing invasive mechanical ventilation. Forty-nine out of 83 (59%) patients died and 34 (41%) patients survived after 28 days of observation. Cardiac, liver, and kidney injury may be associated with death for critically ill patients with COVID-19 undergoing invasive mechanical ventilation. The severity of pre-intubation hypoxia may be associated with a poorer outcome of patients with COVID-19 undergoing invasive mechanical ventilation.

In accordance with the findings of other investigators, our critically ill patients with COVID-19 demonstrated leukocytosis, lymphopenia, thrombocytopenia, and high neutrophil levels, as well as developed different degrees of organ injury in a

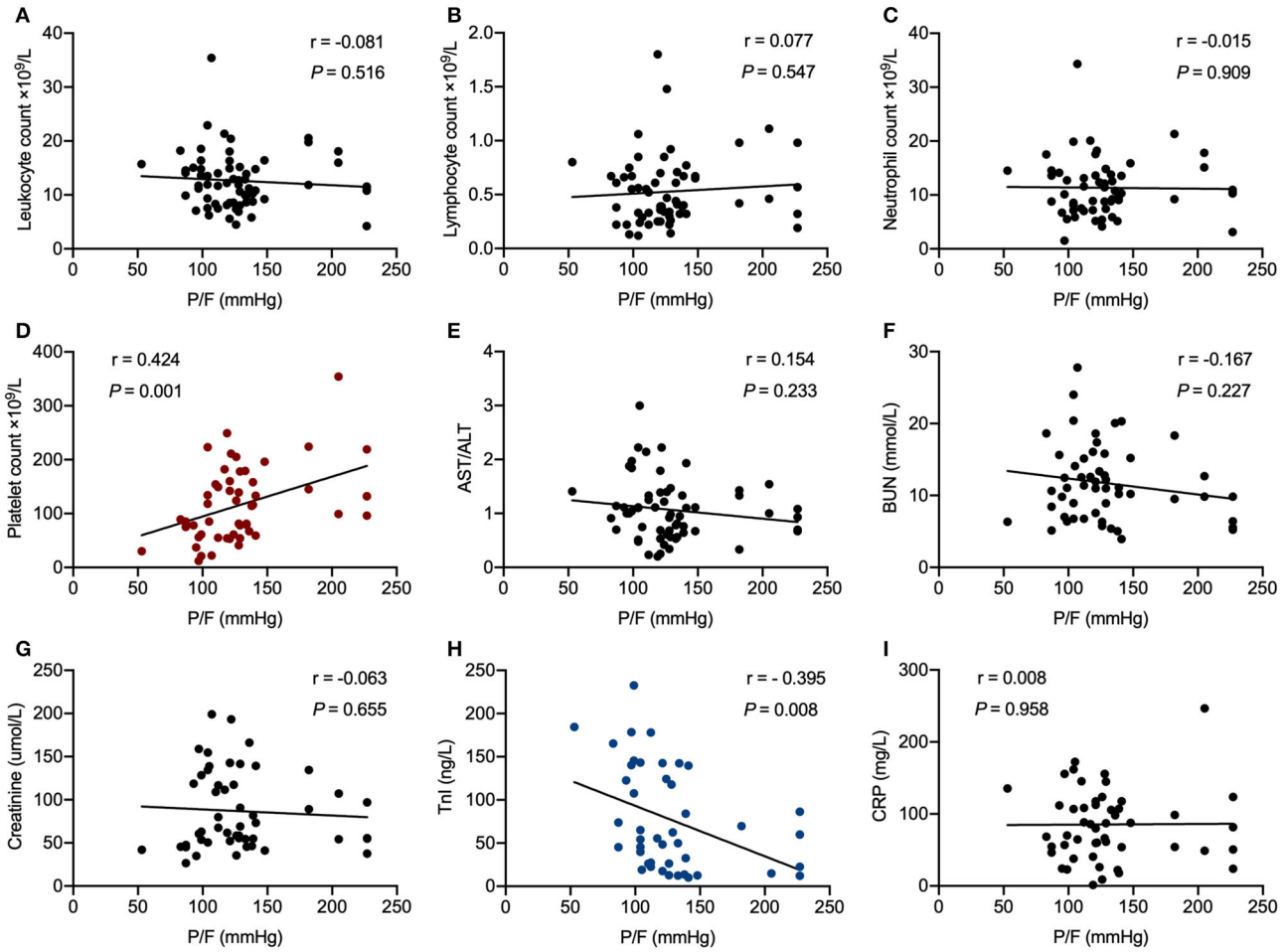

FIGURE 3 | Correlation analysis of PaO_2/FiO_2 ratio before intubation with laboratory parameters in critically ill patients with COVID-19 undergoing invasive mechanical ventilation. **(A)** Leukocyte count, **(B)** Lymphocyte count, **(C)** Neutrophil count, **(D)** Platelet count, **(E)** AST/ALT, **(F)** BUN, **(G)** Creatinine, **(H)** TnI, **(I)** CRP. R represents the Pearson's correlation coefficient. P/F, PaO_2/FiO_2 ratio; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; TnI, troponin I; CRP, C reactive protein.

short period of time (2, 6, 7, 19, 20). Notably, non-survivors showed marked thrombocytopenia, cardiac injury, liver injury, kidney injury, and higher SOFA scores compared with survivors after intubation, even though all patients demonstrated similar SpO_2 levels after the initiation of mechanical ventilation. The incidences of cardiac injury (59.2 vs. 28.0%), liver injury (57.1 vs. 28.0%), and kidney injury (44.9 vs. 37.5%) in this investigation were higher compared to the previous study from Jin Yin-tan Hospital (7). Moreover, cardiac, liver, and kidney injury in non-survivors occurred much earlier: organ failure became prominent around the 3rd day after initiation of invasive mechanical ventilation in non-survivors compared with survivors. SOFA scores at post-intubation day 3 were higher in non-survivors than survivors as well. This may be a manifestation of an accelerated disease progression, with earlier detection and intervention in cardiac, liver, and kidney injury might be used to reduce mortality. Our results of multivariable logistic regression model also preliminarily suggested that cardiac, liver, and kidney injury may be associated with death clinically. In particular, the rapid cardiac function deterioration of these patients may expedite death. Taken as a whole, we speculate that multi-organ injury, especially cardiac, liver, and kidney injury, may be the leading potential causes of death rather than the hypoxemia and severe acute lung injury. Even though our results cannot draw a firm association due to the characteristics of retrospective exploratory study with a relatively small sample size, it could potentially provide a clue for further investigation of the value of these predictors in clinical practice.

Multi-organ function damage, including acute lung injury, acute kidney injury, cardiac injury, and liver dysfunction has been widely reported in COVID-19 (2, 6, 7). Diffuse alveolar damage, pulmonary edema with hyaline membrane formation, and hepatocyte steatosis were reported from pathologic examinations of a patient who died from SARS-CoV-2 (21).

Previous studies have revealed that the SARS-CoV-2 uses the same cell entry receptor, angiotensin-converting enzyme 2 (ACE2), as SARS-CoV, to invade the human host and cause a primary pneumonia (22). ACE2 is widely expressed in the testis, heart, kidney, small intestine, thyroid, and adipose tissue. In the lungs, liver, colon, bladder, and adrenal gland, ACE2 showed moderate expression levels as well (23). It provides potential cues that SARS-CoV-2 may damage other tissues and organs outside the lungs, such as the heart, liver, and kidney. In addition, non-survivors in our study showed lower blood pressure and higher level of C reactive protein (CRP), these changes likely reflected hypoperfusion of organ, increased inflammation and organ injury. However, no direct evidence of the perfusion in lung, heart, and other organs was available.

In our study, the P/F ratio before intubation demonstrated a significantly positive linear correlation with platelet count, and negative linear correlation with TnI. It is notable that patients developed different outcome even though most patients achieved oxygen saturation above 93% after intubation. This may indicate that the correcting hypoxia with mechanical ventilation seems not associated with a better outcome. The early occurrence and continuous increase of TnI and decrease of PLT predict the poor outcome. Multiple organs are sensitive to hypoxic insult under ARDS, including the brain, heart, lung, and kidney (10). Therefore, we speculate that critically ill patients with poor oxygenation are more vulnerable to myocardial damage especially under the cytokine storm induced by SARS-CoV-2 invasion. It is difficult to reverse this progression even when oxygen saturation remains above 93% following initiation of invasive mechanical ventilation. In addition, fulminant myocarditis induced by SARS-CoV-2 has been reported from Jin Yin-tan Hospital and Tongji Hospital (24). Acute cardiac injury may be related to direct and/or indirect effects of the SARS-CoV-2, hypoxia, shock, severe immune injury, and medications. It might be very difficult to distinguish hypoxia triggered cardiac injury vs. innate cardiac injury from the virus. However, given that cardiac injury is characterized by a rapid progression and a severe state of illness, our findings should alert physicians to pay attention not only to the symptoms of respiratory failure but also to the cardiac injury as well.

Although the P/F ratio before intubation was included in the logistic regression analysis, the conclusions that can be drawn from the current results were limited due to the non-controlled intubation timing (P/F ratio pre-intubation), OR (0.97, range 0.95–0.99) value close to 1 and unknown compliance rate with protective mechanical ventilation strategies. Firstly, given the retrospective study design and limited medical resources at the time of study, the timing of invasive mechanical ventilation was not controlled. Secondly, the OR value [0.97 (0.95–0.99)] for the P/F ratio before intubation was very close to 1, which may imply a statistically significant but not clinically meaningful difference. Thirdly, although protective mechanical ventilation strategy was recommended for all patients, the exact data on mechanical ventilation were not recorded and the compliance rate with the protective mechanical ventilation were not known. Thus, the identified association between the P/F ratio before intubation and mortality should be evaluated with cautions. Investigating the association between the management of invasive mechanical ventilation and clinical outcomes in COVID-19 patients is of great importance clinically (25, 26). Different criteria for initiating invasive mechanical ventilation and different management strategies of mechanical ventilation may both affect the overall outcomes of COVID-19 patients. Further study is warranted in a prospective and larger cohort to confirm.

Our study has several limitations. Firstly, no sample size calculation was performed a priori due to the exploratory nature of this study, and thus we included all possible critically ill COVID-19 patients in our institution. Secondly, this was a retrospective exploratory study with relatively small sample size. The associations observed in the retrospective observational study need further confirmation in larger cohorts and prospective studies. Thirdly, mechanical ventilation protocol was adjusted with changes of patients' situations and detailed mechanical ventilation data (tidal volume, PEEP, driving pressure, etc.) were not available.

To the best of our knowledge, this is the largest retrospective cohort study among patients with COVID-19 undergoing invasive mechanical ventilation. We found that cardiac, liver, and kidney injury may be associated with death for critically ill patients with COVID-19 undergoing invasive mechanical ventilation. The severity of pre-intubation hypoxia may be associated with a poorer outcome of patients with COVID-19 undergoing invasive mechanical ventilation. Larger, multicenter, prospective studies should be conducted to confirm these findings.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR'S NOTE

This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

AUTHOR CONTRIBUTIONS

XiC: had full access to all of the data in the study, take responsibility for the integrity of the data and the accuracy of

the data analysis, concept and design, and obtained funding. SZ, YL, CZ, LW, XuC, SC, JH, and XiC: acquisition, analysis, or interpretation of data. SZ and YL: drafting of the manuscript and statistical analysis. SZ, YL, CZ, SC, OA, JH, and XiC: critical revision of the manuscript for important intellectual content. All authors: contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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OPINION
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Medical Simulation: The Least Advertised and Most Versatile Weapon in Pandemic

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Keywords: pandemic, COVID-19, *in situ* simulation, simulation center, adaptability

INTRODUCTION

From America to Europe, world leaders declared war on coronavirus disease (COVID-19), an invisible, poorly understood enemy. Most countries and health-care providers were baffled by the rapid pace of the pandemic. The World Health Organization (WHO) declared the outbreak as a public health emergency of international concern on January 30th. Through simulation scenarios published the next day, it highlighted the need for being prepared and organized to march off into battle. Initial research focused on understanding the virus, testing drugs, and developing strategies. In this fight against the pandemic, a "new" medical weapon has emerged: medical simulation.

Simulation is an agile, concrete, and mobile multi-tool (1), useful for learning in all domains (knowledge, skills, and behavior) (2). It may be used to safely train professionals in real-like conditions (3) at several levels. In times of crisis, simulation is an ideal medium to update and enhance competencies and adapt practices, particularly constantly evolving practices. At a team level, simulation helps to face complex clinical situations like cardiac arrest in an infected patient (4) or prone positioning for managing respiratory distress. The ability of simulation to promote teamwork is also decisive (5). At a department level, a simulation may optimize the patients and working flow within new constraints. At a personal level, simulation equips one with behaviors and skills for safely donning and doffing, as well as technical skills such as intubation with minimal aerosol exposure.

Therefore, simulation in a COVID-19 context is akin to a "Swiss Army knife," as it carries with it extreme utility and applies to several scenarios at hand. This weapon is loaded in simulation centers and its use adapted on sites (*in situ*). On the basis of the experience of two universities located in heavily affected areas (University of Lorraine, Nancy, France, and McGill University, Montréal, Canada), we describe here how this "Swiss Army knife" helped in adapting the answer to COVID-19 with two preferred complementary approaches: *ex situ* and *in situ* simulations, respectively.

ROLES OF SIMULATION IN HEALTH CARE TO FACE THE PANDEMIC

Our simulation centers were leaders in the battle against COVID-19. In March 2020, in Nancy, the Le Centre Universitaire d'Enseignement par la Simulation—l'Hôpital Virtuel de Lorraine opened continuously for 1 month: 350 health professionals, from private and public hospitals, received *ex situ* training by simulation.Simulation sessions were designed to actualize knowledge and retrain and adapt procedures, using COVID-19 personal protective equipment. Thus, simulation centers offered an ideal framework to learn how to adapt aerosol-generating procedures to face COVID-19 and helped in disseminating related learning society recommendations. Despite a

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stressful context, it enabled to train people in a secure and reassuring environment. Older colleagues and retirees mobilized for backup were transmitting their expertise without being exposed to the battlefield and preparing care workers to adapt to a new work reality and to acquire competencies outside their habitual scope of practice (e.g., a surgeon performing the duty of an intensive care nurse). The simulation center acts as an accelerator for new skills acquisition and is an integral part of continuing education programs that maintain and reinforce these skills. As an example, we developed a course to train ear, nose, and throat (ENT) surgeons to perform percutaneous dilatational tracheostomy in intensive care units (6), as recommended by the French ENT Society (Société Française d'Oto-Rhino-Laryngologie). The course gathered ENT surgeons from both public and military hospitals. A brief introduction of the technical aspect of the procedure was followed by training on a low-cost homemade low-fidelity simulator, then various simulation scenarios (common procedure, complicated procedure, and decision making) in a high-fidelity environment. Donning and doffing techniques for COVID-19 were also part of the course. We also tested innovative protective equipment to limit aerosolization during procedures. Thanks to these courses, we were able to propose a checklist to prepare fully before entering the intensive care unit room (6).

At a larger scale, simulation centers were also placed at the front of research and development against COVID-19. This marked a historic turning point for simulation practice and might drive its evolution soon. Particular attention was paid to the protection of caregivers (7), with the development and evaluation of personal protective equipment (8). Studies reported the use of fluorescence to simulate and visualize droplets generated during airway management procedures, providing a direct visualization under ultraviolet light (9). Simulation centers, which ordinarily bring engineers from various backgrounds and health-care professionals together, have played this role even more widely (10). They acted as catalysts for ideas.

The simulation also helped craft new equipment and train teams that faced a critical shortage of supplies. Many solutions were developed, such as modified full-face snorkel masks for non-invasive ventilation (11), adapted ventilators to allow ventilation of multiple simultaneous patients (12), and techniques to help teams move intensive care unit patients to spare human resources, like the use of exoskeletons to help intensive care units with prone positioning (13). Thanks to simulation centers, these innovations could be designed, tested, and adapted in real-like conditions and in a record time (14). During crises, simulation centers may act as the rear base of the fight, becoming training camps for care teams and a place for developing strategies.

However, medical simulation is not restricted to simulation centers. In the short history of the COVID-19 pandemic, the first reported feat of arms of *in situ* simulation (15) tested the preparedness of teams and isolation of operating rooms in Singapore. Bringing simulation to the hospital grounds made possible large-scale training, facilitated by the proximity of real equipment to full teams (16). *In situ* simulation may help to improve plans by discovering their practical shortcomings and allows operational feedback such as lack of medical devices or human resources. At the McGill University Health Center, a number of *in situ* simulations were developed, as illustrated in **Table 1**. These improved team efficiency (17) and patient safety and became models for other hospitals, as many were posted freely on social media platforms and forums (WhatsApp "covid" group). *In situ* simulation also enables the extension and repetition of the training outside of the usually formatted curriculum. With teams and equipment on-site, it becomes possible to carry out simulations and training on a large scale (18). It also helps the organization adapt quickly by enabling teams to continuously update actions and plans against rapidly shifting challenges (19). Examples of simulation scenarios applied *in situ* at McGill are freely available online (20).

DISCUSSION

In situ simulation may encounter major limitations in hospitals: for instance, care units are not optimized for audiovisual assessment, and clinical activity imposes its own constraints (efficiency, the pressure to succeed, workforce issues, etc.) to the detriment of medical simulation. Fortunately, medical simulation is increasingly entering into hospitals in all its aspects: trainees are committed to the field with their trainers at their side. Hence, the influence of medical simulation is changing the culture of the physicians, who are increasingly applying the fundamentals of simulation in hospitals: systematic feedback, briefings, and debriefings. Some institutions took this to heart and integrated simulation centers directly on-site, like the Shriner's Simulation Center in Montréal or a

TABLE 1 | *In situ* simulation scenarios during COVID-19 outbreak.

Team protection
Donning and doffing: surgeons, nurses, respiratory therapist, anesthesiology, emergency room, intensive care unit, residents, medical students, allied health professionals
Cardiopulmonary resuscitation in a coronavirus disease-positive patient
N-95 fit check, N-95 application and removal, and surgical scrubs removal
Minimizing aerosol generation/protecting airway
Rigid bronchoscopy, suspension laryngoscopy, tracheostomy, and sinus surgery
Intubation, extubation, difficult airway, endoscopies, and resuscitation
Transport throughout the hospital: operating room/emergency room/elevators/intensive care unit
Clinic space reorganization
Performing endoscopies in negative pressure rooms
Social distancing measures, scheduling, and patient flow
Clinical care reorganization
Telemedicine scenarios, advance health care directive, and levels of care
Dealing with clinical uncertainty
Prioritization of clinical consultations/operating room case waitlist

branch of the Virtual Hospital of Lorraine in the University Hospital of Nancy. Easy access to simulation centers is critical to facilitate the coming of hospital staff and equipment. In the fight against COVID-19, simulation centers can repurpose simulation equipment for clinical use (21). The simulation center of Nancy directly engaged its training equipment on the combat front by providing the hospital with several supplies, including ventilators, protective equipment, syringe pumps, and video laryngoscopes.

Thus, in addition to its usefulness for learning, medical simulation proved to be effective in diagnosing shortcomings and establishing strategies. What was true during the outbreak certainly applies in all circumstances. The simulation creates more alert workers, trains reflective practitioners, and makes them aware of team working difficulties. Applied in everyday life, a medical simulation may help in reducing risks and increasing the quality and safety of care. Simulation may help in building teams and creating emulation to find solutions to potential problems and thereby instills a culture and a pattern of cognition among health-care workers and simulation trainers. Although trying to define medical simulation's fields of application is already restricting its use: by definition, a Swiss Army knife can be useful for unintended uses. Therefore, the investment in simulation is definitely a good placement for the future.

However, investing in a Swiss Army knife is only useful if it does not stay in your pocket, and the investment must be made in a simulation capable of being deployed in the field. The future of health-care simulation will either be agile or it would not be. This implies thinking upstream about resource allocation and scriptwriting. Future investments should be designed with this idea of mobile deployment in mind. Of course, simulation centers must be able to (1) host planned simulation training courses, but they should also enable to (2) create mobile teams for *in situ* simulation, (3) contribute to the war effort by supplying devices and expert advice in the field, (4) identify the changing needs of care workers and teams, (5) continuously adapt training to the clinical situations encountered, and (6) draw lessons from health-care crisis to upgrade daily practice.

The existence of prior links between simulation centers (or simulation teams) and institutions is a key to the successful use of simulation (in centers or *in situ*) in times of crisis. The simulation needs directly came from the field: simulation trainers were at the bedside, facing practical shortcomings. Trainers summarized team needs, then created and adapted simulation solutions. However, this was possible only because of the preexisting culture of simulation and the well-established partnership between our hospitals and simulation centers.

In the case of COVID-19, perhaps, our most potent weapon is this Swiss Army knife model, vital to our capacity to adapt swiftly. This weapon developed quickly and effectively through seamless partnerships between our university simulation centers and the hospitals with their *in situ* teams transcending the current crisis and enhancing our ability and our nimbleness in fighting this war. National and international simulation networks have contributed to the fight against COVID-19, especially for the dissemination of simulation scenarios and courses to help the simulation community. In Canada, Simulation Canada had quickly proposed dedicated online courses to face the pandemic (22) and shared simulation scenarios to help the simulation community, which was very helpful. The WHO made a great effort by providing COVID-19 tabletop exercise packages (23) to prepare countries for the outbreak. In July 2020, they also published a technical guidance (24) preconizing that "countries should be actively engaging all relevant ministries and stakeholders across multiple sectors (…) so as to broaden health security capacity building, including through simulation exercises during opportune periods."

However, the COVID-19 outbreak has also unmasked disparities in access to simulation and a lack of organization. In France, for instance, the collaboration between simulation centers and most of the main private or university hospitals is well-established, but the vast majority of health-care facilities are still not part of a simulation network. Similarly, in other countries, access to simulation is not systematic even for university hospitals: in an international survey on simulation among ENT surgeons (residents and faculty staff) during the pandemic, more than 20% stated they did not have access to simulation resources in their institution (whatever the type of simulation), mainly in South America and in Europe (25). Furthermore, some countries had to close their simulation centers during the crisis (26), which has restrained access to simulation resources.

The current way of doing (building emergency responses based on requests in the field) has allowed a great adaptation to the needs but also turned out to be highly improvised and disparate. A well-thought plan is half the battle, and the COVID-19 outbreak clearly exposes the need for a much more organized, planned response. To illustrate the importance of an established plan, high-speed trains were used in France to transport critically ill COVID-19 patients from Nancy to other regions where hospitals had more capacity. This exceptional deployment was not conceived in an emergency but simulated a few years ago as a potential response to terrorist attacks. By simulating future crises, unlikely or never encountered situations, lessons can be learned for tomorrow, and plans can be developed. Coordination and allocation of resources on a large scale in times of crisis are also a major challenge, which could benefit from a dedicated steering committee that goes beyond local networks. Such committees could benefit policymakers, head of simulation centers, and care workers (nurses and physicians at least) as suggested by the WHO (24). A collective thinking process will indubitably improve our flexibility to face future problems and help answer the questions raised by this vision, i.e., to choose (i) leadership, (ii) steering indicators, (iii) means to collect needs and relevant information, and (iv) means to monitor and evaluate outcomes.

Other health crises will likely occur in the coming years. Caregiver training is paramount, and simulation is an attractive option to achieve this. Access to health-care simulation must be optimized, and a collective reflection must be carried out to this end: simulation definitely has its place in the centers, but pre-established partnerships and an army of trainers are the keys

to rapid *in situ* deployment. Simulation is a "Swiss Army knife" that must be in everyone's pocket.

AUTHOR CONTRIBUTIONS

VF, PG, SD, and MB: design. VF and PG: first draft of the manuscript. SD: supervision. SD and MB: critical revision. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CASE REPORT
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Delirium During Recovery in Patients With Severe COVID-19: Two Case Reports

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Novel coronavirus disease (COVID-19), caused by SARS-CoV-2, has rapidly evolved into a worldwide pandemic, leaving patients with life-threatening respiratory, cardiovascular, and cerebral complications. Here we reported on two patients with severe COVID-19 who experienced delirium in the early stage of recovery and mental illness including fatigue, anxiety, and post-traumatic stress disorder in the post-illness stage of COVID-19. Two patients were admitted to hospital due to clinical symptoms and features of CT and were confirmed for COVID-19 by positive results of a throat swab for SARS-CoV-2. Due to severe respiratory symptoms and a low oxygenation index, they were transferred to the ICU and received invasive mechanical ventilation and sedation. Hyperactive delirium was observed after being transferred out of the ICU. Different treatment measures were taken in time. Delirium did not occur again in hospital, but they showed mental suffering, including fatigue, anxiety, and post-traumatic stress disorder (PTSD), during the 5 month follow-up after discharge.

Keywords: COVID-19, delirium, neuropsychiatric adverse events, severe patients, case report

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HIGHLIGHTS

- These two cases shared a cluster of specific characteristics and risk factors, including the patients being >60 years old, having severe COVID-19, receiving invasive mechanical ventilation and related sedation, high-dose and long-term corticosteroids treatment, and delirium occurring transiently during their recovery period with negative SARS-CoV-2 results and improved laboratory results. These detailed manifestations with dynamic changes in disease and related treatments might provide some clues to clarify the mechanism of psychiatric complications of COVID-19 and further inform targeted interventions.
- Although there was transient delirium during the early phase of recovery, moderate levels of fatigue, anxiety, and PTSD persisted for 5 months after discharge. Long-term follow-up of chronic neuropsychiatric sequelae of SARS-Cov-2 infection is as important as follow-ups on acute neuropsychiatric complications.

INTRODUCTION

Delirium, a disorder characterized by confusion, inattentiveness, disorientation, illusions, agitation, and in some instances autonomic nervous system overactivity, is common in the ICU and exceedingly challenging during the COVID-19 pandemic. However, neuropsychiatric events of COVID-19, including hyperactive and hypoactive delirium, have so far been underreported. Here

we reported on two patients with severe COVID-19 who, in the absence of direct brain infection, experienced hyperactive delirium and agitation during the recovery period after being transferred out of the ICU.

CASE 1

A 65-year-old female with fever, cough, and shortness of breath on exertion for six days was admitted to hospital. She had normal consciousness and cognition during admission and denied any underlying disease. Abnormal laboratory workup included decreased lymphocytes, elevated inflammatory markers CRP, PCT, and ferroprotein, elevated LDH, and increased markers of liver injury AST and ALT (**Figure 1**). Arterial blood gas analysis showed a low oxygenation index of 229.7, which suggested acute lung injury (ALI). Chest CT presented with typical ground-glass lesions and diagnosis of COVID-19 was confirmed subsequently by positive results of a throat swab for SARS-CoV-2.

With the diagnosis of severe COVID-19 and hepatic insufficiency, she was transferred to an isolation ward and received support treatments. Unfortunately, her condition continued to deteriorate with severe respiratory symptoms, declining lymphocytes, elevating CRP, PCT, and LDH, emerging hypoalbuminemia, and coagulation dysfunction (**Figure 1**). Thirteen days after admission, her condition became critical, with the progress of lung lesions in CT, and her oxygenation index declined to 119, which indicated ARDS. She was transferred to the ICU and was given invasive mechanical ventilation immediately. Other treatments, including antivirals, anti-inflammatories, nutritional support, mechanical ventilation-related sedation, and high dose corticosteroids, were given. After 10 days in the ICU, extubation was performed after pulmonary function improved. Two days later, she was transferred back to the isolation ward with improved dyspnea.

At day 2, after leaving the ICU, the patient suddenly developed CNS symptoms, including confusion, disorientation and agitation, without symptoms of Peripheral Nervous System (PNS) and skeletal muscle injury, that met the delirium diagnostic criteria of Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) (1), including an acute onset of mental status changes (Feature 1), attention disorder (Feature 2), and disorganized thinking (Feature 3). Meanwhile, her condition worsened again with respiratory failure at the lowest level of oxygenation index of 106. However, except for IL-6, other laboratory tests indicated improved results and the RT-PCR of the throat swab for SARS-CoV-2 came back negative. Surazepam (2 mg, daily) was given for 3 days with other treatments including oxygen therapy, anti-inflammatories, and anti-infection. Three days later, on day 5 after leaving the ICU, her mental state gradually returned to normal. She was discharged to a rehabilitation facility at Day 29 after leaving the ICU and delirium did not appear again. At a 3 month follow-up after discharge, she expressed experiencing serious fatigue, anxiety, and post-traumatic stress disorder (PTSD). At a 5 month follow-up, her fatigue, anxiety, and PTSD persisted but had improved to a moderate level.

CASE 2

Due to cough, chest tightness, and shortness of breath for 3 days, a 60-year-old male without consciousness or cognitive impairment was admitted to the hospital. His medical history included well-controlled coronary heart disease, poorly-controlled type 2 diabetes with a high glycosylated hemoglobin, and a surgery for cholecystectomy. The blood samples (**Figure 1**) revealed decreased lymphocytes, elevated inflammatory markers CRP and PCT, elevated LDH, and a high blood sugar level. In addition, hypoalbuminemia and coagulation dysfunction were confirmed according to laboratory tests. Arterial blood gas analysis showed an ALI with a low oxygenation index of 201.1. A chest CT presented with typical ground-glass changes and COVID-19 was confirmed with a positive result of a throat swab for SARS-CoV-2.

The treatment regimen was supplemental oxygen therapy, antiviral treatment, nutritional support, and correcting the coagulopathy. Ten days later, his respiratory symptoms deteriorated significantly with an oxygenation index of 131.7. He was transferred to the ICU and received invasive mechanical ventilation. In addition to strengthening the above treatments, sedatives, corticosteroids, and endotracheal suctioning under fiberoptic bronchoscope was applied with much sputum. At day 18 in the ICU, his lung function improved and extubation was performed. Two days later, he was transferred back to an isolation ward.

At day 3, after being released from the ICU, the patient experienced hyperactive delirium characterized by confusion, disorientation, and agitation with self-extubation of an indwelling gastric tube, without PNS and skeletal muscle injury manifestation. His delirium was measured by the diagnostic criteria of CAM-ICU with an acute onset of mental status changes (Feature 1), inattention (Feature 2), and disorganized thinking (Feature 3). Meanwhile, SARS-CoV-2 turned out to be negative. Physiotherapy was applied, unnecessary psychoactive medication was stopped, and verbal communication (consoling and reminding him of his location and the time) and family presence (his family contacted him via phone or video conversation regularly) was encouraged. Four days later, the delirium completely disappeared. He was discharged at day 30 after leaving the ICU and the delirium did not appeared again. At 3 and 5 month follow-ups after discharge, he still had moderate levels of fatigue and anxiety.

DISCUSSION

To our knowledge, this is the first detailed report of delirium in two severe COVID-19 patients during the recovery period with negative SARS-CoV-2 results and improved laboratory findings. These two cases shared a cluster of specific characteristics and risk factors, including the patients being >60 years old, having severe COVID-19, receiving invasive mechanical ventilation and related sedation, and high-dose and long-term corticosteroids treatment. Their delirium occurred transiently and did not happen again, however, according to recent follow-ups, moderate levels

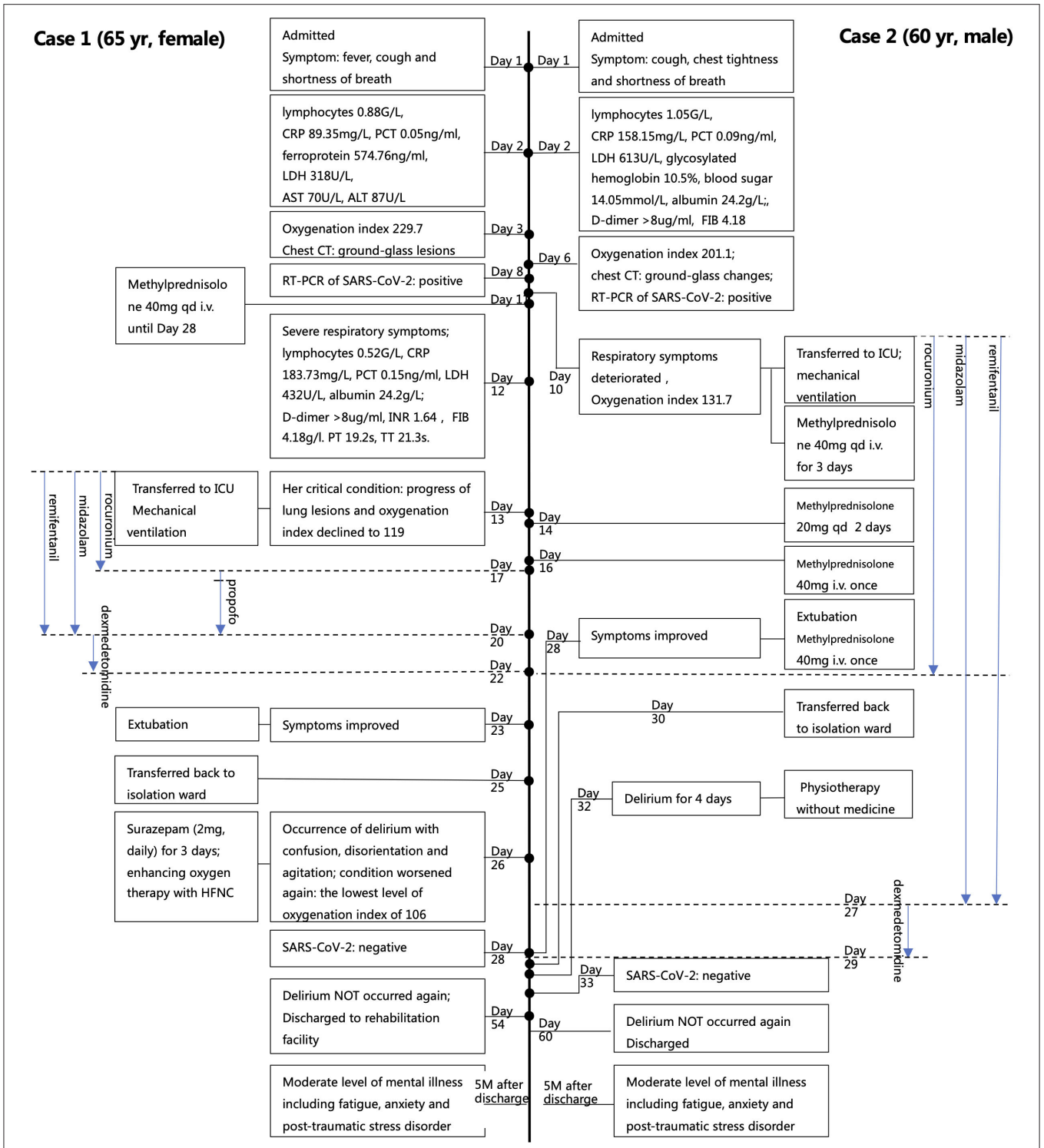

FIGURE 1 | Time-line of main events of two patients. Numbers in the middle line represents the days in hospital. Lymphocytes 1.1–3.2 G/L, CRP 0–8 mg/L, PCT <0.05 ng/ml, Ferroprotein 21.81–274.66 ng/ml, LDH 109–245 U/L, AST 8–40U/L, ALT 5–40 U/L, Albumin 33–55 g/L, Glycosylated hemoglobin 4–6%, Blood sugar 3.9–6.1 mmol/L, D-dimer 0–0.5 ug/ml, PT 11.0–16.0 s, APTT 27.0–45.0 s, INR 0.83–1.36, FIB 2.00–4.00 g/l, TT 14.0–20.0s, Oxygenation index 400–500 mmHg. HFNC, High-flow nasal cannula oxygen therapy.

of fatigue, anxiety, and PTSD have persisted for 5 months after discharge.

Delirium is very common in critical illness, especially in the ICU, with a high prevalence of up to 85% (2). However, the incidence of delirium in COVID-19 is unknown. Mao et al. (3) reported that "impaired consciousness" occurred in only 14.8% of patients with severe COVID-19. A recent study of 58 patients with COVID-19 reported agitation in 40 (69%) patients after the withdrawal of sedation and neuromuscular blockades in the ICU (4). Similarly, agitation, confusion, and hallucinations occurred in 61% of patients in the acute stage of SARS (5). Underreporting of delirium may be common because it is hard to screen delirium and other mental illness under a heavy workload and epidemiologic precautions during this pandemic (6). In the post-illness stage of SARS and MERS, persistent psychiatric impairment, including depression, anxiety, post-traumatic stress disorder, and fatigue, are rather common, but there is little data yet on COVID-19 (7). More attention should be paid to the long-term psychological prognosis related to COVID-19 recovery.

Potential mechanisms of delirium in COVID-19 might be heterogeneous and multifactorial, including direct effects of the virus infiltration, hypoxia, sepsis, and/or the subsequent host immunologic response, medical interventions, and so on. Direct CNS invasion by the virus appears to occur rarely and might be not the related factor in these two cases because of the absence of manifestations of brain infection. Our guess may be further supported by the negative SARS-CoV-2 results and improved laboratory results during delirium. Although the patients experienced severe hypoxia and high inflammatory reactions complicated with coagulation dysfunctions, hepatic insufficiency, and heart failure, delirium occurred after extubation and leaving the ICU. Correspondingly, we speculated that the possible mechanism of delirium in these two cases might not be the direct effect of viral infection, but might be a post-infection immunologic response and immunomodulatory treatment (corticosteroid therapy). In addition, persistant invasive mechanic ventilation and related sedation might also take part in and/ or aggravate the neuropsychiatric complications. It is reported that steroid-induced psychotic disorder occured in 13 (0.7%) of 1,744 patients with SARS in the acute stage (8). In addition, the environment factors caused by being isolated from family and limited support from healthcare workers contributed to the occurrence of delirium. Thus, from the two cases, more exploration on psychoneuroimmunology mechanisms, including the characterization of immune host responses, exploration of genetic associations, and comparison with different medical interventions, especially immunomodulatory treatments, might be useful.

Although data about the acute effects of the illness on neuropsychiatric complications are limited, the evidence from SARS and MERS suggested the high mortality might be linked with poor prognosis of psychosis (9, 10). So far, no medical intervention can be routinely recommended to apply for prevention and management (11, 12). Non-pharmacological interventions, such as comfort and regular orientation from family, friends, and healthcare workers, have proven to be safe and effective methods for treating delirium (13, 14).

There are several limitations in our case reports. First, during the period of the COVID-19 outbreak, in order to avoid cross-infection and reduce the burden on front-line health workers, advanced neuroimaging techniques such as CT and MRI and diagnostic procedures were purposefully avoided, which is necessary to elucidate the causality and etiopathogenic mechanisms. Second, we here reported about delirium in only two patients and obtained information on a recent follow-up period of 5 months after discharge, which is not enough to evaluate the neuropsychiatric impact of COVID-19. Population-based multi-center research about delirium and longitudinal monitoring of neuropsychiatric complications of COVID-19 is still needed.

In summary, we reported on two severe COVID-19 patients who experienced delirium in hospital and persistent psychiatric impairment after discharge. Those detailed manifestations during the dynamic changes of disease and related treatments might provide some clues to clarify the psychoneuroimmunological mechanism of psychiatric complications of COVID-19 and further contribute toward targeted interventions. Long-term follow-ups of chronic neuropsychiatric sequelae of SARS-Cov-2 infection is as important as follow-ups of acute neuropsychiatric complication.

ETHICS STATEMENT

Ethical approval not required according to local legislation and national guidelines. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

DH: acquired, analyzed patient data and drafted the manuscript. CW: acquired, analyzed the data and revised the manuscript. XF: revised the manuscript. JW: design and conceptualized the report, interpreted clinical data, and revised manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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OPINION
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The Diagnostic Significance of Usual Biochemical Parameters in Coronavirus Disease 19 (COVID-19): Albumin to Globulin Ratio and CRP to Albumin Ratio

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The clinical course of patients with COVID-19, and the progression to severe disease, are difficult to predict. There is a growing interest in identifying individuals who could be at greater risk for developing severe or critical COVID-19, acute respiratory distress syndrome (ARDS) in adults, Kawasaki-like disease in young individuals and children, and even death. Several laboratory parameters have been analyzed in conjunction with COVID-19. Specifically, significant elevation of C-reactive proteins, erythrocyte sedimentation rate, interleukin-6, and lactate dehydrogenase has been observed. On the other hand, the total white blood cell count and the eosinophilic and lymphocytic count have been decreased in COVID-19 patients. In a recent meta-analysis, increased CRP, lymphopenia, and increased LDH were significantly associated with the severity of the disease (1). The levels of certain laboratory values that proved to be elevated in cytokine storm (ferritin, procalcitonin, and troponin) may not be available at most hospital laboratories or are mainly used for research purposes (IL-6) (2, 3). On the other hand, CRP, albumin, and globulin are readily available, shortly after admittance, and are often part of an admission workup, in general hospitals and particularly in intensive care units (ICU).

Albumin and globulin are two important components of serum proteins and have been proven to be involved in systemic inflammation. A low serum albumin reflects a poor nutritional status, liver and kidney dysfunction, and has been shown to be an independent predictor of poor survival in critically ill patients. Furthermore, similar results were found regarding MERS (4). Decreased albumin at admission has been an independent risk factor associated with unimprovement during follow-up in COVID-19 patients (5). On the other hand, an increased globulin level may reflect a chronic inflammatory response. Thus, the additive effect of both albumin and globulin would not only be a prognostic factor for potential COVID-19 complications during the course of the illness, but also an initial risk index of SARS-CoV-2 positive individuals. Wu et al. showed recently that the level of albumin is significantly lower [30.40 g/L (27.15–33.35) vs. 33.70 g/L (30.95–36.30), $p < 0.001$] and the globulin level higher [31.60 g/L (29.35–35.05) vs. 30.00 g/L (28.25–32.55), $p = 0.004$] in COVID-19 patients with ARDS comparative with those without ARDS (6).

The albumin to globulin ratio (AGR) is calculated according to the following formula: AGR = albumin/globulin. In young children, who to date are not at a high risk for developing critical COVID-19, the AGR is higher than in adults due to constitutionally lower globulin. Contrary to this, in hypertension, diabetes, cardiovascular disease, and cancer, which frequently are comorbidities in critical COVID-19, the AGR is lower than normal mainly due to

hypoalbuminemia. In different solid tumor patients, a high AGR has a significant positive prognostic effect on survival (7). In patients hospitalized with H_1N_1 infection, AGR reversal (ratio < 1) was associated with prolonged hospital stay, ICU admission, and ventilator use (8).

Two months after the spread of SARS-CoV-2 in Italy, Verdoni et al. found a 30-fold increased incidence of Kawasaki-like disease in children (9), a rare acute hyper-inflammatory syndrome emerging during the COVID-19 pandemic (10) with coronary artery aneurysms as its main complication. The potential for missed or late diagnosis and consequently delayed treatment of Kawasaki disease in children leading to an increased risk of coronary artery aneurysms, is of particular concern during this pandemic (11). Just before the pandemic, Mammadov et al. using a multivariate analysis found that a lower AGR served as an independent predictor of coronary artery aneurysms in children with Kawasaki disease and had a sensitivity of 56.25% and a specificity of 61.11% at a cutoff value of <1.48 (12).

Older age, chronic lung disease, cardiovascular disease, diabetes mellitus, obesity, immunocompromise, end-stage renal disease, and liver disease have been established as potential risk factors for severe COVID-19 (13). The AGR can be decreased in those conditions. In chronic kidney disease patients, it has been shown that AGR was associated with patient mortality of all causes as well as of cardiovascular diseases (14). Acute liver injury due to COVID-19 is associated with increased death risk, as it has been shown by Fu (15). The total protein, albumin, and albumin/globulin ratio were decreased in critically ill patients with acute liver injury compared with those with a less severe illness. In addition, the albumin levels were lower in patients with concurrent diabetes. In that analysis, it has been also shown that the fatality rate was higher in older patients and in ones with hypoproteinemia. A decreased albumin/globulin ratio has been also identified by Tian et al. as one of the risk factors related with the severity of COVID-19 in patients with cancer (16).

Taking all the above into consideration we believe that to calculate the AGR during a prolonged fever, at admission and also throughout the course of the illness, would be useful as a prognostic index for severe COVID-19 including ARDS and in young individuals and children with Kawasaki-like disease.

C-reactive protein (CRP) induction is part of the acute phase response, in which the synthesis of many plasma proteins is increased, whereas a smaller number, particularly albumin, is decreased (17). It has been reported that the patients who needed invasive ventilation had increased inflammatory markers, including CRP (18). Hypoalbuminemia (5) and elevated CRP (19) has been shown to be associated with severe illness and death in patients with COVID-19. The CRP to albumin ratio has been shown to be more accurate than CRP alone for predicting the 28-day mortality in critically ill patients (20). In addition, a higher CRP to albumin ratio at admission has been determined as a risk factor for in-hospital mortality in elderly patients with acute kidney injury requiring dialysis (21). Similarly, an initial elevated CRP to albumin ratio was significantly related to 28-day mortality associated with infections caused by *Elizabethkingia* spp., a dangerous opportunistic bacterial pathogen causing different illnesses including pneumonia (22). The authors concluded that the prediction of clinical courses using an initial CRP to albumin ratio is a priority to reduce the mortality in these patients. We have calculated the CRP to albumin ratio from the published data of an earlier publication by Liu et al. regarding SARS-CoV-2 infected patients (23). The median (range) of the ratio was 9.6 (1.0–2.5). One patient, who was diagnosed with shock and respiratory failure, had the highest value. It is also interesting to note that the patients with the lowest values were younger and without comorbidities. However, the study was limited to 12 patients.

Xie et al. found that CRP levels had a sensitivity of 65.52% and a specificity of 62.7% for predicting IVIG-resistance at a cutoff point of >100 mg/L in children with Kawasaki disease. In addition, albumin <32 g/L, had a sensitivity and specificity for predicting IVIG-resistance 72 and 83.19%, respectively (24).

The three laboratory values, albumin, globulin, and CRP have been separately reported to be associated with normal aging. Healthy older people have been shown to have low serum levels of CRP and pro-inflammatory cytokines such as IL-6 compared with older people with comorbidities. However, those values are higher in aging people than in the younger population (25). Additionally, the increased levels of those parameters are associated with the raised risk of morbidity and mortality in the older subjects (26).

The albumin serum concentration has been shown to decrease with age (27–30). It has been also demonstrated that the globulin levels are higher in older people compared with younger people (31). Both nutritional and chronic inflammatory status, as it results from different comorbidities and aging, clearly influence the prognostic of COVID-19. In addition, inflammation due to COVID infection is added to this status.

There is an increased urgent need to detect new biomarkers in order to identify cases of COVID-19 that will evolve unfavorably in adults and children. These biomarkers must be easy to measure and accessible to most hospitals that manage COVID-19 cases. The proposed ratios (albumin to globulin and CRP to albumin) seem to be more accurate than each value separately and could be included in the initial assessment of patients that have tested PCR positive for SARS-CoV-2, in order to identify those who are at risk of developing ARDS or Kawasaki disease in young individuals and children. In addition, they can be measured during hospital or ICU admissions to evaluate the course of the illness.

AUTHOR CONTRIBUTIONS

GF and VV contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
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Extracorporeal Carbon Dioxide Removal Using a Renal Replacement Therapy Platform to Enhance Lung-Protective Ventilation in Hypercapnic Patients With Coronavirus Disease 2019-Associated Acute Respiratory Distress Syndrome

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Coronavirus disease 2019 (COVID-19)-associated acute respiratory distress syndrome (ARDS) is associated with high mortality. Lung-protective ventilation is the current standard of care in patients with ARDS, but it might lead to hypercapnia, which is independently associated with worse outcomes. Extracorporeal carbon dioxide removal ($ECCO_2R$) has been proposed as an adjuvant therapy to avoid progression of clinical severity and limit further ventilator-induced lung injury, but its use in COVID-19 has not been described yet. Acute kidney injury requiring renal replacement therapy (RRT) is common among critically ill COVID-19 patients. In centers with available dialysis, low-flow $ECCO_2R$ (<500 mL/min) using RRT platforms could be carried out by dialysis specialists and might be an option to efficiently allocate resources during the COVID-19 pandemic for patients with hypercapnia as the main indication. Here, we report the feasibility, safety, and efficacy of $ECCO_2R$ using an RRT platform to provide either standalone $ECCO_2R$ or $ECCO_2R$ combined with RRT in four hypercapnic patients with moderate ARDS. A randomized clinical trial is required to assess the overall benefit and harm.

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Keywords: continuous renal replacement therapy, respiratory acidosis, SARS-CoV-2, extracorporeal organ support, respiratory dialysis

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INTRODUCTION

The percentages of coronavirus disease 2019 (COVID-19) patients diagnosed with acute respiratory distress syndrome (ARDS) range between 20 and 67% of hospitalized patients (1, 2) and 100% of mechanically ventilated patients (3) and are associated with high mortality (2). Lung-protective ventilation is the current standard of care for ARDS (4), which limits ventilator-induced lung injury but may lead to elevated carbon dioxide (CO_2) levels and respiratory acidosis, which are independently associated with worse outcomes in the setting of ARDS (5, 6). In these patients, extracorporeal CO_2 removal ($ECCO_2R$) may help to avoid the progression of clinical severity (5). Acute kidney injury (AKI) is common among critically ill COVID-19 patients, with ∼20% requiring renal replacement therapy (RRT) (7). Recent studies have proposed the integration of $ECCO_2R$ into continuous RRT (CRRT) platforms to provide combined CO_2 removal and renal support using low blood-flow

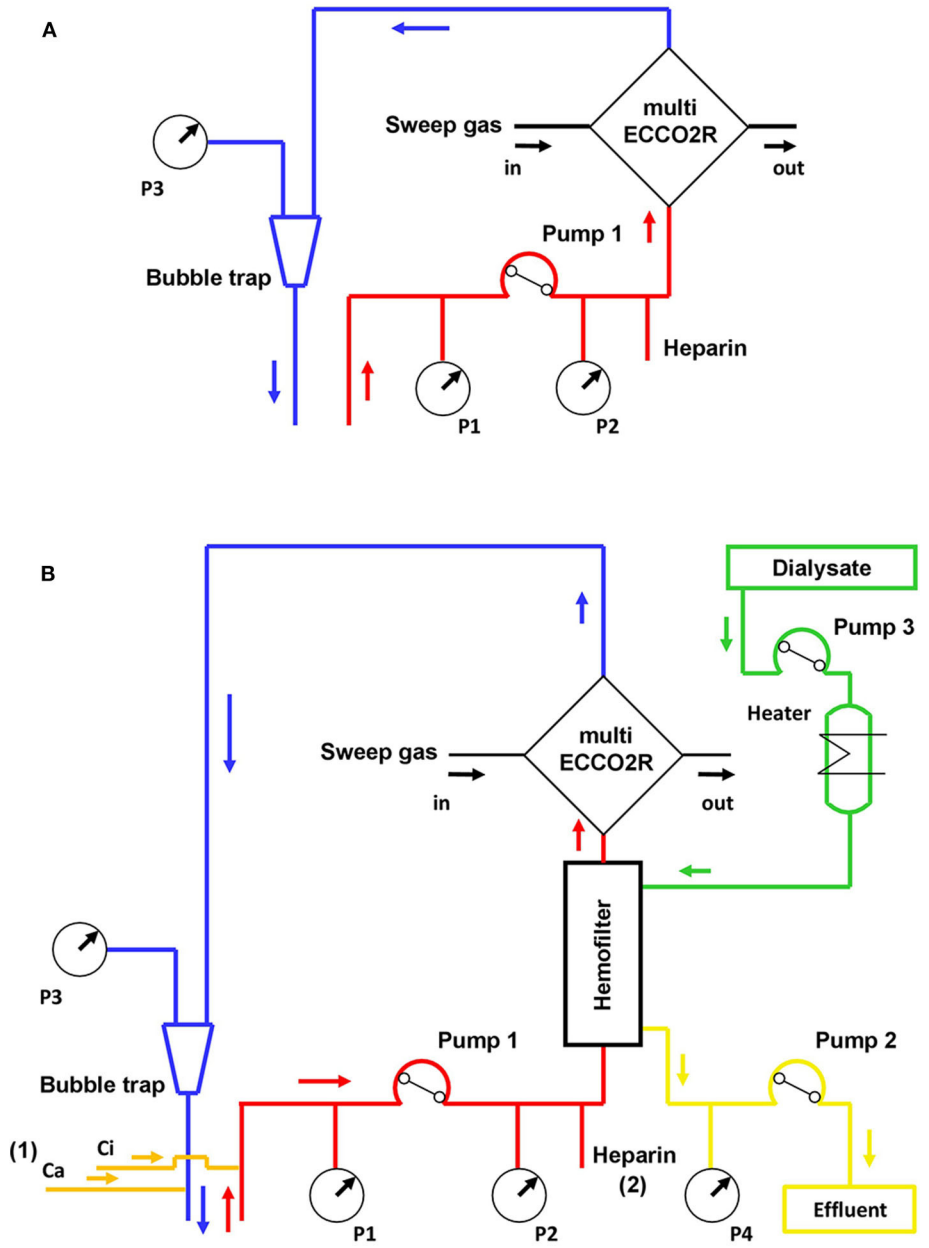

FIGURE 1 | Schematic representation of the $ECCO_2R$ circuit either as standalone therapy **(A)** or in-line after the hemofilter for combined $ECCO_2R$ and RRT **(B)**. $ECCO_2R$ in conjunction with RRT may be performed with regional citrate anticoagulation (1) or systemic heparinization (2). Ca, calcium chloride solution; Ci, trisodium citrate solution; Pump 1, blood line; Pump 2, effluent dialysate line; Pump 3, dialysate line; P1, in-flow pressure sensor; P2, pre-filter pressure sensor; P3, out-flow pressure sensor; P4, effluent dialysate pressure sensor; RRT, renal replacement therapy.

levels (<500 mL/min) (5, 8). Of note, only one study described the use of CRRT platform-driven $ECCO_2R$ without hemofilter to provide standalone $ECCO_2R$ in patients with mild to moderate ARDS. However, that trial used an $ECCO_2R$ membrane with a significantly lower surface area (0.32 m^2 as opposed to 1.35 m^2 in the current study), limiting the rate of maximal CO_2 removal (9). In centers with available dialysis, low-flow $ECCO_2R$ using CRRT platforms might be an option to efficiently allocate resources for patients with hypercapnia as the main indication. The use of $ECCO_2R$ has not been described so far in COVID-19-associated ARDS.

MATERIALS AND METHODS

We report results of a single-center study evaluating the feasibility and safety of $ECCO_2R$ in combination with a CRRT platform as a standalone therapy or combined with CRRT for ARDS patients with refractory hypercapnia (arterial partial pressure of CO_2 [$PaCO_2$] > 55 mmHg) secondary to confirmed COVID-19 to effectively decrease CO_2 levels and enhance lung-protective ventilation.

Study Design and Participants

COVID-19 was diagnosed according to the World Health Organization (WHO) guidance (10). All patients were nursed in an isolation intensive care unit (ICU) with other patients suffering from COVID-19. The study was prospectively registered at http://clinicaltrials.gov (Identifier: NCT04351906). Patients were sedated with fentanyl, midazolam, and propofol. Other medications, including antibiotics, fluids, catecholamines, and transfusions, were left to the discretion of the attending physician.

Participants

In-patients ≥18 years of age with confirmed COVID-19 admitted to the University Hospital Giessen and Marburg, Giessen Medical Center, were enrolled in the feasibility study. Inclusion criteria were mild-to-moderate ARDS according to the Berlin definition (11), 100 mmHg < partial alveolar oxygen pressure/fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg with positive end-expiratory pressure >5 cmH_2O on mechanical ventilation expected to last >24 h; hypercapnia >55 mmHg with or without metabolic acidosis (pH < 7.3); bilateral opacities on chest imaging; with or without AKI requiring dialysis. Exclusion criteria were age <18 years, pregnancy, patients with decompensated heart failure or acute coronary syndrome, respiratory acidosis with persistent partial pressure of blood carbon dioxide ($PaCO_2$) levels >80 mmHg, acute brain injury, severe liver insufficiency (Child–Pugh scores > 7) or fulminant hepatic failure, decision to limit therapeutic interventions, catheter access to a femoral vein or jugular vein impossible, and pneumothorax.

Extracorporeal Carbon Dioxide Removal Operational Characteristic

$ECCO_2R$ was provided using a polymethylpentene, hollow fiber, gas-exchanger membrane (multiECCO$_2$R; Eurosets, Medolla, Italy), a labeled and certified European device to be used in conjunction with multiFiltrate CRRT platforms (Fresenius Medical Care, Bad Homburg, Germany) for combined respiratory and renal support. The manufacturer determined the multiECCO$_2$R membrane's maximum duration to be 72 h. A 13.5-Fr dual lumen hemodialysis catheter (Niagara, Bard Access, Heidelberg, Germany) was percutaneously inserted under in the femoral vein. Sweep gas flow was set at a gas/blood flow ratio of 15:1. Data were collected before starting $ECCO_2R$ (baseline) and 1, 4, 24, and 48 h after initiation of $ECCO_2R$. A bloodline warmer (Barkey S-line) and a thermal pad (both from Barkey, Leopoldshöhe, Germany) wrapped around the multiECCO$_2$R, as well as a warming blanket, were used to avoid undercooling of the patient.

Figure 1 depicts a schematic representation of the $ECCO_2R$ setup used in this study, either as standalone therapy (**Figure 1A**) or in conjunction with RRT (**Figure 1B**). The technical terminology of the extracorporeal circuit was based on a nomenclature developed for RRT (12). For standalone $ECCO_2R$, the multiFiltrate was set in hemoperfusion mode. $ECCO_2R$ was commenced at a blood flow of 400 mL/min. Systemic heparinization was started after catheter insertion aiming for an activated partial thromboplastin time of 60–80 s.

For $ECCO_2R$ + CRRT, the multiFiltrate was set in continuous venovenous hemodialysis (CVVHD) mode, and the multiECCO$_2$R was inserted in series after the hemofilter (Ultraflux AV 1000S, Fresenius Medical Care, Bad Homburg, Germany). $ECCO_2R$ + CRRT was commenced at a blood flow of 200 mL/min. CVVHD was delivered with an effluent dose of 25 mL/kg/h and regional citrate anticoagulation aiming a post-filter ionized calcium concentration of ∼0.25–0.35 mMol/L.

Definitions

Lung-protective ventilation strategies were the standard of care for invasive mechanical ventilation (4). Treatment strategies for COVID-19-associated ARDS were based on the WHO interim guidance (10), which were in line with our institutional standard of care for other forms of ARDS. Of note, at the time of patient recruitment, the WHO guidance on corticosteroids to treat patients with severe and critical COVID-19 was not available (13). Therefore, we did not routinely use corticosteroids for this patient population. Severe adverse events were defined as recently described (14). The feasibility of $ECCO_2R$ was assessed using Bowen et al.'s (15) feasibility framework. The use of RRT was at the discretion of the attending physician rather than by predefined biochemical or clinical criteria. However, RRT was initiated emergently when life-threatening changes in fluid, electrolyte, and acid-base balance occurred (16). The Institute of Medical Virology (Justus Liebig University Giessen, Germany) processed nasopharyngeal swabs and bronchoalveolar lavage fluid specimens, and severe acute respiratory syndrome coronavirus 2 infection was confirmed by real-time PCR according to the previously described protocols (17).

TABLE 1 | Characteristics of four patients with COVID-19 before $ECCO_2R$ initiation.

	Patient 1	Patient 2	Patient 3	Patient 4*
Demographics				
Sex	Male	Male	Male	Male
Age, years	57	74	67	52
Body mass index, kg/m^2	29.4	24.3	26.8	42.1
Comorbidities	Hypertension, diabetes	Hypertension, diabetes, CAD, COPD, CKD	Hypertension, diabetes, CAD, CKD	Hypertension, diabetes, COPD, CKD
Clinical characteristics				
SAPS II	37	51	54	43
SOFA score	7	9	8	11
ICU length of stay before $ECCO_2R$ initiation, days	23	6	25	8
Pre-$ECCO_2R$ adjuvant therapy				
Prone positioning	Yes	Yes	Yes	Yes
Nitric oxide	Yes	No	Yes	Yes
Duration of $ECCO_2R$, days	6	4	5	8
V_T, mL/kg PBW	5.6	7.2	6.5	7.3
RR, breaths/min	30	19	31	21
V_E, L/min	10.3	10.1	10.5	13.8
P_{PLAT}, cmH_2O	30	26	31	27
PEEP, cmH_2O	10	11	6	11
Driving pressure, cmH_2O	20	15	25	16
Compliance, mL/mbar	18.4	34.6	18.4	41.2
PaO_2/FiO_2 ratio	153.3	150.6	160.0	140.0
$PaCO_2$, mmHg	57.4	70.0	56.6	58.7
pH	7.38	7.29	7.41	7.23
Arterial HCO_{3-}, mMol/L	33.3	32.3	35.1	21.4
LVEF, %	60	40	65	60
Norepinephrine dose, μg/kg/min	0.002	0.336	0.219	0.038
Laboratory findings				
White cell count, g/L	7.1	12.9	26.3	17.1
Total lymphocytes	1.54	0.94	1.94	1.26
Hemoglobin, g/dL	84	95	90	93
Platelet count, giga/L	316	357	288	301
Creatinine, mg/dL†	0.5	1.9	1.0	2.0
Urea, mg/dL‡	37	197	101	230
Lactate dehydrogenase, U/L	311	492	237	365
Alanine aminotransferase, U/L	104	378	40	212
Aspartate aminotransferase, U/L	44	359	35	363
Albumin, g/L	24.9	23.6	29.2	29.7
B-type natriuretic peptide, pg/mL	48	591	93	9
C-reactive protein, mg/L	71.1	164.5	113.9	197.7
Procalcitonin, μg/L	0.5	6.1	7.5	1.6
Interleukin-6, μg/L	74	2150	95	55
Ferritin, μg/L	1588	2107	723	1076
D-dimer, mg/L	3.1	15.3	1.77	3.9

**Patient received $ECCO_2R$ + CRRT.*

† To convert the values for serum creatinine to mg/dL, multiply by 88.4.

‡ To convert the value for urea to blood urea nitrogen, multiply by 0.467.

CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRRT, continuous renal replacement therapy; $ECCO_2R$, extracorporeal carbon dioxide removal; FiO_2, fraction of inspired oxygen; HCO_3^-, bicarbonate; ICU, intensive care unit; LVEF, left ventricular ejection fraction; NA, not applicable/not available; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; PBW, predicted body weight; PEEP, positive end-expiratory pressure; P_{PLAT}, plateau pressure; RR, respiratory rate; SAP, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; V_E, minute volume; V_T, tidal volume.

TABLE 2 | Individual time course of operational characteristics, blood gas, ventilatory, and hemodynamic parameters during $ECCO_2R$.

	Patient 1					Patient 2					Patient 3					Patient 4*				
Operational characteristics	**Baseline**	**1 h**	**4 h**	**24 h**	**48 h**	**Baseline**	**1 h**	**4 h**	**24 h**	**48 h**	**Baseline**	**1 h**	**4 h**	**24 h**	**48 h**	**Baseline**	**1 h**	**4 h**	**24 h**	**48 h**
Blood flow, mL/min	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	200	200	200	200	200
Sweep gas flow, L/min	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	3.5	3.5	3.5	3.5	3.5
CRRT ultrafiltration rate, mL/h	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	0	0	0	100†
CRRT effluent rate, mL/kg/h	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	25	25	25	25	25
aPTT, s	30	NA	67	98	93	48	80	79	79	NA	85	NA	NA	56	65	27	26	NA	26	25‡
Blood gas parameters																				
Arterial																				
$PaCO_2$, mmHg	57.4	43.5	43.0	38.3	42.4	70.0	50.0	54.7	53.1	52.8	56.6	42.1	42.6	42.4	46.5	58.7	46.5	46.8	47.2	46.3
pH	7.38	7.48	7.48	7.53	7.47	7.29	7.44	7.38	7.39	7.35	7.41	7.53	7.51	7.50	7.47	7.23	7.30	7.36	7.38	7.40
PaO_2, mmHg	69.2	63.0	71.0	71.0	66.0	68.0	66.0	69.0	74.0	62.0	80.0	65.0	79.0	82.0	79.0	77.0	81.0	89.0	71.0	94.0
HCO_{3^-}, mMol/L	33.3	32.0	31.6	31.9	30.8	32.3	33.1	32.3	32.4	28.1	35.1	34.6	33.8	33.0	33.3	21.4	21.9	25.9	27.2	27.8
BE, mMol/L	7.6	8.3	7.9	8.7	6.9	4.8	8.2	6.2	6.6	2.5	9.4	10.8	10.2	9.1	8.9	−5.5	−3.9	0.8	2.3	3.0
Pre-$ECCO_2R$																				
PCO_2, mmHg	NA	54.2	53.2	42.5	55.9	NA	58.3	57.0	55.1	52.8	NA	52.4	50.0	51.2	54.0	NA	49.8	41.4	44.5	48.7
HCO_{3^-}, mMol/L	NA	33.9	33.2	33.4	31.8	NA	34.5	31.4	30.6	25.7	NA	33.5	34.7	35.0	35.7	NA	20.7	24.9	27.2	28.7
BE, mMol/L	NA	8.4	7.9	9.6	6.2	NA	8.6	8.0	7.2	0.0	NA	12.0	12.0	10.0	10.5	NA	−5.9	0.5	2.6	3.6
Post-$ECCO_2R$																				
PCO_2, mmHg	NA	15.0	13.4	14.1	18.6	NA	14.3	12.5	13.6	11.9	NA	8.2	10.7	12.4	15.7	NA	7.6	9.5	11.3	8.5
HCO_{3^-}, mMol/L	NA	32.3	29.5	30.3	27.4	NA	27.2	25.6	26.3	24.6	NA	29.0	34.9	28.5	29.9	NA	9.6	15.8	17.0	17.1
BE, mMol/L	NA	8.3	10.5	11.1	7.4	NA	10.2	7.7	7.9	0.2	NA	11.4	11.1	11.2	11.2	NA	−9.5	−1.8	−1.1	0.6
Ventilator parameters																				
V_T, mL/kg PBW	5.6	5.6	5.3	5.3	5.2	7.2	7.2	7.4	6.3	6.4	6.5	5.9	5.6	4.4	4.9	7.3	7.4	7.4	7.2	7.0
RR, breaths/min	30	30	28	26	24	19	19	18	18	18	31	30	30	30	26	21	21	21	21	21
V_E, L/min	10.3	10.6	10.8	10.7	7.5	10.1	9.5	9.2	8.6	9.4	10.5	11.5	10.0	9.2	6.2	13.8	13.8	13.9	13.7	13.4
P_{PLAT}, cmH_2O	30	30	29	22	22	26	26	25	24	24	31	31	31	30	28	27	27	27	26	25
PEEP, cmH_2O	10	10	9	8	8	11	11	11	11	11	6	6	6	6	6	11	11	11	11	11
Driving pressure, cmH_2O	20	20	20	14	14	15	15	14	13	13	25	25	25	24	22	16	16	16	15	14
Compliance, mL/mbar	18.4	18.5	17.5	24.9	24.5	34.6	32.5	27.1	33.2	31.4	18.4	15.8	14.3	13.7	13.6	41.2	41.4	41.5	43.5	45.6
PaO_2/FiO_2 ratio	153.3	153.3	157.8	157.8	165.0	150.6	132.7	153.3	160.0	157.8	160.0	130.0	143.6	136.7	134.0	140.0	147.3	161.8	157.8	175.1
Hemodynamic parameters																				
Mean arterial pressure, mmHg	71	74	74	76	75	64	89	82	69	66	79	79	77	74	66	63	62	66	67	77
Heart rate, beats/min	93	83	84	92	78	70	58	66	72	70	105	95	92	90	88	84	83	76	72	86
Norepinephrine dose, μg/kg/min	0.002	0.002	0.002	0.002	0.002	0.336	0.336	0.420	0.428	0.430	0.219	0.274	0.192	0.205	0.207	0.038	0.038	0.038	0.038	0.038

**Patient received $ECCO_2R$ + CRRT.*

†CRRT ultrafiltration was started at 38 h post-$ECCO_2R$ initiation.

‡$ECCO_2R$ + CRRT was performed with regional citrate anticoagulation.

aPTT, activated partial thromboplastin time; BE, base excess; COVID-19, coronavirus disease 2019; CRRT, continuous renal replacement therapy; $ECCO_2R$, extracorporeal carbon dioxide removal; FiO_2, fraction of inspired oxygen; HCO_{3^-}, bicarbonate; $PaCO_2$, arterial partial pressure of carbon dioxide; PCO_2, venous partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; PBW, predicted body weight; PEEP, positive end-expiratory pressure; P_{PLAT}, plateau pressure; RCA, regional citrate anticoagulation; RR, respiratory rate; NA, not applicable/not available; V_E, minute volume; V_T, tidal volume.

RESULTS

We report data of four male patients (median age: 62 [range, 52–74] years) admitted to our ICU between April and May 2020 due to ARDS secondary to confirmed severe acute respiratory syndrome coronavirus 2 infection (for clinical data, see **Table 1**). After implementing adjunctive measures for ARDS, all patients showed an improvement in oxygenation (PaO_2/FiO_2 ratio); however, in the later course of intensive care, all patients developed severe hypercapnia despite escalated ventilation parameters. In patients 1 and 3, hypercapnia was seen as the result of diffuse consolidations and fibrotic remodeling of the lungs as indicated by the low compliance (18.4 mL/mbar), whereas patients 2 and 4 developed hypercapnia, at least in part, secondary to underlying chronic obstructive pulmonary disease.

$ECCO_2R$ was implemented at a blood-flow rate of 400 mL/min in patients 1–3, resulting in a $PaCO_2$ decrease from a median 57.4 [56.6–70.0] to 43.5 [42.1–50.0] mmHg within 1 h, whereas pH increased from a median 7.38 [7.29–7.41] to 7.48 [7.44–7.53] mmHg within 1 h (**Table 2**). Patient 4 developed combined respiratory and metabolic acidosis secondary to hypercapnia and AKI, and $ECCO_2R$ + CRRT was commenced with a blood-flow rate of 200 mL/min, leading to a decrease of $PaCO_2$ from 58.7 to 46.5 mmHg within 1 h while pH and bicarbonate levels progressively increased. CRRT ultrafiltration (100 mL/h) was started at 38 h post-$ECCO_2R$ initiation due to oliguria. Tidal volume, plateau and driving pressure, as well as respiratory rate could be reduced during the second day of $ECCO_2R$ (from median 6.9 [5.6–7.3] to 5.8 [4.9–7.0] mL/kg PBW, median 28.5 [26.0–31.0] to 24.5 [22.0–28.0] cmH_2O, median 18.0 [15.0–25.0] to 14.0 [13.0–22.0] cmH_2O, and median 25.5 [19.0–31.0] to 21.5 [18.0–26.0] breaths/min, respectively; **Figure 2A**). The PaO_2/FiO_2 ratio remained unchanged throughout the study period (from median 152.0 [140.0–160.0] to 161.4 [134.0–175.1]). There was no detectable impact of $ECCO_2R$ on hemodynamics and vasopressor support. A comparison of pre- and post-$ECCO_2R$ PCO_2 values showed a ∼30 mmHg decrease (**Figure 2B**). No patient- or $ECCO_2R$/CRRT-related adverse events occurred. Downtime ranged from 2 to 8% of the total treatment time owing due to the turning of patients into the prone position. In all four patients, the $ECCO_2R$ treatment could be terminated after a median of 5.5 (4.5–7.5) days due to a sustained improvement in hypercapnia. In patient 4, however, CRRT was continued for another 4 days due to oliguria. Furthermore, patient 2 developed AKI stage 3, necessitating CRRT 6 days after the termination of $ECCO_2R$ as a sequel to septic shock.

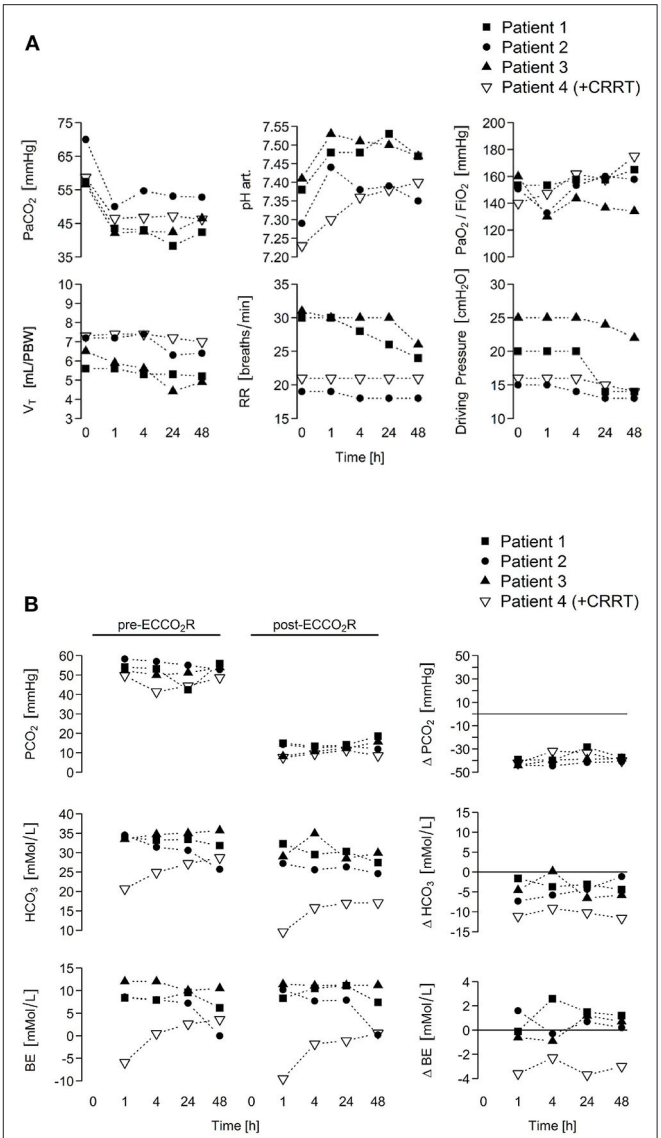

FIGURE 2 | $ECCO_2R$ rapidly normalizes arterial hypercapnia in patients with ARDS secondary to COVID-19, allowing de-escalation of ventilatory parameters. **(A)** To enhance carbon dioxide removal, $ECCO_2R$ was applied with a constant blood flow of 400 mL/min (patients 1–3) or 200 mL/min (patient 4; combined with CRRT) administering a sweep gas flow at a gas/blood flow ratio of 15:1 (6 or 3.5 L/min, respectively). Time course of blood gases and ventilator parameters is depicted. **(B)** Pre- to post-$ECCO_2R$ changes in PCO_2, bicarbonate, and base excess levels in all four patients that simultaneously points as in **(A)** are shown upon $ECCO_2R$ therapy. ARDS, acute respiratory distress syndrome; BE, base excess; COVID-19, coronavirus disease 2019; CRRT, continuous renal replacement therapy; $ECCO_2R$, extracorporeal carbon dioxide removal; FiO_2, fraction of inspired oxygen; HCO_3, bicarbonate; $PaCO_2$, arterial partial pressure of carbon dioxide; PBW, predicted body weight; PCO_2, venous partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; RR, respiratory rate; V_E, minute volume; V_T, tidal volume.

DISCUSSION

Our data indicate that low-flow $ECCO_2R$ using CRRT platforms might be safe and feasible to provide either standalone $ECCO_2R$ or $ECCO_2R$ combined with CRRT. This minimally invasive approach leads to efficient CO_2 removal in the setting of moderate ARDS. No patient- or ECCO2R/CRRT-related adverse events occurred. Importantly, these data also implicate that every ICU with available dialysis may apply RRT platform-driven $ECCO_2R$ to limit ventilator-induced lung injury or rescue uncontrollable respiratory acidosis even in situations where

"standard" $ECCO_2R$ consoles are not available. To the best of our knowledge, this is the first description of $ECCO_2R$ in COVID-19. Although these data may provide the rationale for randomized clinical trials, the following limitations need to be acknowledged. Given the invasive nature of an $ECCO_2R$ therapy, future randomized trials are required to assess the overall benefit and harm before widespread implementation can be recommended. Also, eligibility criteria should be further examined, particularly in those without an indication for CRRT. Furthermore, if the $ECCO_2R$ is intended to be continuous, sustaining a blood flow of 400 mL/min with a temporary catheter may be challenging, particularly in patients with COVID-19 who are obese or require prone positioning. COVID-19 induces a hypercoagulable state in many patients, which may result in premature extracorporeal circuit failure (18). No studies are available to date to aid in the selection of anticoagulation strategy, in particular when introducing an extracorporeal circulation. Thus, close monitoring of the extracorporeal circuit performance is advisable to ensure maximal circuit patency, as the initial anticoagulation strategy may not be effective in all patients, and a stepwise escalation and/or alternative plans (e.g., combination of different anticoagulation strategies) may be required. However, if using CRRT, we suggest CVVHD or continuous venovenous hemodiafiltration to decrease filtration fraction and reduce the risk of circuit clotting (19). In addition, COVID-19-associated ARDS may follow uncontrolled host immune response to the virus with the release of various immune mediators, especially cytokines, damage-associated molecular patterns, and pathogen-associated molecular patterns (20, 21). Extracorporeal blood purification techniques (e.g., hemoperfusion; RRT with surface-modified AN69, polymethylmethacrylate, or high-cut off membranes) have been proposed as adjuvant therapy for critically ill patients with COVID-19 to restore immune homeostasis through the removal of these circulating mediators (7). As many healthcare agencies have authorized emergency use of various extracorporeal blood purification techniques, these treatments might be indicated as sequential extracorporeal therapies in special cases in which immuno-dysregulation is evident, inflammatory parameters or cytokines are elevated, and other supportive therapies are failing or insufficient. Nonetheless, careful patient selection is required if these are to be used, as the benefits and adverse effects in COVID-19 patients have not been formally studied. Finally, additional costs associated with the use of $ECCO_2R$ in conjunction with RRT platforms in COVID-19-associated ARDS may be offset by a potential cost reduction through the elimination of daily rental costs for standalone $ECCO_2R$ consoles, the recruitment of dialysis professionals in centers with available dialysis to operate $ECCO_2R$, and a shorter length of ICU and hospital stay. However, large, multicenter randomized clinical trials are required to support the cost–benefit ratio of $ECCO_2R$ in conjunction with RRT platforms.

In conclusion, our data indicate that low-flow $ECCO_2R$ using CRRT platforms might be safe and feasible to provide either standalone $ECCO_2R$ or $ECCO_2R$ combined with CRRT. A multicenter randomized trial is warranted to assess the effects of CRRT platform-driven $ECCO_2R$ on clinical outcomes of patients with ARDS secondary to COVID-19 or other pathogenic factors.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study protocol was approved by the Ethics Committee of the Medical Faculty of the Justus Liebig University Giessen (AZ 63/20) and complied with the Declaration of Helsinki. Legally authorized representatives of the patients provided written informed consent.

AUTHOR CONTRIBUTIONS

FH-S, H-WB, CR, H-DW, WS, and IV: concept and design of the study. VR, BK, SK, KT, MH, RM, SH, and OK: literature research and clinical advice. FH-S, H-WB, JW, CR, VR, BK, SK, KT, MH, RM, SH, OK, H-DW, WS, and IV: acquisition, analyses, or interpretation of data, and critical revision of the manuscript for important intellectual content. FH-S and IV: manuscript drafting and had full access to all study data and had final responsibility for submitting for publication. FH-S, JW, and IV: figure illustration. H-WB, H-DW, WS, and IV: study supervision. All authors shared the study design, data collection, data analyses, data interpretation, as well as preparation, review, and approval of the manuscript.

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Conflict of Interest: WS received personal fees for consulting from Bayer Pharma, Liquidia Technologies, and United Therapeutics outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The Impact of the COVID-19 Pandemic on Incidences of Atrial Fibrillation and Electrical Cardioversion at a Tertiary Care Emergency Department: An Inter- and Intra-year Analysis

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Schnaubelt S, Domanovits H, Niederdoeckl J, Schuetz N, Cacioppo F, Oppenauer J, Spiel AO and Laggner AN (2020) The Impact of the COVID-19 Pandemic on Incidences of Atrial Fibrillation and Electrical Cardioversion at a Tertiary Care Emergency Department: An Inter- and Intra-year Analysis. Front. Med. 7:595881. doi: 10.3389/fmed.2020.595881

Background: National authorities have introduced measures as lockdowns against spreading of COVID-19 and documented incidences of multiple non-COVID-19 diseases have dropped. Yet, data on workload dynamics concerning atrial fibrillation and electrical cardioversion whilst a national lockdown are scarce and may assist in future planning.

Methods: Documented cases of atrial fibrillation and respective electrical cardioversion episodes at the Emergency Department of the Medical University of Vienna, Austria, from 01/01/2020 to 31/05/2020 were assessed. As reference groups, those incidences were calculated for the years 2017, 2018, and 2019. Inter- and intra-year analyses were conducted through Chi-square test and Poisson regression.

Results: A total of 2,310 atrial fibrillation-, and 511 electrical cardioversion episodes were included. We found no significant incidence differences in inter-year analyses of the time periods from January to May, or of the weeks pre- and post the national lockdown due to the COVID-19 pandemic. However, the intra-year analysis of the year 2020 showed a trend toward decreased atrial fibrillation incidences (rate-ratio 0.982, CI 0.964–1.001, $p = 0.060$), and significantly increased electrical cardioversion incidences in the post-lockdown period (rate ratio 1.051, CI 1.008–10.96, $p = 0.020$).

Conclusion: The decreased atrial fibrillation incidences are in line with international data. However, an increased demand of electrical cardioversions during the lockdown period was observed. A higher threshold to seek medical attention may produce a selected group with potentially more severe clinical courses. In addition, lifestyle modifications during isolation and a higher stress level may promote atrial fibrillation episodes to be refractory to other therapeutic approaches than electrical cardioversion.

Keywords: atrial fibrillation, electrical cardioversion, COVID-19, lockdown, critical care

INTRODUCTION

During the ongoing corona virus disease 2019 (COVID-19) pandemic, national authorities have introduced measures to control the outbreak and avoid overloading already-strained healthcare resources such as intensive care units (1–4). Following recommendations by the World Health Organization (5), the response in Austria was local distancing, quarantines and a general public lockdown, starting in mid-March 2020. These precautionary measures have been extensively communicated through media, with information reaching a high percentage of the population. People subsequently isolated themselves, and the national healthcare focus was lying on outbreak control and treatment of infected patients. Therefore, it was hypothesized that non-COVID-19 diseases received less attention than usually. On the one hand, patients had to endure longer waiting times until definitive medical care, and on the other hand patients might have not been treated at all because of staying isolated, fearful of contracting COVID-19 in health care facilities (6).

International data indeed show decreased incidences and delayed treatment timeframes of acute coronary syndrome, stroke, or pulmonary embolism (2, 3, 7–10), but also an increase in out-of-hospital cardiac arrest (11), further stressing the hypothesis of patients not seeking medical attention too late or not at all (7).

The suspicion of dysrhythmia such as atrial fibrillation (AF) being associated with COVID-19 has been claimed before (12–14), and general AF incidences have been reported to have decreased during lockdown periods (1, 15). Since AF poses a prominent cardiovascular issue requiring medical attention and correct timely treatment (16), consequences of a pandemic and a subsequent lockdown on AF incidences, patient flow, and treatment details seem inevitable.

We therefore aimed at validating the reports from Holt et al. (1) in a Viennese tertiary care Emergency Department (ED), assessing the dynamics in the ED workload concerning AF, and clarifying if the need for interventions such as electrical cardioversion (eCV) follows the hypothesized decreased AF incidences.

METHODS

Study Population and Data Acquisition

Within the present population-based retrospective observational study, primarily all cases of AF documented at the Emergency Department of the Medical University of Vienna, Austria, between 01/01/2020 and 31/05/2020 were included. As reference groups, all AF cases of the time periods of 01/01 to 31/05 of the years 2017, 2018, and 2019 were assessed. The respective data (incl. patients' age and gender) were culled from the department's anonymized case records, and AF was defined in accordance with the guidelines of the European Society of Cardiology (16). Apart from an age <18 years and a positive COVID-19 status, no specific exclusion criteria were applied. The Emergency Department of the Medical University of Vienna, Austria, was a designated non-COVID-19 hospital during the observational period. Due to fully anonymized data and because no direct clinical data were processed, informed consent was waived. The study was conducted under a positive ethics vote by the Ethics Committee of the Medical University of Vienna (EC-No. 1568/2014, registered at NCT03272620), and complies with the declaration of Helsinki.

COVID-19 Dynamics

COVID-19 was first detected in Austria on 25/02/2020, and reached the city of Vienna on 27/02/2020. Details and dynamics of epidemiological data concerning the pandemic within the observation period (starting with the first case on 25/02/2020 until 31/05/2020) were obtained from official government records (4).

Statistical Analysis

Incidences of AF and electrical cardioversion were calculated per week. Continuous data are presented as median and the respective interquartile range (IQR) and compared among subgroups using Mann-Whitney-*U*-test. Categorical parameters are presented as counts and percentages and were analyzed using Chi-square test including testing for linear association. For intra-year analyses of incidences in 2020, Poisson regression was conducted. Statistical significance was assumed through two-sided $p < 0.05$. Statistical analyses were performed using SPSS 24.0 (IBM SPSS, USA).

RESULTS

In the observational periods of January to May 2017, 2018, 2019, and 2020, a total of 2310 AF episodes were noted, of which 511 episodes (22.1%) necessitated electrical cardioversion. This leads to an average of 116 AF episodes and 26 electrical cardioversions per month. No significant differences were seen when comparing patients' age and gender in the single year periods of 2017, 2018, 2019, and 2020, and the cumulative values of 2017–2019 (**Table 1**).

Four-Year Dynamics

In an inter-year analysis of the observational periods within the years 2017, 2018, 2019, and 2020, only a trend, but no significant differences were found in AF incidences (596 vs. 571 vs. 614 vs. 529 episodes, respectively, $p = 0.232$). Thereby, similar results could be shown for the therapeutic approach of eCV (130 vs. 133 vs. 120 vs. 128 episodes, respectively, $p = 0.479$). Moreover, these results remained non-significant in a differentiated analysis of the weeks before- (weeks 1–11) and after (weeks 12–22) the national lockdown due to COVID-19 in 2020 (**Table 2**).

An Intra-Year Analysis of 2020

Within the weeks of January to May 2020, a total of 6,678 patients had been treated at the study center's ED for internal medicine diseases, resulting in an average of 1,336 patients per month or 44 patients a day, with a fluctuation toward higher numbers on

TABLE 1 | Patients' age and gender characteristics for the atrial fibrillation (AF) and electrical cardioversion episodes of the respective weeks 1–22 of the years 2017, 2018, 2019, 2020, and the cumulative values for 2017–2019 for comparison.

AF episodes	2017	2018	2019	2017–2019	2020	*p*-value
Age, years (IQR)						
Weeks 1–22	75 (65–81)	74 (65–81)	75 (66–82)	75 (66–82)	76 (67–83)	0.354
Weeks 1–11	74 (64–79)	76 (65–80)	75 (65–83)	75 (65–81)	76 (66–82)	0.299
Weeks 12–22	75 (65–80)	75 (66–81)	75 (66–83)	75 (65–82)	76 (66–82)	0.301
Male gender, *n* (%)						
Weeks 1–22	288 (48.3)	281 (49.1)	307 (50.0)	876 (49.2)	261 (49.3)	0.293
Weeks 1–11	168 (50.3)	149 (49.0)	149 (48.9)	462 (49.0)	143 (49.3)	0.098
Weeks 12–22	126 (48.1)	133 (49.8)	154 (49.8)	419 (49.9)	117 (49.0)	0.109
Electrical cardioversions	**2017**	**2018**	**2019**	**2017–2019**	**2020**	***p*-value**
Age, years (IQR)						
Weeks 1–22	67 (56–75)	69 (55–75)	65 (55–75)	67 (55–75)	63 (54–75)	0.180
Weeks 1–11	67 (56–77)	68 (54–74)	65 (55–74)	67 (55–76)	64 (55–77)	0.200
Weeks 12–22	66 (56–74)	69 (55–74)	64 (54–74)	66 (54–74)	63 (54–75)	0.198
Male gender, *n* (%)						
Weeks 1–22	76 (58.5)	74 (55.6)	83 (69.2)	233 (60.8)	77 (60.2)	0.092
Weeks 1–11	42 (59.2)	37 (56.1)	38 (69.1)	117 (60.9)	34 (60.7)	0.103
Weeks 12–22	34 (57.6)	37 (55.2)	45 (69.2)	116 (60.7)	43 (59.7)	0.099

Continuous data are presented as median and the respective interquartile range (IQR) and compared among subgroups using Mann–Whitney–U–test.

TABLE 2 | The number of atrial fibrillation (AF) episodes and electrical cardioversions in an inter–year analysis.

Number of AF episodes	2017	2018	2019	2020	*p*-value
Weeks 1–22	596	571	614	529	0.232
Weeks 1–11	334	304	305	290	0.174
Weeks 12–22	262	267	309	239	0.369
Number of electrical cardioversions	**2017**	**2018**	**2019**	**2020**	***p*-value**
Weeks 1–22	130	133	120	128	0.479
Weeks 1–11	71	66	55	56	0.878
Weeks 12–22	59	67	65	72	0.457

Weeks 12–22 of 2020 depict the COVID−19 pandemic period after the national lockdown. Categorical parameters are presented as counts and percentages and analyzed using Chi–square test. Statistical significance was defined by two-sided $p < 0.05$.

weekends and national holidays, and lower numbers on work days. The number of ambulatory patients having been treated in an out-patient manner amounted to 4,897 (73.3%; 979 per month or 32 per day), that of admitted patients to 1,779 (26.6%; 355 per month or 12 per day). A more detailed analysis revealed a noticeable damper in overall patient numbers and numbers of patients requiring intermediate care unit (IMCU) treatment with the introduction of the national lockdown in mid-March 2020 (**Figure 1**).

Poisson regression analysis for the weeks stratified in before- and after the national lockdown revealed a trend toward a decrease in the incidence of AF (rate ratio 0.982, CI 0.964–1.001, $p = 0.060$) (**Figure 2**). Of importance, the same analysis conducted for eCV episodes yielded a significant increase toward the lockdown period (rate ratio 1.051, CI 1.008–10.96, $p = 0.020$) (**Figure 3**); this continuous rise in eCV numbers is unique to the year of 2020.

DISCUSSION

The presented data highlight the notch in general patient flow in our study center during the lockdown due to the COVID-19 pandemic. Moreover, we demonstrate a decrease of AF-, but an increase in eCV incidences from the pre-lockdown- toward the lockdown phase within the year 2020. To our knowledge, this analysis presents the first data on AF dynamics in a tertiary non-COVID-19 ED during the COVID-19 pandemic.

A Decreased Workload of Specialized Centers

Our data on a designated non-COVID-19 tertiary care university hospital ED that serves—amongst others—as a primary contact point for acute coronary syndrome, stroke and as a cardiac arrest center in the city of Vienna, showed a decreased general patient flow and an associated reduced workload, being in accordance with international literature: Numbers of patients with the described diseases have dropped during national lockdown measures in numerous countries, including Austria. A fear of COVID-19 infection and a "watchful waiting" approach of medical caregivers toward less-symptomatic patients have been suggested as major drivers for this (2, 3, 7–10), also

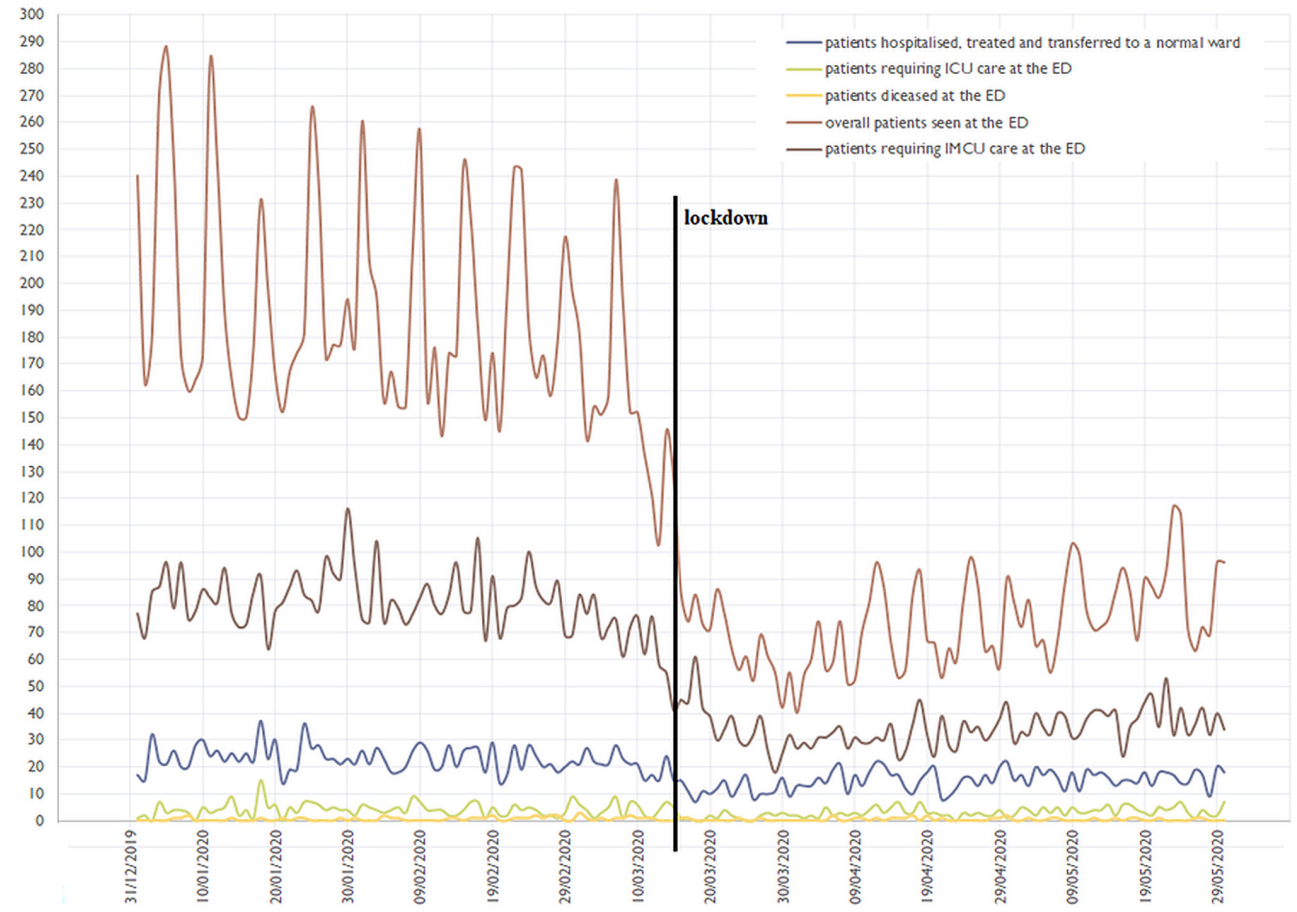

FIGURE 1 | Depiction of the Emergency Department's (ED) patient flow from January to May 2020. The bold vertical line shows the national lockdown due to COVID-19 in mid-March; a decrease in overall- and intermediate care unit (IMCU) patients is seen. ICU, intensive care unit.

acting as a reasonable explanation for our findings. This effect might be gravest in ambulatory out-patient-department patients, not seeking medical attention themselves anymore (**Figure 1**), bearing the risk of a high rate of undetected diseases actually requiring treatment. To countersteer, a public information campaign addressing this dilemma in times of lockdowns might be reasonable. Of utmost importance, whenever COVID-19 numbers should rise to a state that tertiary care centers cannot longer be reserved as "non-COVID-19" facilities, the dilemma might become even worse: General COVID-19 patients and especially those in need of tertiary care (e.g., extra-corporal membrane oxygenation) could further crowd out others in need.

Dropping AF Rates Fitting in the Picture

Before the background of AF as a possible complication of COVID-19 (12), it seems imperative not to oversee non-COVID-19 AF patients within the bigger picture. Even though our trend of decreased non-COVID-19 AF rates in an inter-year analysis did not reach statistical significance, our findings are in line with recent international data: Holt et al. report on a nationwide 47%-decrease in new-onset AF coded by the registry-based healthcare system, and warn of complications of underdiagnosis (1). Again, fear of contagion and a higher threshold of seeking medical attention has been discussed as the main reason (1, 15). We strengthen these data with our intra-year analysis of 2020 showing a trend toward a drop of AF incidences in the lockdown period (rate ratio 0.982, CI 0.964–1.001, $p = 0.060$).

Our data on decreasing AF rates not reaching statistical significance might have various explanations:

First, various factors may counteract the effect of the general reluctance of presenting to an ED or calling emergency medical services: Lifestyle modifications such as higher calories intake, a lack of physical activity or higher stress levels have all been reported both as being highly prevalent in lockdown periods, and as AF facilitators (1, 17–19). Indeed, severe emotional stress has been noted in populations after COVID-19 lockdowns (20, 21), and mental health seems to be affected (22). In particular, economic insecurity and unemployment, as often found during lockdown periods, are known risk factors for AF development (23, 24).

Secondly, a shift of AF patients from more specialized AF centers or cardiologic out-patient-departments to the ED could

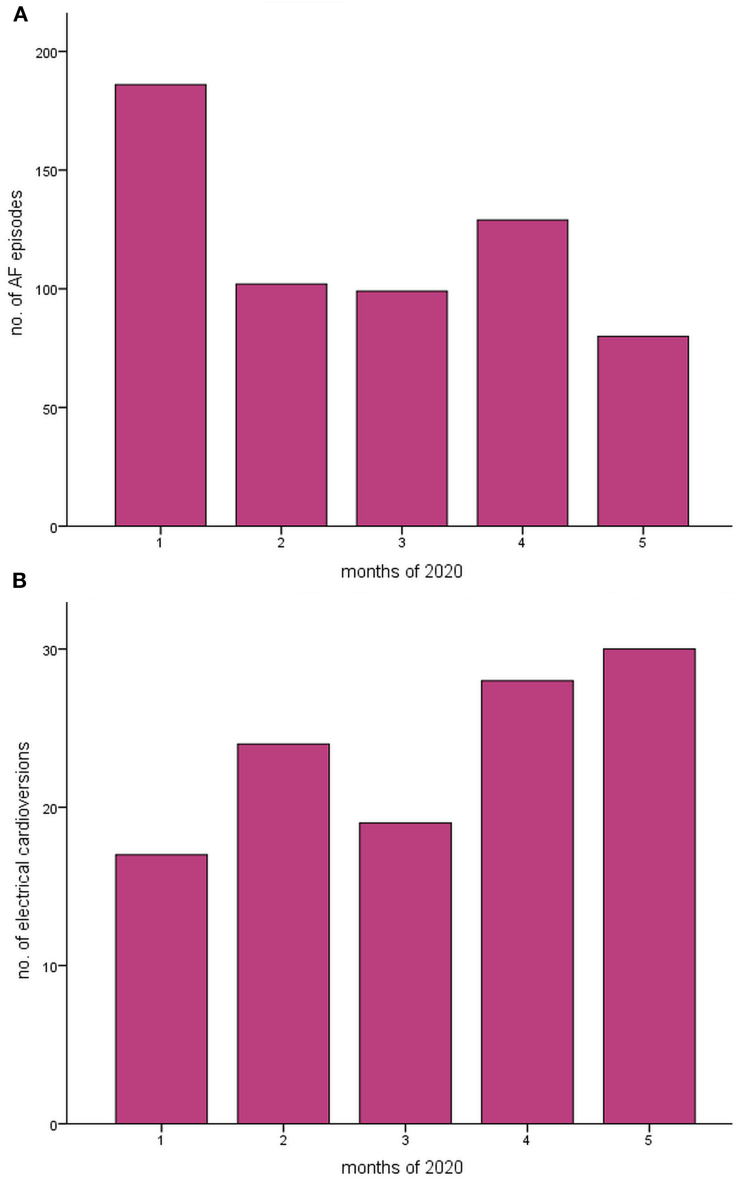

FIGURE 2 | The incidences of **(A)** atrial fibrillation (AF) and **(B)** of electrical cardioversion in an intra-year analysis of the year 2020 National lockdown due to COVID-19 was conducted in mid-March. Poisson regression analysis was used to compare weeks 1–22 of 2020. A trend toward a decrease in AF could be found, corresponding to a rate ratio of 0.982 [95% CI 0.964–1.001, $p = 0.060$], and a significant increase in electrical cardioversions was seen, corresponding to a rate ratio of 1.051 [95% CI 1.008–1.096, $p = 0.020$].

have taken place since those might have been closed during the lockdown.

The Higher Demand of Electrical Cardioversion

Surprisingly, our data showed a significant increase of eCV rates toward the lockdown period in the intra-year analysis of 2020 (rate ratio 1.051, CI 1.008–10.96, $p = 0.020$), which cannot explained by a sudden increase in patients' age or significant dynamics in patients' gender (**Table 1**). This has not been reported before and stands in contrast to falling AF incidences in the same time period. Similar explanatory hypotheses apply as to the fact of AF rates not dropping as severely as in other literature: A modified lifestyle and increased stress levels during lockdown and a shift of patients from specialist centers toward the ED can be assumed. However, the increased demand of eCV parallel to dropping general AF incidences can also depict a higher necessity of rhythm control in AF patients presenting to the ED. In patients developing AF, the above mentioned factors might pose promotors of an increased chance for the current episode

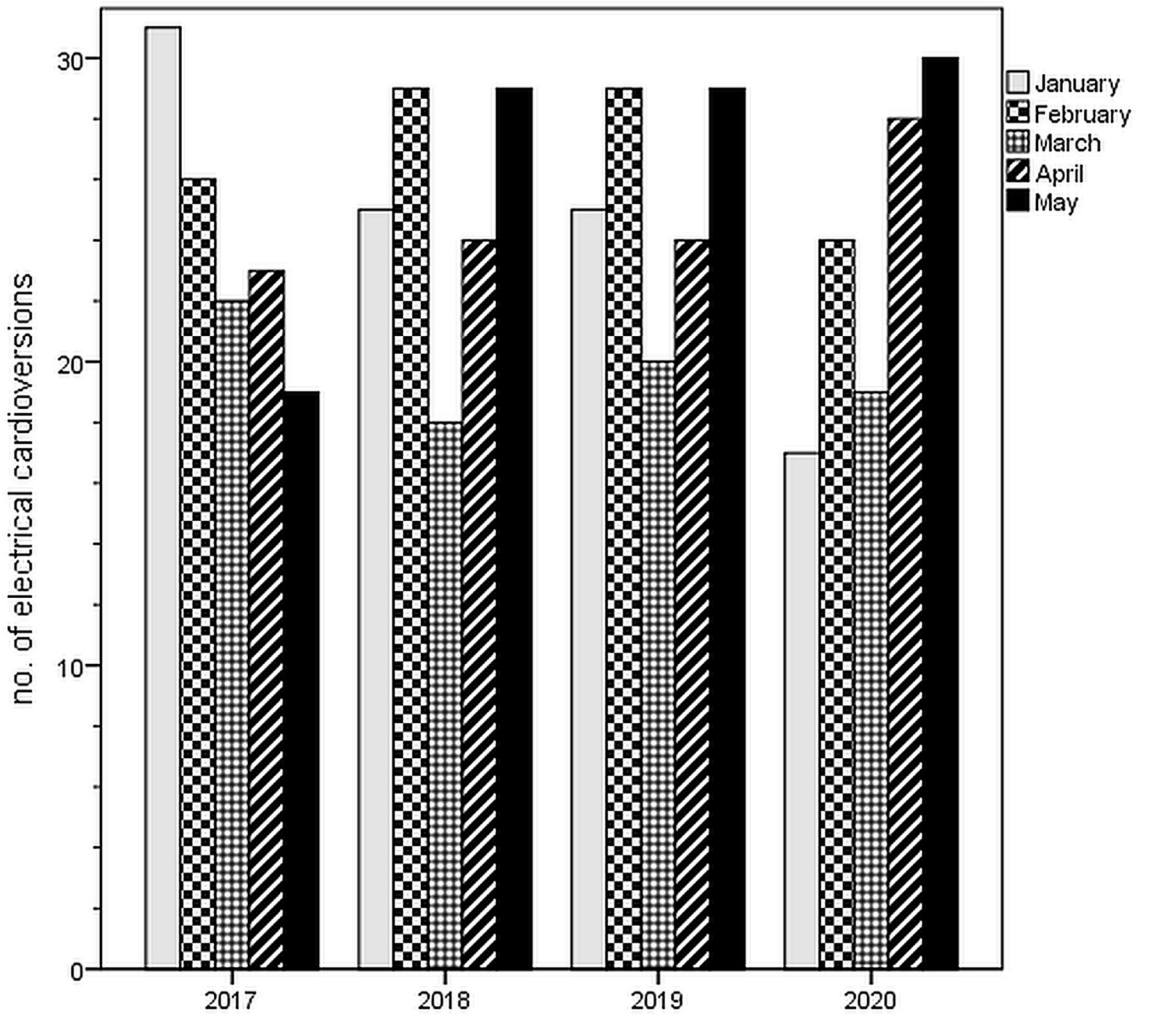

FIGURE 3 | Numbers of electrical cardioversions from January to May in the years 2017, 2018, 2019, and 2020 (corresponding to **Table 1**). For a detailed analysis of the year 2020, see **Figure 2**.

to be refractory to other therapeutic approaches (frequency control, electrolyte adjustment, symptomatic treatment, and even pharmacological cardioversion), therefore making eCV necessary in more cases than usual. In addition, the higher threshold of seeking medical attention might "sort out" the lesser-severe AF cases that usually also present to the ED, leaving more complex, more therapy-refractory episodes. This hypothesis could mean that—if validated in future research—special attention should be paid to those AF patients reaching medical attention regardless of a lockdown: These could be the patients needing a smooth workflow toward eCV.

Study Limitations

The main limitation of the present analysis represents its single center setting. Our results are therefore prone to potential selection bias or further unknown factors influencing patient counts at our study center. Moreover, we do not have sufficient information about other medical centers potentially shifting AF and eCV cases to our center due to the lockdown. Also, the interesting finding of a notch in eCV numbers in March of each observed year (**Figure 3**) cannot be fully explained. Seasonal dynamics in AF incidences might play a role (25), but other influencing factors not identified by us can also not be ruled out. Lastly, no in-depth epidemiological patient data could be provided in order to further understand the described dynamics—this should be focus of further research.

CONCLUSION

Our data of atrial fibrillation and electrical cardioversion incidences before and during a national lockdown due to COVID-19 show a trend toward decreased atrial fibrillation incidences, but a higher demand of electrical cardioversions during the lockdown period. A higher threshold of patients

to seek medical attention may result in a subsequently selected group with potentially more severe clinical courses. In addition, lifestyle modifications during isolation and a higher stress level may promote atrial fibrillation episodes to be refractory to other therapeutic approaches than electrical cardioversion.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical University of Vienna, Austria (EC-No. 1568/2014). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR'S NOTE

All listed authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

AUTHOR CONTRIBUTIONS

SS, JN, NS, FC, and JO collected the study data and comprised the manuscript. HD, AS, and AL comprised further manuscript versions and supervised the research process. All authors multiply revised the manuscript critically and approved of the final version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Medicine

ORIGINAL RESEARCH
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A Novel Risk-Stratification Models of the High-Flow Nasal Cannula Therapy in COVID-19 Patients With Hypoxemic Respiratory Failure

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Background: High-flow nasal cannula (HFNC) has been recommended as a suitable choice for the management of coronavirus disease 2019 (COVID-19) patients with acute hypoxemic respiratory failure before mechanical ventilation (MV); however, delaying MV with HFNC therapy is still a dilemma between the technique and clinical management during the ongoing pandemic.

Methods: Retrospective analysis of COVID-19 patients treated with HFNC therapy from four hospitals of Wuhan, China. Demographic information and clinical variables before, at, and shortly after HFNC initiation were collected and analyzed. A risk-stratification model of HFNC failure (the need for MV) was developed with the 324 patients of Jin Yin-tan Hospital and validated its accuracy with 69 patients of other hospitals.

Results: Among the training cohort, the median duration of HFNC therapy was 6 (range, 3–11), and 147 experienced HFNC failure within 7 days of HFNC initiation. Early predictors of HFNC failure on the basis of a multivariate regression analysis included age older than 60 years [odds ratio (OR),1.93; 95% confidence interval (CI), 1.08–3.44; $p = 0.027$; 2 points], respiratory rate-oxygenation index (ROX) <5.31 (OR, 5.22; 95% CI, 2.96–9.20; $p < 0.001$; 5 points) within the first 4 h of HFNC initiation, platelets $<125 \times 10^9$/L (OR, 3.04; 95% CI, 1.46–6.35; $p = 0.003$; 3 points), and interleukin 6 (IL-6) >7.0 pg/mL (OR, 3.34; 95% CI, 1.79–6.23; $p < 0.001$; 3 points) at HFNC initiation. A weighted risk-stratification model of these predictors showed sensitivity of 80.3%, specificity of 71.2% and a better predictive ability than ROX index alone [area under the curve (AUC) = 0.807 vs. 0.779, $p < 0.001$]. Six points were used as a cutoff value for the risk of HFNC failure stratification. The HFNC success probability of patients in low-risk group (84.2%) was 9.84 times that in the high-risk group (34.8%). In the subsequent validation cohort, the AUC of the model was 0.815 (0.71–0.92).

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Conclusions: Aged patients with lower ROX index, thrombocytopenia, and elevated IL-6 values are at increased risk of HFNC failure. The risk-stratification models accurately predicted the HFNC failure and early stratified COVID-19 patients with HFNC therapy into relevant risk categories.

Keywords: COVID-19, HFNC, ROX, mechanical ventilation, thrombocytopenia, risk-stratification

INTRODUCTION

Severe coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was characterized by progressive dyspnea and hypoxemia within 1 week after onset of the disease (1–4). As of August 23, 2020, more than 1.7 million new COVID-19 patients were reported in the last 7 days, by the World Health Organization Region. For most patients, they recovered on conventional oxygen therapy. However, some patients, mainly critically ill patients, progressed to severe respiratory distress, and needed advanced oxygen therapy, including high-flow nasal cannula (HFNC) therapy and mechanical ventilation (MV) (2).

HFNC can bring high concentrations of humidified oxygen with low level of positive end-expiratory pressure; facilitate the elimination of carbon dioxide, allowing one to rapidly relieve the acute hypoxemic respiratory failure (AHRF) symptoms (5, 6); and apply in critical care resource-limited countries. During the ongoing pandemic, HFNC has been recommended as a bridge for management of patients with severe or critical COVID-19 on the basis of the evidences from non-coronavirus-related pneumonia (6–9). To our best knowledge, however, one important concern during HFNC therapy in non-COVID-19 patients with AHRF is to not delay the need of MV (10), and the association between HFNC therapy and its outcome (need or not for MV) and its early predictors has not been explored.

Here, we reported the clinical course of COVID-19 patients receiving HFNC and explored the predictors and attempted to develop a novel risk-stratification model that predicts the failure (the need for MV) of HFNC therapy for COVID-19 patients and early stratifies them into relevant risk categories.

METHODS

Study Design and Participants

This was a multicenter retrospective observational study on adult COVID-19 patients receiving HFNC oxygen therapy in Union Hospital, Wuhan Third Hospital, Union Hospital West Campus, or Jinyintan Hospital between December 29, 2019, and April 30, 2020. The training cohort was set up in Jin Yin-tan Hospital, and the validation cohort was set up in the other hospitals. All patients with a diagnosis of COVID-19 according to guidelines released by the National Health Commission of the People's Republic of China were screened (11). Patients were excluded if they never received HFNC, received HFNC after MV, deceased within 12 h after admission, had important information that was missing within 12 h of HFNC therapy, or were included in previous studies (2, 4, 12, 13). Research approval (2020-0041-1) was granted by the ethics board of Wuhan Union Hospital as the central coordinating center. The need for informed consent was waived.

HFNC Device and Treatment

HFNC was considered if a patient with COVID-19 required a conventional oxygen therapy with oxygen flow higher than 10 L/min to achieve SpO_2 of >90% or a respiratory rate (RR) >30 breaths per min (bpm) despite adequate oxygen supplementation or showed persistent signs of respiratory distress (10, 14–17).

The included COVID-19 patients received HFNC oxygen therapy via HFNC device (Fisher & Paykel, Auckland, New Zealand). The temperature of the heated humidification system was adjusted between 31 and 37°C to provide optimal humidity; the flow was initiated with a minimum flow at 30 L/min, and FIO_2 was adjusted to reach SpO_2 >90% or higher (10, 14, 18, 19).

The discontinuation of HFNC oxygen therapy and the switch to either conventional oxygen therapy or MV, was made at the discretion of the treating physicians. If respiratory failure improved, a trial of intermittent HFNC therapy was performed, and the duration of HFNC was gradually shortened until the HFNC was totally substituted by conventional oxygen therapy. If the respiratory failure progressively deteriorated, non-invasive or invasive MV was used. The decision to intubate was at the discretion of the treating physicians in accordance with published guidelines [26].

Data Collection

Patient identification in these ICUs was achieved by reviewing admission logs from available medical records. After several cycles of feedback and pilot testing, modified standardized International Severe Acute Respiratory and Emerging Infection Consortium case report forms for COVID-19 were utilized (12). Data were extracted from local servers by experienced research physicians at each center.

Demographic data, preexisting comorbidities (chronic cardiac disease, chronic pulmonary disease, hypertension, cerebrovascular disease, chronic liver disease, diabetes, and malignancy), vital signs (RR, heart rate, blood pressure), and laboratory values [white blood cell count, platelets, prothrombin time (PT), activated partial thromboplastin time (APTT), plasma D-dimer, plasma fibrinogen, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine, hypersensitive troponin I (hsTNI), IL-6, arterial blood gas analysis], complications [acute cardiac injury, acute kidney injury (AKI), liver dysfunction, coagulopathy, and hospital acquired infection], and treatments (oxygen therapy, corticosteroids) were collected at admission and HFNC and MV initiation.

Definitions

AKI was diagnosed based on the serum creatinine criterion of KDIGO (20). Acute cardiac injury was diagnosed if the serum concentration of hsTNI was measured in the laboratory above the upper limit of the reference range (>28 pg/mL) (12). Liver dysfunction was diagnosed if serum ALT >50 U/L or AST >40 U/L (21). Coagulopathy was defined if PT >16.5 s or APTT >42 s (13). Shock was defined according to the 2016 Third International Consensus Definition for Sepsis and Septic Shock (22). Respiratory rate–oxygenation (ROX) was defined as the ratio of SpO_2/FIO_2 to respiratory rate (18, 23). HFNC therapy failure was defined as need for MV within 7 days of HFNC initiation (24). The criteria for typical HFNC failures include failures to maintain SpO_2 >90%, hypercapnic respiratory failures with pH <7.2 or $PaCO_2$ of arterial blood >55 mm Hg, worsening respiratory distress, or need for airway protection due to altered mental state or aspiration (10, 14, 15, 18, 19).

Statistical Analysis

No hypothesis was made for the present study, so sample size estimation was unavailable. Data were expressed as mean ± standard deviation, median [interquartile range (IQR)] or median (range) for continuous variables, and number (%) for categorical variables. Differences between patients with failure and success of HFNC oxygen therapy, and between survivors and non-survivors of MV after HFNC failure, were explored using two-sample *t*-test for parametric variables, Wilcoxon rank-sum test for non-parametric variables, and Fisher exact test for categorical variables. Age was dichotomized at 60 years (25). IL-6, D-dimer, and platelet count were dichotomized at the clinically relevant cutoff. ROX index was also included and dichotomized at the optimal cutoff point following Youden index of receiver operating characteristic (ROC) curve (18). Dichotomized age, IL-6, platelet counts, comorbidities, and complications showing a $p < 0.1$ in univariate analysis were included for multiple logistic regression analysis. The scores were assigned as integer values relative to the regression coefficient of each predictor. The predictive value of the risk-stratification models was assessed by the area under the curve (AUC). Cutoff points were calculated according to Youden index of ROC. Success curves of HFNC oxygen therapy between low-risk and high-risk of HFNC failure following the cutoff value and survival analysis for the patients who received MV before and after 48 h of HFNC initiation were developed using the Kaplan–Meier method.

All statistical tests were 2-tailed with significance set at $p < 0.05$. The Stata/IC 15.1 software (StataCorp, College Station, TX, USA) was applied for all analyses.

RESULTS

Demographic Data and Clinical Parameters of Included Patients

We screened 3,102 patients with confirmed COVID-19 between December 29, 2019, and March 30, 2020, of which 546 patients (17.6%) with severe AHRF were identified, and 324 patients were included into training cohort, and 69 patients formed the validation cohort.

Among the training cohort, the mean age of COVID-19 patients was 63.2 ± 14.5 years, of whom 211 patients (65.1%) were older than 60 years, and 219 (67.6%) were male (**Table 1** and **Supplementary Table 1**). The proportion of patients with coexisting conditions were not significantly different between the HFNC success group and the HFNC failure group except for malignancy ($p = 0.024$). The ratio of positive SARS-CoV-2 RNA at HFNC initiation and the duration of HFNC initiation to the negative conversion of SARS-CoV-2 RNA for the survivors was not different between the two groups.

At HFNC initiation, compared with patients in the HFNC success group, the HFNC failure group had a higher level of D-dimer [4.8 (1.1–17.7) vs. 2.6 (0.8–8.8); $p = 0.0203$] and more patients with IL-6 >7.0 pg/mL [124 (84.4%) vs. 99 (55.9%); $p < 0.001$] and with platelets $<125 \times 10^9$/L [22 (12.4%) vs. 43 (29.3%), $p < 0.001$], but no differences in eosinophils, lymphocytes, the proportion of elevated D-dimer, and concentration of plasma fibrinogen and IL-6 were observed between the two groups. Moreover, there was a higher prevalence of AKI [26 (17.7%) vs. 11 (6.2%); $p = 0.001$] and acute cardiac injury [97 (66.0%) vs. 91 (51.4%); $p = 0.006$] in the HFNC failure group, but no differences in shock, liver dysfunction, coagulopathy, and corticosteroids treatment were observed between the two groups.

Respiratory Variables During HFNC Treatment of the Training Cohort

At baseline, 218 patients had analyses of arterial blood gas, and the number of patients with PaO_2/FIO_2 <200 mm Hg was 174. The patients in the HFNC failure group had lower levels of PaO_2/FIO_2 [129.6 (100.0–163.4) vs. 151.2 (122.8–199.2) mm Hg; $p < 0.001$].

After HFNC therapy, the patients in the HFNC success group had higher SpO_2/FIO_2 [134.2 (117.5–158.3) vs. 108.7 (94.6–116.3) fold; $p < 0.001$] and lower RR [22 (20–24) vs. 23 (22–25); $p < 0.001$] (**Table 2**), but no differences in systolic arterial pressure were observed between the two groups. The RR alone had an AUC of 0.65 (0.59–0.71). Higher ROX index values with an AUC of 0.779 (0.73–0.83) were observed in the HFNC success group [5.9 (5.0–7.5) vs. 4.8 (4.1– 5.3); $p < 0.001$]. The optimal cutoff point for the ROX index within the first 4 h was estimated to be 5.31 in accordance to the ROC curve, more patients in the HFNC failure group had an ROX index score <5.31 [114 (77.6%) vs. 60 (33.9%), $p < 0.001$].

The Outcomes of HFNC Therapy of the Training Cohort and Its Predictors

The median duration of HFNC therapy was 6 (range, 3–11). One hundred forty-seven (46.4%) experienced HFNC failure within 7 days of HFNC initiation.

Multiple logistic regression analysis revealed the independent predictors of HFNC failure (**Figure 1**), comprising age older than 60 years [odds ratio (OR) 2.54; 95% CI, 1.39–4.65; $p = 0.003$], platelets $<125 \times 10^9$/L (OR, 3.18; 95% CI, 1.36–7.46; $p = 0.008$), and IL-6 >7.0 pg/mL (OR, 3.07; 95% CI, 1.67–5.62; $p < 0.001$;) at

TABLE 1 | Baseline characteristics of the included 324 patients with COVID-19 at HFNC initiation.

Characteristics	All patients ($n = 324$)	HFNC success ($n = 177$)	HFNC failure ($n = 147$)	*p*-value success vs. failure
Age, mean ± SD, years	63.2 ± 14.5	60.6 ±15.5	66.3 ± 12.5	0.0005
Age ≥60 years	211 (65.1%)	99 (55.9%)	112 (76.2%)	<0.001
Male	219 (67.6%)	119 (67.2%)	100 (68.0%)	0.487
Preexisting comorbidities				
Hypertension	147 (45.4%)	78 (44.1%)	69 (46.9%)	0.343
Diabetes	60 (18.5%)	34 (19.2%)	26 (17.7%)	0.419
Chronic cardiac disease	42 (13.0%)	22 (12.4%)	20 (13.6%)	0.440
Chronic pulmonary disease	26 (8.0%)	13 (7.3%)	13 (8.8%)	0.385
Chronic liver disease	27 (8.4%)	14 (8.0%)	13 (8.8%)	0.464
Cerebrovascular disease	25 (7.7%)	10 (5.7%)	15 (10.2%)	0.094
Malignancy	15 (4.6%)	4 (2.3%)	11 (7.5%)	0.024
Time from illness onset to HFNC, days	14 [10–19]	14 [11–19]	14 [10–18]	0.7615
Time from admission to HFNC, days	2 [0–5]	2 [1–4]	2 [0–6]	0.5397
SOFA at HFNC onset (n = 218)‖	3 [2–4]	2 [2–3.5]	4 [3–5]	<0.001
Laboratory findings at HFNC initiation				
SARS-CoV-2 RNA positive	108 (33.3%)	64 (36.2%)	44 (29.9%)	0.143
Time to negative of SARS-CoV-2 RNA, days‖‖	6 [0–16]	7.5 [0–16]	5.5 [0 –6]	0.1612
Neutrophils, 10^9/L	7.9 [5.6–11.1]	7.4 [5.3–9.8]	8.5 [6.0–11.8]	0.0058
Neutrophils >6.3 × 10^9/L‖	220 (67.9)	114(64.4%)	106 (72.1%)	0.087
Lymphocytes, 10^9/L	0.6 [0.4–0.9]	0.6 [0.4–0.9]	0.6 [0.4–0.8]	0.2715
Platelets 10^9/L	187 [140.5–246.5]	200 [149–255]	177 [119–234]	0.0087
Platelets <125 × 10^9/L‡	65 (20.1%)	22(12.4%)	43 (29.3%)	<0.001
D-Dimer, μg/mL	3.3 [1.0–14.1]	2.6 [0.8–8.8]	4.8[1.1–17.7]	0.0203
Elevated d-dimer level†	210 (64.8%)	109 (61.6%)	101 (68.7%)	0.111
Fibrinogen, g/L	4.8 [3.4–6.1]	4.8 [3.2–6.6]	4.8 [3.6–5.8]	0.5825
IL-6¶, pg/mL	9.7 [7.0–14.5]	9.6 [6.6–14.5]	10.0 [7.8–14.7]	0.1509
Elevated IL-6 level ¶	223 (68.8%)	99 (55.9%)	124 (84.4%)	<0.001
Complications at HFNC initiation				
Shock	2 (0.62%)	0 (0.0%)	2(1.36%)	0.36
AKI	37 (11.4%)	11 (6.2%)	26 (17.7%)	0.001
Acute cardiac injury	188 (58.0%)	91 (51.4%)	97 (66.0%)	0.006
Liver dysfunction	189 (58.3%)	97 (54.8%)	92 (62.6%)	0.096
Coagulopathy	30 (9.3%)	12(6.8%)	18 (12.2%)	0.067

AKI, acute kidney injury; COVID-19, coronavirus disease 2019; IQR, interquartile range; SD, standard deviation; HFNC, high-flow nasal cannula; IL-6, interleukin 6; SOFA, Sequential Organ Failure Assessment.

Data were expressed median [interquartile range] or as mean ± standard deviation.

‖ *SOFA scores at HFNC initiation were available in 218 patients, because arterial blood gas analysis was conducted in 132 HFNC failure patients and 86 success patients.*

‖‖ *Durations of negative conversion of SARS-CoV-2 RNA were available in 136 survivors, of 126 survivors from HFNC success group and 10 from HFNC failure group.*

‖ *The upper limit of normal range of neutrophil count was 6.3 × 10^9/L.*

† *The upper limit of normal range of d-dimer was 1.5 μg/mL.*

‡ *The lower limit of normal range of platelet count was 125 × 10^9/L.*

¶ *The upper limit of normal range was 7 pg/mL.*

HFNC initiation, ROX index <5.5 (OR, 5.92; 95% CI, 3.31–10.58, $p < 0.001$) within the first 4 h of HFNC therapy.

Risk-Stratification Models of HFNC Therapy in COVID-19 Patients

A special risk-stratification model with relative weights according to the regression coefficient of each independent predictors is shown in **Figure 1**. Patients with older than 60 years were assigned a score of 2; platelets >125 × 10^9/L and IL-6 >0.7 pg/mL were given a score of 3; ROX index <5.31 was assigned a score of 5.

The models had an AUC of 0.807 (0.76–0.85), 80.3% sensitivity, 71.2% specificity, and a greater accuracy than the ROX index alone (AUC = 0.779) in predicting the HFNC failure for COVID-19 patients (**Figure 2A**). The cutoff value of the models for the risk of HFNC failure stratification was six points.

For all patients allocated into training cohort, 55 patients were deceased on HFNC therapy due to do-not-intubate (excluded

TABLE 2 | Physiologic variables at HFNC initiation and 12 h of HFNC onset.

Parameters	All patients (n = 324)	HFNC success (n = 177)	HFNC failure (n = 147)	p-value success vs. failure
Heart rate at HFNC initiation	88.8 ± 16.3	87.0 ± 13.8	91.0 ± 18.7	0.0121
Systolic arterial pressure at HFNC initiation	129.2 ± 17.4	128.3 ± 17.0	130.3 ± 17.8	0.1612
Arterial blood gas analysis at HFNC initiation ‖				
pH	7.47 ± 0.05	7.46 ± 0.04	7.47 ± 0.07	0.1103
$Paco_2$, mm Hg	34.3 ± 7.7	34.9 ± 6.5	33.5 ± 9.1	0.0106
HCO_3^-, mmol/L	25.1 ± 5.4	25.6 ± 4.8	24.3 ± 6.1	0.1430
Pao_2/Fio_2, mm Hg	141.1 [115.6–188.9]	151.2 [122.8–199.2]	129.6 [100.0–163.4]	<0.001
<200 mm Hg	174 (79.8%)	96 (75.0%)	78 (86.7%)	0.025
Respiratory parameters at HFNC initiation				
Spo_2	86 [80–90]	88 [83–92]	84 [75–89]	<0.001
Spo_2/Fio_2	108.7 [91.6–143.3]	121.4 [100.0–150.0]	97.8 [85.4–112.5]	<0.001
RR (beats per minute)	25 [22–30]	24 [22–30]	26 [22–30]	0.1319
ROX index	4.3 [3.4–5.5]	4.9 [3.8–6.1]	3.8 [3.0–4.7]	0.0001
After HFNC treatment				
Spo_2	93 [90–96]	95 [92-96]	92 [89–94]	<0.001
Spo_2/Fio_2	117.5 [105.0–141.0]	134.2 [117.5–158.3]	108.7 [94.6–116.3]	<0.001
RR (beats per minute)	22 [21–24]	22 [20–24]	23 [22–25]	<0.001
Flow (L/min)	55.0 [50.0–60.0]	50.0 [50.0–60.0]	60.0 [50.0–60.0]	0.0005
ROX index	5.2 [4.6–6.4]	5.9 [5.0–7.5]	4.8 [4.1– 5.3]	<0.001
Length of HFNC, median [IQR], days	6.0 [3.0–11.0]	10.0 [7.0–15.0]	3.0 [1.0–4.0]	<0.001
Median time to MV, days¶	3 [1–6]	11 [9–18]	2 [1–4]	<0.001

COVID-19, coronavirus disease 2019; Fio_2, fraction of inspired oxygen; IQR, interquartile range; Pao_2, partial pressure of oxygen; $Paco_2$, partial pressure of carbon dioxide. ROX, Respiratory rate-oxygenation; SD, standard deviation; Data were expressed median [interquartile range] or as mean ± standard deviation.

‖*Arterial blood gas analysis was conducted in 90 HFNC failure patients and 128 success patients.*

¶*Median time to MV were available in 141 patients, because do-not-intubate or non-invasive ventilation intolerance was 32 in HFNC failure patients and 23 in success patients.*

from the further analysis); 142 (60.5%) patients required MV. The HFNC success probability (84.2%) for the patients who were divided into low-risk groups following the models was 9.84 times that in the high-risk group (34.8%) in hospital (**Figure 3A**).

External Validation of the Models in COVID-19 Patients With HFNC Therapy

Sixty-nine patients with COVID-19 were included into validation cohort. Baseline characteristics of the patients are shown in **Supplementary Tables 1**, **2**, and there was no significant difference in most characteristics between the two cohorts.

Twenty-six (34.7%) patients experienced HFNC failure within 7 days of HFNC initiation. The AUC of the novel models is 0.815 (0.70–0.93) (**Figure 2B**), sensitivity of prediction is 83.8%, and the specificity is 78.1% in prediction of HFNC failure on the basis of the variables from the scoring system. The HFNC success probability of patients is shown in **Figure 3B**.

DISCUSSION

Early identification of COVID-19 patients with AHRF during HFNC therapy at risk of failure will be beneficial for optimal use of medical resources. This retrospective cohort study on COVID-19 patients with AHRF showed that age older than 60 years, thrombocytopenia, elevated levels of IL-6 at HFNC initiation, and an ROX index <5.31 within the first 4 h of HFNC therapy initiation were independent predictors of HFNC failure. The risk-stratification model developed for HFNC therapy early predicts the need for MV with greater accuracy than the ROX index alone in COVID-19.

To our knowledge, this report was the largest cohort study to date regarding COVID-19 patients with HFNC therapy. Of patients with analyses on arterial blood gas, the median PaO_2/FIO_2 of 141.1 (IQR, 115.6–188.9) indicated the severity of respiratory failure. The HFNC functioned as a bridge between conventional oxygen therapy and MV (8, 16, 19). In our cohort, 36.7% patients with severe AHRF were successfully weaned from HFNC, which provided evidence to the recommendations of a trial of HFNC for COVID-19 patients with moderately severe hypoxemia to avoid the need for MV from recent WHO and other guidelines (7, 8, 26). It is reasonable that COVID-19 patients with less severe hypoxemia are more likely to wean from HFNC. In a study of 17 COVID-19 patients with HFNC in Chongqing, China, compared with 10 HFNC success patients with PaO_2/FIO_2 of 209 (IQR, 179–376) mm Hg, the seven HFNC failure patients had a median PaO_2/FIO_2 of 159 (IQR, 137–188) mm Hg (19). In another study, all the eight COVID-19 patients with a baseline mean PaO_2/FIO_2 of 259.88 mm Hg weaned from HFNC successfully and discharged from the hospital subsequently (27).

The global COVID-19 pandemic has led to an exploding demand for ventilators and medical service worldwide, for which many nations, including China, United States, United Kingdom, and Australia, struggled (28, 29). In face of severe shortage of ventilators and health care workers, a trial of HFNC treatment seems plausible, but brings new problems. Some patients may suffer from sudden respiratory arrest and even death during the trial, especially older patients. Our finding of variables derived before, at, and shortly after HFNC initiation predicting its success or failure is very promising to balance the need and the risk associated with the trial.

Tests on peripheral neutrophil count, thrombocyte count, and plasma IL-6 level are commonly conducted. Higher numbers of neutrophils in the peripheral blood correlated with the severity of lung damage (30). In our cohort, patients in the HFNC failure group had significantly higher neutrophil counts than those in the HFNC success group, but no difference in the proportion of neutrophilia was observed between the two groups. Most likely, of these COVID-19 patients with HFNC therapy, the severity of lung damage was comparable. In unselected COVID-19 patients, a low lymphocyte count indicates poor outcome, typically higher

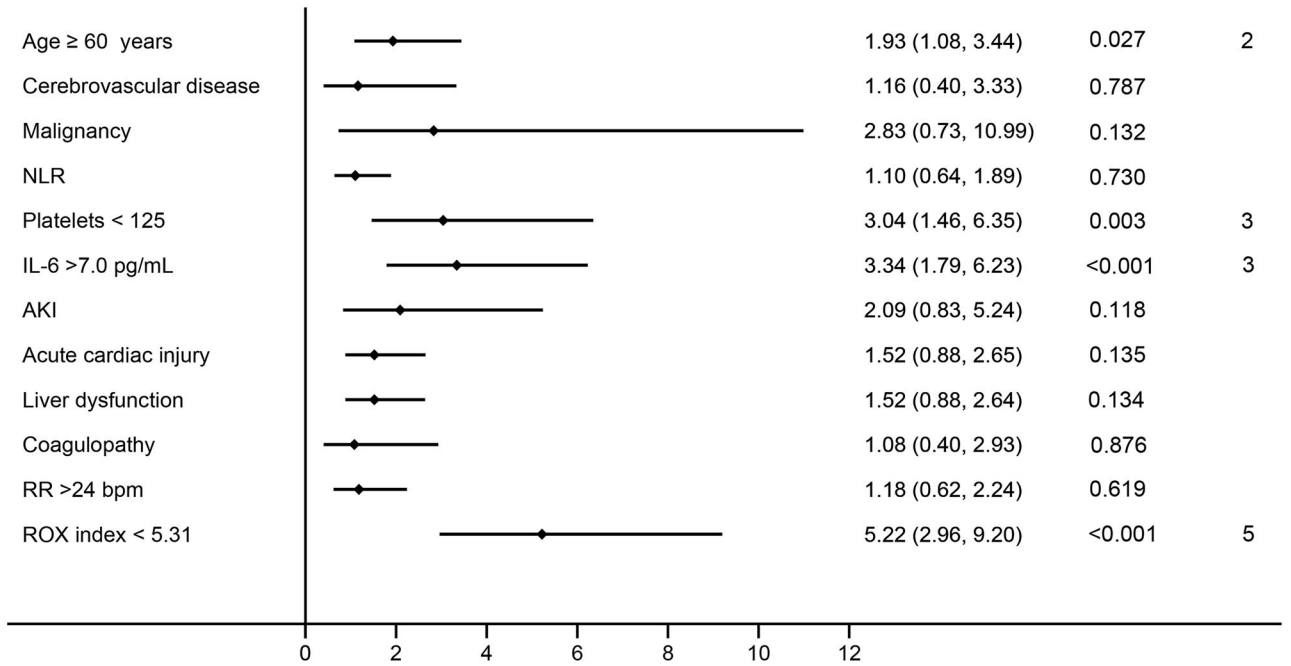

FIGURE 1 | Multivariate analysis and risk-stratification models of HFNC failure in COVID-19 patients. AKI, acute kidney injury; CI, confidence interval; HFNC, high-flow nasal cannula; IL-6, interleukin 6; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PLT, platelets; ROX, respiratory rate-oxygenation; RR, respiratory rate.

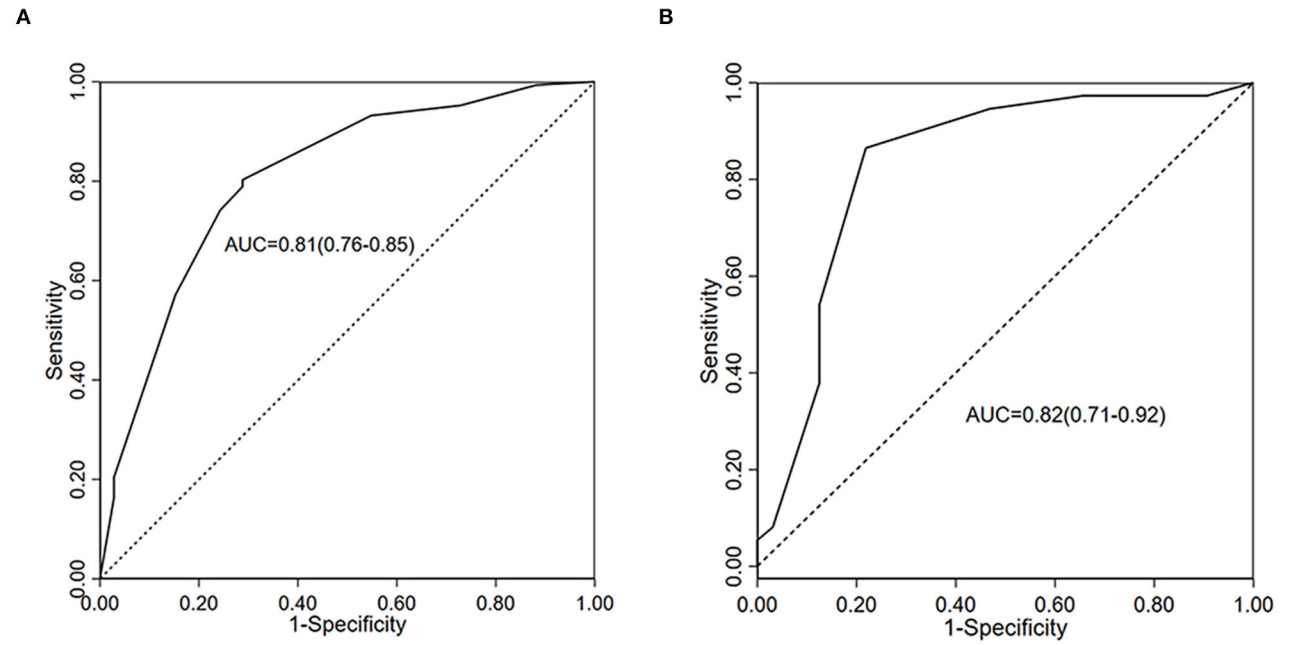

FIGURE 2 | ROC curves for prediction of HFNC failure in COVID-19 patients. **(A)** AUC of the full regression model in train cohort ($n = 324$); **(B)** AUC of the Validation cohort ($n = 69$). COVID-19, coronavirus disease 2019; HFNC, high-flow nasal cannula; ROC, receiver operator characteristic; AUC, area under the curve.

mortality. However, the lymphocyte counts were not different between patients in HFNC failure group and in the HFNC success group in our study. The primary reason is that the patients in our study were specifically selected. Only critically ill patients were included, and their median lymphocyte count was 0.6×10^9/L, which was the same as that in the non-survivors previously

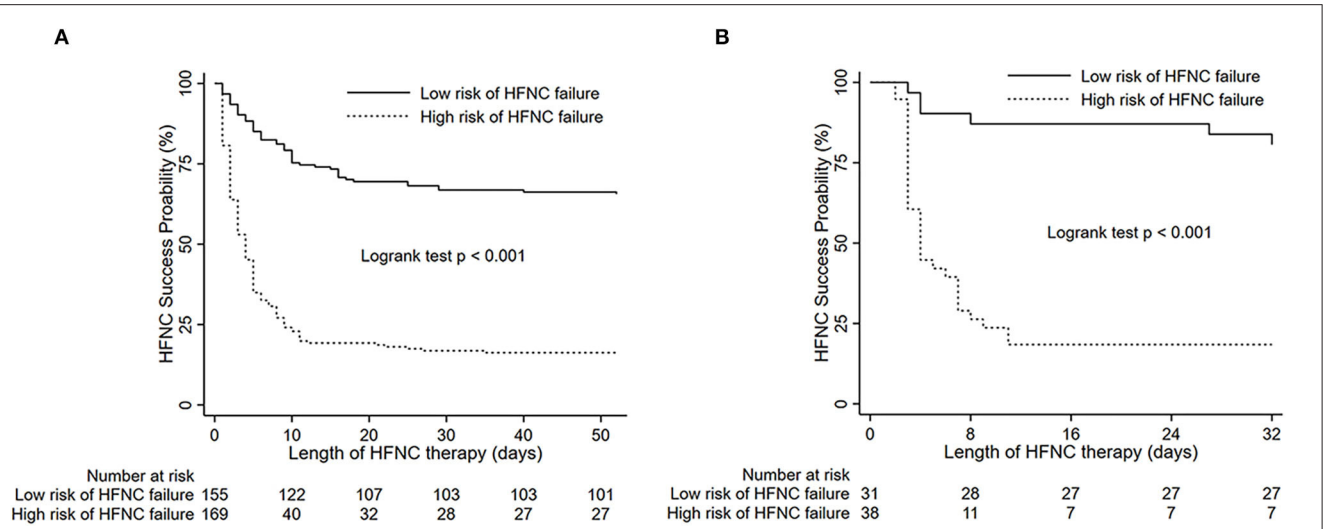

FIGURE 3 | Success curves of HFNC therapy in patients from HFNC onset to termination according to different levels of score. **(A)** Training cohort; **(B)** validation cohort; For HFNC failure in hospital: weighted score 0–6 = low risk; ≥6 = high risk. HFNC, high-flow nasal cannula.

reported (12, 13, 31). To explore the difference in lymphocyte count between the critically ill and the extremely critically ill, a cohort of much larger sample size will be needed. Elevated levels of IL-6, which appears to be from myeloid cells in COVID-19 patients, could predict the severity of the disease and the need for intensive care (32, 33). It occurred in 68.8% of patients in the present study, and the HFNC failure group had more patients with IL-6 above the upper limit of normal range.

ROX index, defined as the ratio of Sp_{O_2}/F_{IO_2} to RR, is easily measured at bedside, which has been considered a better predictor of HFNC success compared with Sp_{O_2}/F_{IO_2} or RR alone when measured at 2, 6, or 12 h after HFNC initiation in patients with severe community or hospital-acquired pneumonia (18, 23). ROX index ≥4.88 measured within 2–12 h of HFNC therapy was associated with increased likelihood of HFNC success in non-virus pneumonia (18, 23). In our study, COVID-19 patients who had an ROX index ≥5.31 within the first 4 h of HFNC therapy were less likely to need MV.

Advanced age, comorbidities, neutrophilia, and organ and coagulation dysfunction were statistically associated with the development of acute respiratory distress syndrome (ARDS) for COVID-19 patients, which is a determinant of the outcome of HFNC therapy (4); it is thus not reasonable to deny the important of characteristics and clinical parameters. Our novel scoring system covering COVID-19 patients' conditions, physiological variables, and laboratory detection had better predictive capacity in comparison with ROX index alone. Moreover, our scoring system shows promise for the early risk stratification of COVID-19 patients with HFNC therapy after appropriate weight.

MV is the rescue therapy for severe AHRF after HFNC failure (5, 7, 10, 34). In our study, among the patients receiving subsequent MV, 78.5% of these patients were deceased. When comparing the COVID-19 patients who received MV before and after 48 h of HFNC, there are no significant differences in 90-day mortality (**Supplementary Figure 1**). The proportion of patients who received the MV was different from the HFNC failure rate of patients within 7 days of HFNC onset. We postulated that the primary contributor for the difference was the progressive pathophysiological processes.

During the relatively early stage in patients with severe COVID-19, platelets take part in the formation of pulmonary microthrombi to block the viral invasion into bloodstream when SARS-CoV-2 infects the lung (35, 36). The pathophysiological process causes thrombocytopenia and elevation of IL-6, a key proinflammatory cytokine in thromboinflammatory processes (37–39). In general, pulmonary microthrombi lead to shunt in the lung vasculature, but not to decrease in lung volume, which explains the development of atypical ARDS, and so-called silent hypoxemia (40–42).

This study had several limitations. First, during the pandemic of COVD-19, oxygen therapy was the cornerstone of treating severe and critically ill patients, on which it was hard to conduct randomized controlled study. Our study was a retrospective study from a severely stricken place by the disease. The findings were at least informative to physicians from similar locations. Second, some important data, for example, Pa_{O_2}/F_{IO_2}, were not available for all the patients and were not included in the regression model. However, all the identified predictors were readily accessible, except for places with extremely limited resources. Third, the sample size is not large enough, and we are expecting further studies.

CONCLUSIONS

Thrombocytopenia, elevated levels of IL-6 at HFNC initiation, and an ROX index <5.31 within the first 4 h of HFNC therapy were independent predictors of HFNC failure, and the risk-stratification model on the basis of the four parameters, has a strong predictive ability for the need for MV in COVID-19 patients with HFNC therapy and can further classify the risk

of HFNC failure. The mortality of HFNC failure patients who received MV before and after 48 h of HFNC therapy was not associated with a worse prognosis. A practical oxygen therapy for severe COVID-19 based on our findings may be proposed to prevent from or relieve the overwhelmed health care systems in resource-limited countries, where ICU devices and techniques may not be available or ICU care cannot be provided.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Wuhan Union Hospital (2020-0041-1). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JX, XY, CH, XZo, TZ, SP, LY, YWu, YO, YWa, HQ, and SF collected the epidemiological and clinical data. JX, XY, XZh, WX, DX, LY, and LR summarized all data. JX, XY, LY, YY, HL, YS, and SF contributed to literature search and drafted the manuscript. DC, SY, DZ, and YS designed the study, have full access to all the data and take full responsibility for accuracy of the analyses and their interpretation. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2020.607821/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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D-dimer, Troponin, and Urea Level at Presentation With COVID-19 can Predict ICU Admission: A Single Centered Study

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Background: Identifying clinical-features or a scoring-system to predict a benefit from hospital admission for patients with COVID-19 can be of great value for the decision-makers in the health sector. We aimed to identify differences in patients' demographic, clinical, laboratory, and radiological findings of COVID-19 positive cases to develop and validate a diagnostic-model predicting who will develop severe-form and who will need critical-care in the future.

Methods: In this observational retrospective study, COVID-19 positive cases (total 417) diagnosed in Al Kuwait Hospital, Dubai, UAE were recruited, and their prognosis in terms of admission to the hospital and the need for intensive care was reviewed until their tests turned negative. Patients were classified according to their clinical state into mild, moderate, severe, and critical. We retrieved all the baseline clinical data, laboratory, and radiological results and used them to identify parameters that can predict admission to the intensive care unit (ICU).

Results: Patients with ICU admission showed a distinct clinical, demographic as well as laboratory features when compared to patients who did not need ICU admission. This includes the elder age group, male gender, and presence of comorbidities like diabetes and history of hypertension. ROC and Precision-Recall curves showed that among all variables, D dimers (>1.5 mg/dl), Urea (>6.5 mmol/L), and Troponin (>13.5 ng/ml) could positively predict the admission to ICU in patients with COVID-19. On the other hand, decreased Lymphocyte count and albumin can predict admission to ICU in patients with COVID-19 with acceptable sensitivity (59.32, 95% CI [49.89–68.27]) and specificity (79.31, 95% CI [72.53–85.07]).

Conclusion: Using these three predictors with their cut of values can identify patients who are at risk of developing critical COVID-19 and might need aggressive intervention earlier in the course of the disease.

Keywords: COVID-19, severe COVID-19 prediction, risk stratification, ICU - Intensive care unit, SARS-CoV-2

BACKGROUND

The pandemic of (COVID-19), which began at the end of 2019, represents an international public health emergency (1). Most patients with this disease suffer from mild to moderate illnesses (2). However, a small percentage of those patients suffer from more severe illnesses that can rapidly progress into a more critical form. This includes ARDS and acute respiratory failure, in addition to metabolic acidosis, coagulopathies, and septic shock (3). Depending on patient characteristics and the studied population, ICU admission varies between 5 and 16% of the total number of patients (4). The widespread of the disease led to a rapid overwhelming of the public health system of different countries, including the intensive care units (5), with some countries reaching a critical care crisis (6).

The current pandemic increased the burden substantially on acute and critical care services exceeding existing hospital capacity around the world (7). Managing the expected surges in intensive care capacity requires focused intensive care abilities and requirements to minimize loss of life and maintain control (8). Due to the increasing numbers of recorded positive COVID-19 cases, the medical teams in the front line are in urgent need of a tool that helps their clinical judgment to identify the few that will progress to critical cases.

A stratification tool for non-severe COVID-19 patients at admission can direct the resources and control the spread more efficiently and persevere the health team's power (9). The use of prediction models for COVID-19 will support medical decision making but are still poorly reported (10). The decisions of easing the preventive measures in countries that passed the peak of transmission are complicated with the anticipation of a second wave that necessitates a sufficiently prepared action plan for handling cases on admission (11). Identifying clinical features or a scoring system to predict a benefit from hospital admission for patients with COVID-19 can be of great value for the decision-makers in the health sector.

Right now, there are few reliable, applicable, or useable clinical models or scoring systems to predict if a tested positive for COVID-19 should be admitted to the hospital or asked to stay home especially in regions like the middle east using local patients parameters for prediction (12). During the manuscript writing, a scoring system of COVID-19 (CSS) was suggested that could help clinicians to identify high-risk patients with poor prognosis (13). Another promising predictive tool PREDI-CO score was suggested to be useful in resource allocation and treatment prioritization during the COVID-19 pandemic (14). We aimed to identify differences in patients' demographic, clinical, laboratory, and radiological findings between mild, severe, and critical cases of COVID-19 positive cases to develop and validate a diagnostic model predicting who will develop severe form and who will need critical care throughout the course of the disease.

MATERIALS AND METHODS

Patients Data Collection

In this observational retrospective study, COVID-19 positive patients (total 417) admitted between January to June 2020 were recruited from Al Kuwait Hospital, Dubai, UAE. Those patients are consecutive patients approaching the hospital for COVID-19 related symptoms and were enrolled with the following inclusion criteria: Adult patients (above 18 years) with COVID-19 (confirmed by nasopharyngeal polymerase chain reaction; PCR positive sample). Complete current and past medical history, along with their demographic data, a history of a recent travel or contact with a confirmed or suspected case were documented.

The cohort was divided into two subgroups, the training group to identify predictors of ICU admission ($n = 128$) who were admitted between January and February and the validation group ($n = 289$) who were admitted in March till June 2020. The study was approved by the Ministry of Health and Prevention (MOHAP) Research Ethics Committee number (MOHAP/DXB-REC/MMM/NO.44/2020). The main presenting symptoms were enlisted, including [fever, cough, fatigue, anorexia, shortness of breath (SOB), sputum production, myalgias, headache, confusion, rhinorrhea, sore throat, hemoptysis, vomiting, diarrhea, nausea, anosmia, and ageusia]. Risk factors for severe illness were examined, including old age, cardiovascular diseases (CVD), diabetes mellitus (DM), hypertension (HTN), prior stroke and or transient ischemic attack, cancer, chronic lung disease, and chronic kidney disease (CKD).

Patients Classification

Patients were classified according to "Clinical Management of Critically Ill COVID-19 Patients" guidelines (Version 1- April 15, 2020) issued by MOHAP (6). Accordingly, patients were classified into mild illness, pneumonia, and severe pneumonia (fever or suspected respiratory infection, plus one of the following: respiratory rate >30 breaths/min, severe respiratory distress, and SpO2 $\leq$ 93% on room air). Severe cases that needed oxygen therapy with no response to titrated oxygen therapy will require ICU treatment.

Criteria for ICU Admission

All patients were managed by same protocol and were evaluated by the same intensivists available during their admission period. Admission criteria for ICU followed the hospital policy ABH/CLN/033/V02, 2017, revised 2020. All physicians followed the same protocol. Severity at the time of admission (as per the criteria already defined): Severe disease: 9/39, and Critical disease: 30/39.

Blood and Radiological Tests

Laboratory tests were retrieved that include (1) complete blood count, including neutrophil count lymphocyte count, heamoglobin; Hb, white cell count; WCC, and platelets count, (2) coagulation profile, including interenational normalized ratio; INR, Prothrombin time; PT, (3) electrolytes, including sodium; Na and potassium; K, (4) renal function tests, including urea, creatinine, and estimated glomerular filtration rate; eGFR, (5) liver function tests, including total serum bilirubin, alanine aminotransferase; ALT, aspartate aminotransferase; AST, alkaline phosphatase; ALP, and albumin, (6) inflammatory markers, including C-reactive protein; CRP, D-dimers, lactate dehydrogenase; LDH, procalcitonin and ferritin. For risk of

severe cases, the presence of lymphopenia, neutrophilia, high ALT/AST, high LDH, high CRP, high ferritin, high d-dimer, and high pro-calcitonin, above the age and gender-matched references were used as indicators of risk. Admission chest X-Ray (presence of bilateral air consolidation), and computerized tomography (CT) scan (presence of bilateral peripheral ground-glass opacities) were documented.

Statistical Analysis

For all statistical analyses and tests, SPSS was used (Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). The Chi-Square Test of Independence was used to examine the association between categorical variables while student's *t*-test was used for continuous variables groups means comparison.

Patients were grouped into those that didn't need ICU and those who needed it. ROC Curve, Precision-Recall Curve, and Overall model quality options in SPSS were used to identify predictors of ICU admission and their cutoff values.

The normality test for all groups was done by Shapiro-Wilk tests using SPSS, and sig. of all independent variables> 0.05 means that all groups were normally distributed.

RESULTS

Patients Needed ICU Were Older Men With Less Contact History

Training cohorts ($n = 128$) were divided into those who needed ICU ($n = 39$, 30.5%) "ICU" and those who didn't need ICU ($n = 89$, 69.5%) "No ICU." Patients who needed ICU were older (57 ± 13 years old) than No ICU patients (44 ± 15 years old) ($p = 0.0001$). 36 (92.3%) of the ICU group were males compared to 66 (74.2%) in the No ICU group ($p = 0.019$). Documented contact history with a positive case of COVID-19 was more prevalent in the No ICU group ($n = 26$, 29.2%) compared to ($n = 3$, 7.7%) in ICU patients, as shown in **Table 1**. There was no difference in their BMI (28.42–27.49) or Duration of illness before approaching the hospital ($5–7 \pm 3$ days).

Patients Needed ICU Presented More With SOB and Fever

Patients needed ICU admission presented more SOB ($n = 29$, 74.4%) than No ICU ($n = 33$, 37.1%), $P < 0.001$ and with fever ($n = 30$, 76.9%) compared to No ICU ($n = 53$, 59.6%), $p = 0.05$), as shown in **Table 2**.

Patients Needed ICU Showed Distinct Laboratory Findings

Patients needed ICU admission showed a higher Neutrophil count, WCC, Urea, creatinine, AST, CRP, D Dimer, LDH, Ferritin, and Troponin but lower Hb, eGFR, and albumin compared with No ICU patients, as shown in **Table 3**.

Patients Needed ICU Showed More CXR and Less CT Scan Opacities

Patients needed ICU admission showed more frequency of consolidations identified by chest X-Ray ($n = 32$, 82.1%) than No ICU group ($n = 43$, 57.3%), $p = 0.001$. Bilateral peripheral ground-glass opacities (GGO) documented by chest CT scan was higher in No ICU patients ($n = 64$, 71.9%) compared to ($n = 23$, 59.0%) in ICU patients, as shown in **Table 4**.

Patients Needed ICU Required Multiple In-patient Treatments

More patients needed ICU admission were treated with Lopinavir-ritonavir ($n = 32$, 82.1%); $p = 0.05$, Favipiravir ($n = 19$, 48.7%); $p = 0.024$, intravenous (IV) AB($n = 38$, 97.4%); $P < 0.001$, IV steroids ($n = 32$, 100%); $P < 0.001$, Tocilizumab ($n = 26$, 66.7%); $P < 0.001$, and Antifungal ($n = 10$, 25.6%); $P < 0.001$ than No ICU patients, as shown in **Table 5**.

Patients Needed ICU Showed a Higher Rate of Clinical Complications and Death

Patients needed ICU admission developed more complications like Acute cardiac injury, Acute kidney injury, acute liver injury, Acidosis, Ventilated, Acute Respiratory Distress Syndrome (ARDS), Septic shock with higher mortality when compared to No ICU patients, as shown in **Table 6**.

High D Dimer, Troponin, and Urea Can Positively Predict the Admission to ICU in Patients With COVID-19

Probabilistic forecasts for binary classification (ICU vs. NO ICU) predictive modeling using ROC Curves and Precision-Recall curves showed that among all variables D dimers (>1.5 mg/dl), Urea (>6.5 mmol/L), and Troponin >13.5 ng/ml) can positively predict the admission to ICU in patients with COVID-19. On the other hand, decreased Lymphocyte count and albumin can predict admission to ICU in patients with COVID-19, as shown in **Table 7** and **Figure 1**.

Validation of the Three Predictors on a Larger Cohort of COVID-19 Patients

In order to validate the performance of these three markers in a larger cohort, we explored the Sensitivity and Specificity of using these parameters in the 289-validation cohort who attended the hospital between March and June 2020. Patients who showed D dimers (>1.5), Urea (>6.5 mmol/L), and Troponin >13.5 ng/ml were checked whether they would need ICU admission or not. Using the three markers gave low sensitivity (30.25%; 22.17–39.35%) but high specificity (93.10%; 88.26–96.39%) to predict ICU admission. Using any two of the three markers gave moderate sensitivity (59.32%, 49.89–68.27%) but high specificity (79.31%; 72.53–85.07%) to predict ICU admission. Using any one of the three markers gave high sensitivity (85.47%; 77.76–91.30%) but low specificity (45.98%; 38.41–53.68%) to predict ICU admission, as shown in **Table 8**.

DISCUSSION

Better understanding and identification of risk factors that might predispose for ICU admission might be essential for more active medical decision-making that might lead to optimal clinical

TABLE 1 | Demographic characteristics of the training and validation cohort.

Training cohort		**ICU_Admin**						
		No ICU			**ICU**			***P*-value**
		Count	**Row *N* %**	**Column *N* %**	**Count**	**Row *N* %**	**Column *N* %**	
Sex	F	23	88.5	25.8	3	11.5	7.7	0.019*
	M	66	64.7	74.2	36	35.3	92.3	
Travel history	No	83	68.6	93.3	38	31.4	97.4	0.339[b]
	Yes	6	85.7	6.7	1	14.3	2.6	
Contact history	No	63	63.6	70.8	36	36.4	92.3	0.007*
	Yes	26	89.7	29.2	3	10.3	7.7	
Validation cohort		**ICU_Admin**						
		No ICU			**ICU**			***P*-value**
		Count	**Row *N* %**	**Column *N* %**	**Count**	**Row *N* %**	**Column *N* %**	
Sex	F	70	89.7%	30.3%	8	10.3%	6.3%	0.000*
	M	161	57.5%	69.7%	119	42.5%	93.7%	
Travel history	No	211	62.8%	91.3%	125	37.2%	98.4%	0.008*
	Yes	20	90.9%	8.7%	2	9.1%	1.6%	
Contact history	No	165	59.6%	71.4%	112	40.4%	88.2%	0.000*
	Yes	66	81.5%	28.6%	15	18.5%	11.8%	

Pearson Chi-Square Tests.

**The Chi-square statistic is significant at the 0.05 level.*

N, number; F, females; M, males; ICU, intensive care unit; ICU_Admin, admission to the ICU.

practice to improve patients outcomes. Our results showed a significant difference in the pre-admission demographic, clinical, as well as laboratory characteristics of the ICU, admitted group when compared to non-admitted group.

Our study showed that patients needed ICU were older men with less contact history. Indeed, the association between ICU admission and elder age group was previously described in several reports that also showed the median age of critical/death groups to be higher than that of non-critical group groups (15–17). Older age and male sex were found to be independent risk factors for poor outcome of the illness in many reports (18). Specifically, older patients (>65 years) with comorbidities are at increased risk of death (19) where older age can independently predict the 60-day mortality after ICU admission (20). Such patients need careful observation and early intervention to prevent the potential development of severe COVID-19 (21).

On the other hand, disparities in the sex and gender observed in COVID-19 vulnerability was documented in many parts of the world (22). The majority of affected patients have been male who had more refractory disease and death (23). Gender differences in the COVID-19 outbreak should be taking into consideration in understanding the disease burden and dynamics of health emergency on individuals and communities (24). Male patients with heart injury, hyperglycemia, and high-dose corticosteroid were shown to have a high risk of death (21).

Our note that documented contact history with a positive case of COVID-19 was more prevalent in the No ICU group compared to ICU patients brings attention to the importance of the part of the asymptomatic carrier of the stories. Having contact with such asymptomatic carriers might be long enough to have more chances to present with the severe disease than the COVID-19 patients who came with known contact history as he will seek help earlier in the course of the disease. Asymptomatic carriers are prone to be mildly ill with the communicable period up to 3 weeks, and the communicated patients could develop severe illness (25).

Patients needed ICU admission presented more SOB and fever than No ICU patients. A systematic literature review and meta-analysis showed that among clinical manifestations, like fever, shortness of breath, or dyspnea, were associated with the progression of the disease (15). It is widely accepted that most of the COVID-19 patients will present with fever, cough, fatigue, and dyspnea, and fever is the most common symptom in patients with COVID-19 (26). Patients with severe COVID-19 are reported to have more silent hypoxemia, and coronavirus was suspected of having an idiosyncratic action on receptors involved in chemosensitivity to oxygen (27). Additionally, higher ferritin was higher in our cohort, which needed ICU admission compared to the No ICU group. Some reports document that high serum ferritin is a poor prognostic factor (28) as it represents a crucial mediator of immune dysregulation, contributing to the cytokine storm with fatal outcomes in COVID-19 (29).

Patients needed ICU admission showed a lower hemoglobin level compared with No ICU patients. So another explanation was linked to a hemoglobinopathy, hypoxia, and cell iron overload in COVID-19 patients due to direct SARS-CoV-2 interaction with hemoglobin molecule or hepcidin-mimetic

TABLE 2 | Chief presentation in the training cohort.

		ICU_Admin						*P*-value
		No ICU			ICU			
		Count	Row *N* %	Column *N* %	Count	Row *N* %	Column *N* %	
SOB	No	56	84.8	62.9	10	15.2	25.6	0.000*
	Yes	33	53.2	37.1	29	46.8	74.4	
Fever	No	36	80.0	40.4	9	20.0	23.1	0.058
	Yes	53	63.9	59.6	30	36.1	76.9	
Cough	No	43	70.5	48.3	18	29.5	46.2	0.822
	Yes	46	68.7	51.7	21	31.3	53.8	
Fatigue	No	81	68.1	91.0	38	31.9	97.4	0.191
	Yes	8	88.9	9.0	1	11.1	2.6	
Anorexia	No	88	69.8	98.9	38	30.2	97.4	0.545
	Yes	1	50.0	1.1	1	50.0	2.6	
Sputum production	No	87	69.6	97.8	38	30.4	97.4	0.913
	Yes	2	66.7	2.2	1	33.3	2.6	
Myalgias	No	74	67.3	83.1	36	32.7	92.3	0.170
	Yes	15	83.3	16.9	3	16.7	7.7	
Headache	No	82	68.9	92.1	37	31.1	94.9	0.577
	Yes	7	77.8	7.9	2	22.2	5.1	
Rhinorrhea	No	85	69.1	95.5	38	30.9	97.4	0.604
	Yes	4	80.0	4.5	1	20.0	2.6	
Sore throat	No	82	68.9	92.1	37	31.1	94.9	0.577
	Yes	7	77.8	7.9	2	22.2	5.1	
Vomiting	No	88	69.3	98.9	39	30.7	100.0	0.506
	Yes	1	100.0	1.1	0	0.0	0.0	
Diarrhea	No	85	69.1	95.5	38	30.9	97.4	604
	Yes	4	80.0	4.5	1	20.0	2.6	
Nausea	No	87	69.0	97.8	39	31.0	100.0	0.345
	Yes	2	100.0	2.2	0	0.0	0.0	

Pearson Chi-Square Tests.

**The Chi-square statistic is significant at the 0.05 level.*

N, number; ICU, intensive care unit; ICU_Admin, admission to the ICU; SOB, shortness of breath.

action of a viral spike protein leading to an oxygen-deprived blood disease, with iron metabolism dysregulation (30). In a case study, recombinant human erythropoietin (rhEPO) was suggested to attenuate respiratory distress syndrome by enhancing leukocyte release from bone marrow and iron redistribution away from the intracellular virus (31).

Patients needed ICU admission showed a higher Neutrophil count and WCC compared with No ICU patients. Autopsy of COVID-19 patient's lungs showed infiltration of neutrophils with an aberrant neutrophil extracellular traps (NETs) formation that correlates with the clinical severity of COVID-19 (32). Enhanced neutrophil infiltration can induce necroinflammation that contributes to the higher mortality of COVID-19 in patients with underlying comorbidities (33). Recently, it was suggested that SARS-CoV2 could evade the innate immune response, causing uncontrolled NETs formation that leads to multi-organ failure (34).

Higher urea, creatine, and lower eGFR in ICU patients indicate the well-documented impact of COVID-19 on renal functions. Preexisting kidney disease on admission and/or the development of acute kidney injury (AKI) in patients with COVID-19 during hospitalization is high and is associated with in-hospital mortality (35). Usually, such AKI is resolved within 3 weeks after the onset of symptoms, but renal complications will lead specifically to higher mortality (36).

Patients needed ICU admission showed a higher AST and lowered albumin compared with No ICU patients that might indicate a hepatic injury. Digestive symptoms and liver injury have been reported during the course of the COVID-19 (37). It is well–known that patients with COVID-19 had liver comorbidities or reported abnormal levels of alanine aminotransferase and aspartate aminotransferase (AST) during disease progression (38). It is uncertain whether the COVID-19-related liver damage/dysfunction is caused by direct

TABLE 3 | Laboratory parameters in the training cohort.

	ICU_Admin				*P*-value
	No ICU		ICU		
	Mean	Standard error of mean	Mean	Standard error of mean	
Neutrophil count (× 10(3)/mcL)	5.44	0.38	8.46	0.74	$P < 0.05$
Hemoglobin (gm/dL)	13.56	0.21	12.58	0.27	$P < 0.05$
WBC (× 10(3)/mcL)	7.69	0.39	9.93	0.83	$P < 0.05$
Urea (mmol/L)	4.90	0.26	11.60	2.53	$P < 0.05$
Creatinine (umol/L)	86.214	5.076	174.188	57.107	$P < 0.05$
eGFR (mL/min/1.73m^2)	95.6	3.1	70.8	5.3	$P < 0.05$
AST (U/L)	44	3	61	6	$P < 0.05$
Albumin (gm/L)	33.1	0.7	25.8	1.1	$P < 0.05$
CRP (mg/l)	64.65	14.48	161.85	16.45	$P < 0.05$
D-dimers (mg/dL)	2	1	7	2	$P < 0.05$
LDH (IU/L)	346	20	530	41	$P < 0.05$
Ferritin (mcg/L)	933	137	1,773	295	$P < 0.05$
Troponin (ng/ml)	25	10	234	122	$P < 0.05$
ALP (IU/L)	87.56	5.26	105.49	10.17	ns
Lymphocyte count (× 10(3)/mcL)	3.62	2.05	0.91	0.07	ns
Platelet count (× 10(3)/mcL)	239	10	243	14	ns
INR (seconds)	1	0	1	0	ns
Prothrombin time (seconds)	13	0	13	0	ns
Na (mmol/L)	136.8	0.4	136.9	0.9	ns
K (mmol/L)	4.09	0.06	4.21	0.12	ns
S bil (μmol/L)	17.3	4.8	17.8	2.1	ns
ALT (IU/L)	62	5	58	6	ns
Procalcitonin (ug/L)	1	1	3	2	ns
Lactic acid	2	0	2	0	ns
Hba1c (%)	7.9	0.3	8.2	0.3	ns

ICU, intensive care unit; ICU_Admin, admission to the ICU; p-value significant > 0.05, WCC, white cell count; eGFR, estimated glomerular filtration rate; AST, Aspartate aminotransferase; CRP, C-reactive protein; LDH, lactate dehydrogenase; ALP, Alkaline phosphatase; INR, international normalized ratio; Na, sodium; K, potassium; S bil, serum bilirubin; ALT, Alanine aminotransferase; HbA1C, glucosylated hemoglobin.
T-test was used to compare means between the groups.

TABLE 4 | Chest X-Ray and CT Scan on admission in the training cohort.

		ICU_Admin						*P*-value
		No ICU			ICU			
		Count	Row *N* %	Column *N* %	Count	Row *N* %	Column *N* %	
CXR	Consolidation	43	57.3	48.3	32	42.7	82.1	0.001*
	Normal	33	91.7	37.1	3	8.3	7.7	
	NOT Done	13	76.5	14.6	4	23.5	10.3	
CT chest:	Bilateral peripheral ground-glass opacities.	64	73.6	71.9	23	26.4	59.0	0.000*
	Normal	23	85.2	25.8	4	14.8	10.3	
	NOT Done	2	14.3	2.2	12	85.7	30.8	

Pearson Chi-Square Tests.
**The Chi-square statistic is significant at the 0.05 level.*
N, number; ICU, intensive care unit; ICU_Admin, admission to the ICU; CXR, chest X-ray; CT, computed tomography.

viral infection, as a consequence of the use of potentially hepatotoxic drugs, or as part of the multiple organ dysfunction in COVID-19 (39).

Patients needed ICU admission showed a higher C-reactive protein (CRP) and LDH compared with No ICU patients. This goes with the reports that found that the level of plasma CRP

TABLE 5 | Major medications used in the training cohort.

In-patient treatment		ICU_Admin						*P*-Value
		No ICU			ICU			
		Count	Row *N* %	Column *N* %	Count	Row *N* %	Column *N* %	
Lopinavir-ritonavir	No	31	81.6	34.8	7	18.4	17.9	0.054
	Yes	58	64.4	65.2	32	35.6	82.1	
Favipiravir	No	64	76.2	71.9	20	23.8	51.3	0.024*
	Yes	25	56.8	28.1	19	43.2	48.7	
IV antibiotics	No	47	97.9	52.8	1	2.1	2.6	0.000*
	Yes	42	52.5	47.2	38	47.5	97.4	
IV steroids	No	57	89.1	64.0	7	10.9	17.9	0.000*
	Yes	32	50.0	36.0	32	50.0	82.1	
Tocilizumab	No	83	86.5	93.3	13	13.5	33.3	0.000*
	Yes	6	18.8	6.7	26	81.3	66.7	
Antifungal	No	84	74.3	94.4	29	25.7	74.4	0.000*
	Yes	5	33.3	5.6	10	66.7	25.6	
Chl/HQ	No	4	44.4	4.5	5	55.6	12.8	0.090
	Yes	85	71.4	95.5	34	28.6	87.2	
Interferon	No	67	72.8	75.3	25	27.2	64.1	0.195
	Yes	22	61.1	24.7	14	38.9	35.9	

Pearson Chi-Square Tests.
**The Chi-square statistic is significant at the 0.05 level.*
N, number; ICU, intenseive care unit; ICU_Admin, admission to the ICU; IV, intravenous; Chl/HQ, chloroquine/hydroxychloroquine.

TABLE 6 | In-hospital complication developed in the training cohort.

Complications		ICU_Admin						*P*-value
		No ICU			ICU			
		Count	Row *N* %	Column *N* %	Count	Row *N* %	Column *N* %	
Acute cardiac injury	No	85	87.6	95.5	12	12.4	30.8	0.000*
	Yes	4	12.9	4.5	27	87.1	69.2	
Acute kidney injury	No	86	89.6	96.6	10	10.4	25.6	0.000*
	Yes	3	9.4	3.4	29	90.6	74.4	
Acute liver injury	No	81	78.6	91.0	22	21.4	56.4	0.000*
	Yes	8	32.0	9.0	17	68.0	43.6	
Acidosis	No	89	89.0	100.0	11	11.0	28.2	0.000*
	Yes	0	0.0	0.0	28	100.0	71.8	
Ventilated	No	88	88.0	98.9	12	12.0	30.8	0.000*
	Yes	1	3.6	1.1	27	96.4	69.2	
ARDS	No	82	94.3	92.1	5	5.7	12.8	0.000*
	Yes	7	17.1	7.9	34	82.9	87.2	
Septic shock	No	88	88.0	98.9	12	12.0	30.8	0.000*
	Yes	1	3.6	1.1	27	96.4	69.2	
Death	No	89	89.0	100.0	11	11.0	28.2	0.000*
	Yes	0	0.0	0.0	28	100.0	71.8	

Pearson Chi-Square Tests.
**The Chi-square statistic is significant at the 0.05 level.*
N, number; ICU, intensive care unit; ICU_Admin, admission to the ICU; ARDS, acute respiratory distress syndrome.

was positively correlated to the severity of COVID-19 pneumonia and can be useful as an earlier indicator for severe illness (40). In severe COVID-19 patients, CRP increased significantly before CT findings. Importantly, CRP, which was associated with disease development (41). Patients with positive RT-PCR had a significantly higher neutrophil count, CRP, lactate dehydrogenase

TABLE 7 | Probabilistic forecasts for binary classification (ICU vs. NO ICU) predictive modeling using ROC Curves and Precision-Recall curves.

Area under the ROC curve					
Test result variable(s)	**Area**	**Std. error**	**Asymptotic Sig.**	**Asymptotic 95% confidence interval**	
				Lower bound	**Upper bound**
Troponin	0.804	0.048	0.000	0.709	0.899
D dimers	0.744	0.053	0.000	0.639	0.848
Urea	0.726	0.056	0.000	0.616	0.836
Lymphocyte count	0.252	0.050	0.000	0.154	0.349
Albumin	0.256	0.056	0.000	0.146	0.366

The test result variable(s): Troponin (high sensitivity troponin I) ND, not done; D, dimers; Urea, Lymphocyte count, albumin has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased+.

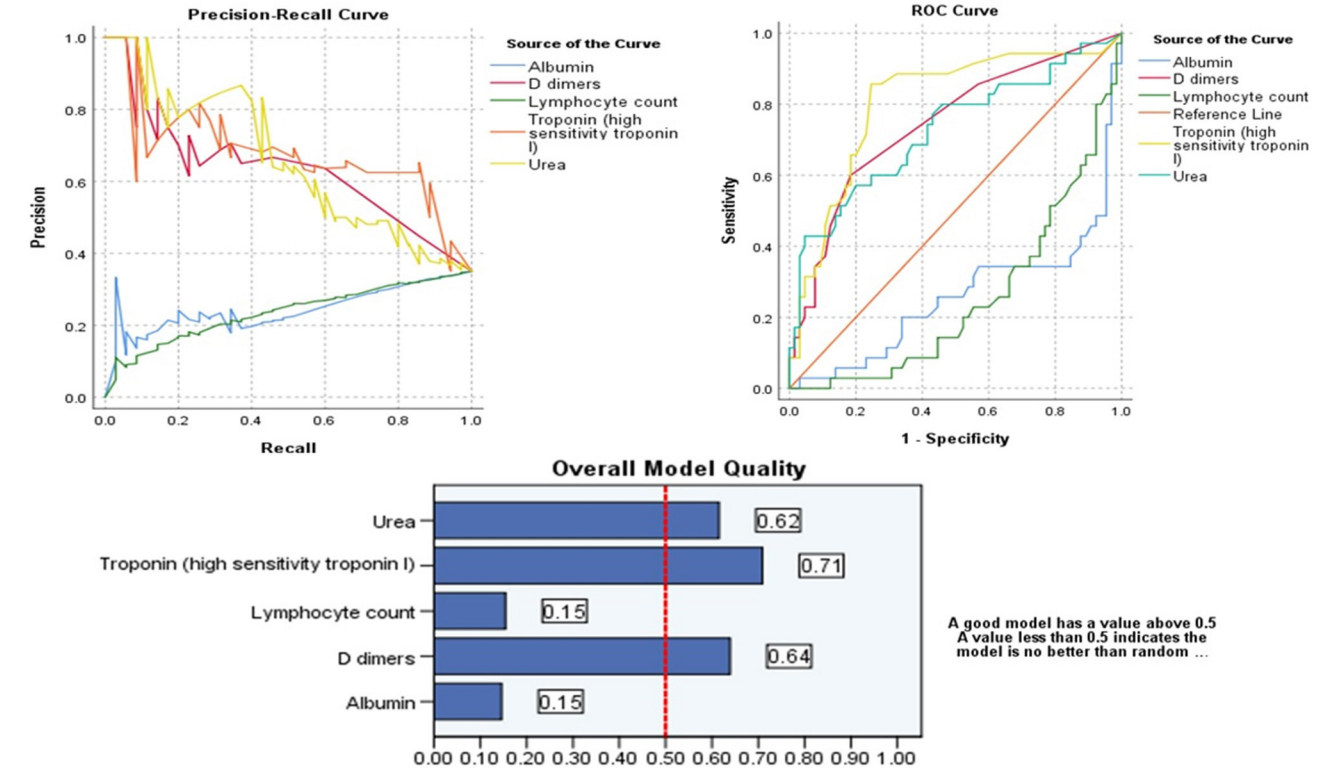

FIGURE 1 | Probabilistic forecasts for binary classification (ICU vs. NO ICU) predictive modeling using ROC Curves, Precision-Recall curves of the significant parameters and Overall Model Quality.

TABLE 8 | Validation of the three predictors on a larger cohort ($n = 289$) of COVID-19 patients suing to show different Sensitivity, Specificity, Positive Likelihood Ratio, and Negative Likelihood Ratio.

	Using the 3 markers		**Using any 2 of the markers**		**Using any 1 of the markers**	
Statistic	**Value**	**95% CI**	**Value**	**95% CI**	**Value**	**95% CI**
Sensitivity	30.25	22.17–39.35	59.32	49.89–68.27	85.47	77.76–91.30
Specificity	93.10	88.26–96.39	79.31	72.53–85.07	45.98	38.41–53.68
Positive likelihood ratio	4.39	2.38–8.08	2.87	2.07–3.98	1.58	1.35–1.85
Negative likelihood ratio	0.75	0.66–0.85	0.51	0.41–0.65	0.32	0.20–0.50

(LDH), and Urea levels in serum (42). Serum LDH decline was shown to predict a favorable response to the treatment of COVID-19 infection (43).

Patients needed ICU admission showed more frequency of consolidations identified by chest X-Ray than the No ICU group. Bilateral peripheral GGO documented by chest CT scan was higher in No ICU patients compared to ICU patients. Chest CT is well-accepted as a standard method for the rapid diagnosis of COVID-19 (44). Typically COVID-19 pneumonia CT imaging abnormalities vary from focal unilateral to diffuse bilateral GGO that can be detected even in asymptomatic patients (45). Identification of GGO and a single lesion on the initial CT scan might suggest early-phase disease (46). So the lower incidence of GGO in the ICU group might indicate either it is not specific to severe cases or might indicate a false indication that the cases are not severe and might delay the actions needed.

Our results showed that patients who showed D dimers (>1.5 mg/dl), Urea (>6.5 mmol/L), and Troponin >13.5 ng/ml will have a higher chance of developing critical COVID-19 and will need ICU admission with higher complications and mortality. Using any two of the three markers gave moderate sensitivity (59.32%; 49.89–68.27%) but high specificity (79.31%; 72.53–85.07%) to predict ICU admission. High serum levels of D-Dimers and LDH in the absence of anticoagulation were associated with 1-month mortality among older inpatients with Covid-19 (47). Du et al. recently identified age ≥65 years, and cardiac troponin I ≥ 0.05 ng·mL-1 as two of four risk factors and predictors for mortality of COVID-19 pneumonia patients (48).

Using those bedside tests that can be done even outside the emergency department can save lives and resources by directing the service provider about the group of patients that might deteriorate and need admission to ICU. Directing such patients earlier to hospital with ICU might decrease the mortality and control the spread.

CONCLUSION

This demonstrated the accuracy of our approach in identifying factors that can predict the COVID 19 patient outcome. For that reason, the stratification of patients according to the parameters discovered by our model might provide a simple and efficient system for patients' risk stratification. This system might help clinicians and health care providers to deliver more efficient medical care for COVID 19 patients. Those factors, in addition to the fact that this report is the first report that uses in house patient cohort from UAE highlight the importance of implementation of such a method in the stratification of our own patients into high or low-risk groups for ICU transfer might be essential for more efficient use of our own resources and infrastructures available to deal with the COVID 19 outbreak.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Scientific Research Committee MOHAP/DXB-REC/MMM/NO.44/2020 and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments ethical standards. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Tracheostomy in 80 COVID-19 Patients: A Multicenter, Retrospective, Observational Study

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Background: The outbreak of coronavirus disease 2019 (COVID-19) has led to a large and increasing number of patients requiring prolonged mechanical ventilation and tracheostomy. The indication and optimal timing of tracheostomy in COVID-19 patients are still unclear, and the outcomes about tracheostomy have not been extensively reported. We aimed to describe the clinical characteristics and outcomes of patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia who underwent elective tracheostomies.

Methods: The multi-center, retrospective, observational study investigated all the COVID-19 patients who underwent elective tracheostomies in intensive care units (ICUs) of 23 hospitals in Hubei province, China, from January 8, 2020 to March 25, 2020. Demographic information, clinical characteristics, treatment, details of the tracheostomy procedure, successful weaning after tracheostomy, and living status were collected and analyzed. Data were compared between early tracheostomy patients (tracheostomy performed within 14 days of intubation) and late tracheostomy patients (tracheostomy performed after 14 days).

Results: A total of 80 patients were included. The median duration from endotracheal intubation to tracheostomy was 17.5 [IQR 11.3–27.0] days. Most tracheotomies were performed by ICU physician [62 (77.5%)], and using percutaneous techniques [63 (78.8%)] at the ICU bedside [76 (95.0%)]. The most common complication was tracheostoma bleeding [14 (17.5%)], and major bleeding occurred in 4 (5.0%) patients. At 60 days after intubation, 31 (38.8%) patients experienced successful weaning from ventilator, 17 (21.2%) patients discharged from ICU, and 43 (53.8%) patients had died. Higher 60 day mortality [22 (73.3%) vs. 21 (42.0%)] were identified in patients who underwent early tracheostomy.

Conclusions: In patients with SARS-CoV-2 pneumonia, tracheostomies were feasible to conduct by ICU physician at bedside with few major complications. Compared with tracheostomies conducted after 14 days of intubation, tracheostomies within 14 days were associated with an increased mortality rate.

Keywords: COVID-19, tracheostomy, mechanical ventilation, intensive care unit, critically ill patients

INTRODUCTION

The novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a worldwide pandemic and a large and increasing number of patients who are critically ill and require endotracheal intubation and mechanical ventilation (1–3).

Tracheostomy is a common procedure for critically ill patients who require long-term mechanical ventilation (4). Compared with an orotracheal tube, a shorter tracheostomy tube that bypasses the mouth and pharynx can avoid oropharyngeal and laryngeal lesions, improve patient comfort and reduce sedative drug use (5). In addition, a tracheostomy tube can provide less airway dead space and thus less work of breathing, facilitate weaning from mechanical ventilation, make airway suctioning much easier, and potentially reduce the incidence of ventilator-associated pneumonia (6). In COVID-19 patients with requirements of prolonged ventilation, tracheostomy is one of the important clinical considerations for optimal management (7). However, in the current pandemic, there is significant uncertainty regarding the indication and timing of tracheostomy.

Several recommendations and guidelines have discussed on when to perform a tracheostomy in COVID-19 patients, while the timing is varied across the literature. Recommendations from the UK and North America suggested that tracheostomy should be delayed until at least 14 days from endotracheal intubation to allow prognostic information to become clear and for viral load to sufficiently decline (1, 8–12). In contrast, recommendations from France proposed a more aggressive approach-favoring early tracheostomy so that patients can be weaned off intubation and transferred to a ventilatory weaning unit thus sparing ICU beds for new patients (13). These recommendations were based on expert opinion, and robust ICU outcome data are needed to give high level of evidence. At present, the outcomes about tracheostomy in COVID-19 patients have not been extensively reported.

In this study, we aimed to describe the clinical characteristics of patients with confirmed SARS-CoV-2 pneumonia who underwent elective tracheostomies and to explore the association between the timing of tracheostomy and the outcomes of these patients.

Abbreviations: COVID-19, Coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ICU, Intensive care unit; COPD, chronic obstructive pulmonary disease; SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation; ECMO, extracorporeal membrane oxygenation; PPE, Personal Protective Equipment; PAPRs, Powered air-purifying respirators.

MATERIALS AND METHODS

Study Design and Patients

This multicenter, retrospective, observational study was conducted in Hubei Province, China. Patients treated in intensive care units (ICUs) of 23 hospitals from January 8, 2020 to March 25, 2020 were screened. All patients who were diagnosed with COVID-19 and underwent elective tracheostomies were included. COVID-19 was diagnosed according to the World Health Organization interim guidance (14). The decision of tracheostomy was made by treating clinicians. This study was approved by the Ethics Committee of Union Hospital, and written informed consent was waived.

Data Collection

Medical records of patients were reviewed, and data were collected by investigators at each ICU by using a standardized case-report form. Sociodemographic and clinical data were collected for all patients, including age, sex, chronic medical histories, vital signs, laboratory tests, acute physiology and chronic health evaluation II (APACHE II) scores and sequential organ failure assessment (SOFA) scores. We also collected details of the tracheostomy procedure, including timing, type (percutaneous or surgical), location, the clinicians performing the procedure, and complications. Whether successful weaning was achieved was also recorded, and successful weaning was

TABLE 1 | Demographic data and vital signs in 80 COVID-19 patients receiving early and late tracheostomies.

	Total ($n = 80$)	Early tracheotomy ($n = 30$)	Late tracheotomy ($n = 50$)	*P*-value
Male	55 (68.8%)	21 (70.0%)	34 (68.0%)	0.852
Age, years	63.9 (14.0)	66.5 (15.1)	62.3 (13.2)	0.194
Duration from intubation to tracheostomy, days	17.5 [11.3, 27.0]	9.5 [5.0, 13.0]	24.5 [18.8, 32.0]	<0.001
Chronic medical illness				
Hypertension	32 (40.0%)	12 (40.0%)	20 (40.0%)	1.000
Coronary heart disease	17 (21.2%)	3 (10.0%)	14 (28.0%)	0.057
Diabetes	14 (17.5%)	6 (20.0%)	8 (16.0%)	0.649
Cerebrovascular disease	8 (10.0%)	4 (13.3%)	4 (8.0%)	0.700
Dementia	5 (6.2%)	3 (10.0%)	2 (4.0%)	0.358
Chronic renal disease	4 (5.0%)	2 (6.7%)	2 (4.0%)	0.628
Chronic hepatic disease	4 (5.0%)	0 (0.0%)	4 (8.0%)	0.291
Cancer	3 (3.8%)	2 (6.7%)	1 (2.0%)	0.553
COPD	2 (2.5%)	0 (0.0%)	2 (4.0%)	0.525
At hospital admission				
Temperature, °C	36.7 [36.3, 37.2]	36.8 [36.4, 37.0]	36.5 [36.3, 37.3]	0.811
Heart rate, beats per minute	96 (18)	97 (20)	96 (18)	0.800
Respiratory rate	22 [19, 30]	22 [19, 30]	23 [19, 30]	0.731
Systolic blood pressure, mm Hg	133 [123,146]	132 [120, 146]	135 [123, 146]	0.827
Diastolic blood pressure, mm Hg	78 [70, 88]	77 [70, 90]	78 [67, 85]	0.365
At ICU admission				
Temperature, °C	36.8 [36.5, 37.2]	36.8 [36.5, 37.5]	36.7 [36.4, 37.2]	0.324
Heart rate, beats per minute	99 (20)	102 (19)	98 (20)	0.334
Respiratory rate	25 [20, 32]	27 [20, 32]	25 [20, 32]	0.988
Systolic blood pressure, mm Hg	133 [121, 148]	136 [114, 155]	133 [123, 146]	0.769
Diastolic blood pressure, mm Hg	75 [65, 87]	76.5 [65, 88]	75 [65, 83]	0.754
SOFA score	5 [4, 7]	6 [4, 9]	5 [4, 7]	0.014
APACHE II score	12 [9, 18]	15 [11, 21]	11 [9, 17]	0.034
On the day before tracheostomy				
Temperature, °C	37 [36.6, 37.7]	36.8 [36.4, 37.7]	37 [36.7, 37.7]	0.260
Heart rate, beats per min	96 (20)	93 (26)	97 (16)	0.212
Respiratory rate	21 [19, 25]	22 [19, 25]	21 [20, 23]	0.595
Systolic blood pressure, mm Hg	129 (18)	129 (21)	129 (16)	0.949
Diastolic blood pressure, mm Hg	70 [61, 78]	69 [60, 78]	71 [62, 78]	0.835
SOFA score	7 [5, 10]	8 [6, 10]	7 [5, 9]	0.371
APACHE II score	15 (5)	17 (6)	13 (4)	0.010

Data were presented as mean (standard deviation), median [interquartile range] or count (%).
COVID-19, coronavirus disease 2019; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation.

defined as no need for mechanical ventilation for more than 48 h at any time after tracheostomy. Treatment was recorded for the duration of hospitalization. The living status at 60 days after intubation was also recorded.

Statistical Analysis

Normally distributed and non-normally distributed continuous variables are presented as the mean (SD) and median [IQR], respectively. Categorical variables are presented as numbers (%). Early tracheostomy was defined as tracheostomy within 14 days of intubation, and late tracheostomy was defined as tracheostomy after 14 days. The comparison between the two groups was conducted using Student's *t*-test, Mann-Whitney U test or Fisher's exact test when appropriate. The Kaplan-Meier method was used to depict survival curves, and the log-rank test was used to compare the survival rates between the early tracheostomy group and the late tracheostomy group. Cox proportional hazards regression analysis was used to explore the hazard ratio (HR) of variables with a $p < 0.05$ in univariate analysis. No imputation was made for missing data. A 2-tailed $p < 0.05$ was regarded as statistically significant. All statistical analyses were performed using the SPSS software system (vision 20.0, SPSS, Inc., Chicago, IL) and GraphPad Prism 5 software.

TABLE 2 | Laboratory tests in 80 COVID-19 patients receiving early and late tracheostomies.

	Normal range	Total ($n = 80$)	Early tracheotomy ($n = 30$)	Late tracheotomy ($n = 50$)	*P*-value
At hospital admission					
White-cell count, $\times 10^9$ /L	3.5–9.5	8.7 [6.2, 12.6]	9.5 [6.8, 11.4]	8.4 [5.7, 14.6]	0.518
Hemoglobin, g/L	130–175	124.0 [104.5, 136.0]	125.0 [103.5, 138.5]	124.0 [103.8, 136.0]	0.760
Platelet count, $\times 10^9$ /L	125–350	154.5 [111.8, 204.8]	152.0 [101.5, 233.0]	157.0 [118.0, 200.5]	0.971
Neutrophil count, $\times 10^9$ /L	1.8–6.3	7.8 [4.7, 11.9]	8.4 [6.1, 10.0]	7.4 [4.4, 14.3]	0.580
Lymphocyte count, $\times 10^9$ /L	1.1–3.2	0.64 [0.42, 0.96]	0.60 [0.40, 0.93]	0.66 [0.43, 1.00]	0.435
Total bilirubin, μmol/L	0–26	15.3 [10.3, 22.4]	16.1 [10.3, 24.1]	15.0 [10.3, 20.6]	0.388
ALT, U/L	9–50	32.0 [21.0, 57.0]	29.0 [20.5, 60.0]	32.0 [22.0, 55.0]	0.683
AST, U/L	15–40	37.5 [24.0, 58.3]	38.0 [23.0, 63.5]	37.0 [27.7, 56.5]	0.852
Albumin concentration, g/L	40–55	32.0 (5.7)	31.5 (6.1)	32.2 (5.5)	0.588
Serum creatinine, μmol/L	57–111	72.1 [54.9, 92.0]	78.8 [55.5, 128.6]	70.7 [54.8, 84.4]	0.174
Blood urea nitrogen, mmol/L	3.6–9.5	7.1 [5.1, 9.9]	8.3 [5.3, 11.5]	6.7 [4.9, 9.4]	0.200
C-reactive protein, mg/L	0–5	73.2 [16.8, 115.5]	57.2 [15.0, 134.0]	76.1 [19.4, 111.5]	0.631
Procalcitonin, ng/mL	<0.5	0.17 [0.08, 0.43]	0.29 [0.10, 0.78]	0.14 [0.08, 0.40]	0.075
At ICU admission					
PH	7.35–7.45	7.42 [7.36, 7.47]	7.42 [7.39, 7.47]	7.41 [7.34, 7.48]	0.737
PaO_2, mm Hg	83–108	68.4 [54.0, 97.0]	68.9 [57.6, 90.8]	66.0 [53.0, 108.0]	0.680
$PaCO_2$, mm Hg	35–48	37.0 [33.0, 48.3]	36.4 [32.2, 46.2]	41.0 [34.0, 49.0]	0.250
Ratio of PaO_2 to FiO_2, mm Hg	400–500	112.0 [72.7, 178.7]	108.5 [63.1, 178.8]	114.0 [75.0, 178.7]	0.552
On the day before tracheostomy					
PH	7.35–7.45	7.41(0.07)	7.41(0.07)	7.41(0.07)	0.671
PaO_2, mm Hg	83–108	88.5 [72.9, 113.5]	82.3 [67.0, 94.8]	91.5 [77.8, 131.3]	0.052
$PaCO_2$, mm Hg	35–48	49.2 (12.9)	51.7 (15.1)	47.8 (11.5)	0.226
Ratio of PaO_2 to FiO_2, mm Hg	400–500	183.0 [126.0, 268.3]	147.6 [93.0, 253.8]	214.5 [146.3, 279.8]	0.061

Data were presented as mean (standard deviation) or median [interquartile range].
COVID-19, coronavirus disease 2019; ICU, intensive care unit; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; FiO_2, fraction of inspired oxygen.

RESULTS

From January 8 to March 25, 2020, a total of 80 patients from 23 hospitals (2 [IQR 1–4] patients per center) in Hubei Province, China, were included in our study. Their mean (SD) age was 63.9 (14.0) years, and 61 (70.1%) were male. The median duration from intubation to tracheostomy was 17.5 [IQR 11.3–27.0] days. Sixty (69.0%) patients had chronic medical illnesses, and the most common illnesses were hypertension (40.0%), coronary heart disease (21.1%), diabetes (17.5%), and cerebrovascular disease (10.0%) (**Table 1**). Thirty (37.5%) patients received tracheostomies within 14 days after intubation, and their median duration between intubation and tracheostomy was significantly shorter than that of the late tracheostomy group (9.5 [IQR 5.0–13.0] days vs. 24.5 [IQR 18.8–32.0] days, $p < 0.001$). Compared with patients in the early tracheostomy group, the patients in the late tracheostomy group had lower SOFA scores (5 [IQR 4–7] vs. 6 [IQR 4–9], $p = 0.014$) and APACHE II scores (11 [IQR 9–17] vs. 15 [IQR 11–21], $p = 0.034$) at ICU admission and lower APACHE II scores [13 (SD 4) vs. 17 (SD 6), $p = 0.010$] before tracheostomy. Among all 80 patients, lymphocytopenia and hypoalbuminemia at hospital admission and hypoxemia at ICU admission were prominent (**Table 2**). However, no differences were identified between the two groups.

Most tracheotomies were performed by ICU physicians [62 (77.5%)] and using percutaneous techniques [63 (78.8%)] at the ICU bedside [76 (95.0%)]. Powered air-purifying respirators (PAPRs) were used by operating teams in 68 (85.0%) tracheostomies (**Table 3**). Furthermore, neuromuscular blocking drugs were applied in 46 (57.5%) patients, which may help avoid coughing-induced viral aerosolization. The most common complication was tracheostoma bleeding, which occurred in 14 (17.5%) patients. Major bleeding occurred in 4 (5.0%) patients, who received transfusion of red blood cells. Other complications included subcutaneous emphysema (2.5%), tracheostoma infection (1.2%), and mediastinal emphysema (1.2%) (**Table 3**). No differences were identified between the early and late tracheostomy groups in terms of complications. For treatments, no differences were identified between the two groups, except extracorporeal membrane oxygenation (ECMO). Compared with early tracheostomy patients, more patients who underwent late tracheostomy received ECMO [19 (8.0%) vs. 2 (6.7%), $p = 0.002$] (**Table 4**).

In the 80 COVID-19 patients who underwent elective tracheostomies, 43 (53.8%) patients had died at 60 days. Higher

TABLE 3 | Details of the Tracheostomies in 80 COVID-19 patients.

	Total ($n = 80$)	Early tracheotomy ($n = 30$)	Late tracheotomy ($n = 50$)	*P*-value
Type of procedure				0.057
Surgical	17 (21.2%)	3 (10.0%)	14 (28.0%)	
Percutaneous	63 (78.8%)	27 (90.0%)	36 (72.0%)	
Location				0.291
Operating room	4 (5.0%)	0 (0.0%)	4 (8.0%)	
Bedside	76 (95.0%)	30 (100.0%)	46 (92.0%)	
Clinicians performing tracheostomy				0.028
ICU physicians only	62 (77.5%)	28 (93.3%)	34 (68.0%)	
Otolaryngologists only	10 (12.5%)	1 (3.3%)	9 (18.0%)	
Both	8 (10.0%)	1 (3.3%)	7 (14.0%)	
PAPRs	68 (85.0%)	24 (80.0%)	44 (88.0%)	0.518
Neuromuscular blocking drugs	46 (57.5%)	12 (40.0%)	34 (68.0%)	0.014
Complications	18 (22.5%)	5 (16.7%)	13 (26.0%)	0.333
Tracheostoma bleeding	14 (17.5%)	4 (13.3%)	10 (20.0%)	
Subcutaneous emphysema	2 (2.5%)	1 (3.3%)	1 (2.0%)	
Tracheostoma infection	1 (1.2%)	0 (0.0%)	1 (2.0%)	
Mediastinal emphysema	1 (1.2%)	0 (0.0%)	1 (2.0%)	

Data were presented as count (%).
COVID-19, coronavirus disease 2019; ICU, intensive care unit; PAPRs, powered air-purifying respirator.

TABLE 4 | Treatments in 80 COVID-19 patients receiving early and late tracheostomy.

	Total ($n = 80$)	Early tracheotomy ($n = 30$)	Late tracheotomy ($n = 50$)	*P*-value
Prone position ventilation	45 (56.2%)	15 (50.0%)	30 (60.0%)	0.383
ECMO	21 (26.2%)	2 (6.7%)	19 (38.0%)	0.002
Renal replacement therapy	37 (46.2%)	14 (46.7%)	23 (46.0%)	0.954
Vasoconstrictive agents	71 (88.8%)	26 (86.7%)	45 (90.0%)	0.927
Antiviral agents	62 (77.5%)	23 (76.7%)	39 (78.0%)	0.890
Antibacterial agents	87 (100.0%)	30 (100.0%)	50 (100.0%)	1.000
Antifungal agents	61 (76.2%)	21 (70.0%)	40 (80.0%)	0.309
Glucocorticoids	53 (66.2%)	20 (66.7%)	33 (66.0%)	0.951

Data were presented as count (%).
COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation.

60 day mortality [22 (73.3%) vs. 21 (42.0%), $p = 0.007$] was identified in patients who underwent early tracheostomy (**Figure 1**). At 60 days after intubation, 31 (38.8%) patients experienced successful weaning from the ventilator, and 17 (21.2%) patients were discharged from the ICU. Because collinearity existed between the SOFA and APACHE II scores at ICU admission, only the SOFA score was incorporated into the Cox proportional hazards regression analysis. After adjusting for SOFA [HR 1.00 (95% CI, 0.91–1.11)] and ECMO [HR 1.06 (95% CI, 0.49–2.28)], late tracheostomy was identified with a decreased risk of death [HR 0.34 (95% CI, 0.17–0.70)] (**Table 5**).

DISCUSSION

As the number of patients infected by SARS-CoV-2 around the world is increasing, the demand for endotracheal intubation and invasive mechanical ventilatory support secondary to acute respiratory failure is increasing accordingly (15, 16). In our study, most procedures were performed by ICU physicians using percutaneous techniques at bedside, which avoided the unnecessary transport of ventilated patients and repeated connection and disconnection of ventilatory circuits during transfer. Regarding the type of tracheostomy performance, one of the concerns is complications of bleeding and stomal infections. Long et al. (17) compared percutaneous with surgical tracheotomy in patients with COVID-19, and they found there were no significant differences in complication rates between the two methods. Another concern is the potential risk of viral transmission. Some argued against percutaneous tracheostomy performed in COVID-19 patients because it usually involves opening the ventilator circuit more frequently than surgical tracheostomy, and serial dilations during the procedure may put

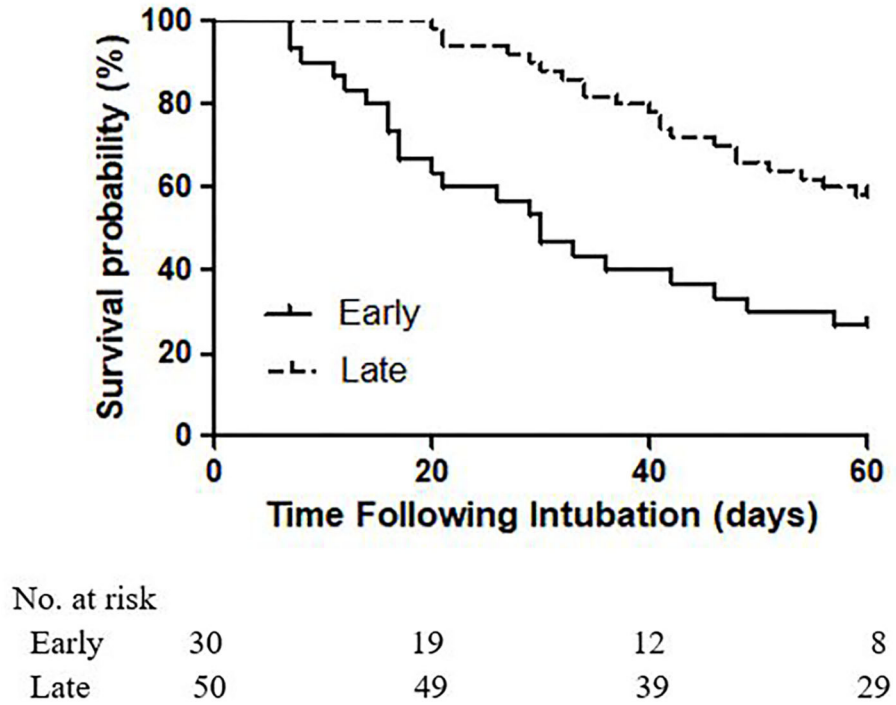

FIGURE 1 | Kaplan-Meier analysis of survival in patients receiving early and late tracheostomies for 60 days ($p_{\log-\text{ranktest}} = 0.0003$).

TABLE 5 | Cox proportional hazards regression analysis in 80 COVID-19 patients receiving tracheostomy.

Characteristics	Hazard ratio and 95% confidence interval	*p*-value
Late tracheostomy	0.34 (0.17–0.70)	0.003
SOFA	1.00 (0.91–1.11)	0.958
ECMO	1.06 (0.49–2.28)	0.881

COVID-19, coronavirus disease 2019; SOFA, sequential organ failure assessment; ECMO, extracorporeal membrane oxygenation.

surgeons in face of the airway from the beginning (18). However, there is currently no evidence across the literature to advise which approach is less aerosol generating (19).

Tracheotomy for patients with COVID-19 is considered a highly-risk procedure, and appropriate personal protective equipment (PPE) is critical to reduce infection rates among health care workers (20). In our study, standard PPE was systematically used in all of the procedures, including N95 mask, gowns, caps, boots, double gloves and face shield/eye protection. Additionally, the PAPR, which was advised by several recommendations (1, 12, 21), was used in more than half of the procedures in our study. Other principles, including limiting the number of personnel present, ensuring complete paralysis, adequate sedation, and minimizing suction during the procedure, also help to improve protection for health care workers from SARS-CoV-2 (22).

Indications for tracheostomy in patients with COVID-19 remain unclear. Mattioli et al. suggested that tracheostomy has the potential to facilitate ventilator weaning and promote early discharge of COVID-19 patients from ICU to lower intensity care wards and thus free up resources (23). However, Shiba et al. argued that tracheostomy does not provide any benefit on the outcome in patients with COVID-19 due to rapid evolution of the disease, and they did not believe that tracheostomy had widespread indication (24). Above all, before consideration of tracheostomy, ICU physicians and surgery teams should fully assess the prognosis and associated benefit from the procedure. Tracheostomy is preferably be offered to patients with an expectation of recovery or a long-term need of an artificial airway.

Timing for elective tracheostomy performance is always controversial. Outside the context of the COVID-19 pandemic, a systematic review suggested that early tracheostomy (within 7 days) was associated with a reduced duration of mechanical ventilation, less mortality rate and shorter length of ICU stay (25). Furthermore, A Cochrane review found lower mortality rates and a higher probability of discharge from the ICU at day 28 among patients with early tracheotomy (26). In contrast, meta-analyses published by Griffiths et al. (27) and Siempos et al. (28) suggested that early tracheostomy is not associated with lower mortality than late tracheostomy. Moreover, a TracMan randomized trial (29), comparing 455 patients undergoing early tracheostomy (within 4 days) and 454 patients undergoing late tracheostomy (after 10 days), found that there were no differences in 30 day mortality and 1 and 2 year survival or length of ICU stay between them. During the pandemic of COVID-19, the focus has changed dramatically. Tracheostomy is an aerosol

generating procedure which theoretically increases the risk of viral transmission, and the viral load may be high in the early course of the disease (7, 21). The timing should balance the benefits of tracheostomy for mechanically ventilated patients and the risk of viral transmission to the team involved in the procedure. Both the US and Canadian recommendations strongly advised that test for COVID-19 should be negative before performing an elective tracheostomy (8, 30).

Our study suggested that, compared with tracheostomies conducted after 14 days of intubation, tracheostomies within 14 days were associated with an increased mortality rate. Univariate analysis showed that patients who underwent early tracheostomies had higher SOFA scores and APACHE II scores, and less of these patients received ECMO. However, after adjusting SOFA and ECMO, the timing of tracheostomy was the only variable significantly associated with mortality. A prospective cohort study assessed 50 patients with confirmed COVID-19 reported that early tracheotomy ($\leq$10 days) was associated with shorter mechanical ventilation duration and hospital stay, and no differences were found in mortality rate (31). The overall mortality in our study was as high as 53.8%, which was consistent with other studies reported $>$ 50% mortality rate for patients who are placed on the ventilator (2, 32, 33). Given the high mortality rate, lack of proven benefit, and concern for viral exposure, it is reasonable to consider tracheostomy no sooner than 14 days of endotracheal intubation, and preferably at least tests of specimens from the respiratory tract for SARS-CoV-2 RNA are negative.

This study has several limitations. First, the sample size of our study was relatively small, which might cause bias and limit the reliability or generalizability of our results. Second, some patients were still hospitalized at the end of this study, so some clinical outcomes, such as length of ICU stay and hospital stay, were unavailable at the time of analysis. Third, due to its retrospective design, the lack of randomization for patients who underwent early and late tracheostomy may increase the possibility of confounding in the subsequent comparison. Forth, results of SARS-CoV-2 tests from clinicians involved in tracheostomies were not available. Even if they were test positive for SARS-CoV-2-RNA, we were unable to ascertain whether the clinicians contracted it during the procedures. In future research, rigorous prospective randomized trials with large samples are needed to elucidate any potential benefit from tracheostomy in COVID-19 patients and determine the optimal timing of this procedure.

CONCLUSION

In patients with severe SARS-CoV-2 pneumonia, tracheostomies were feasible to conduct by ICU physicians at bedside with few major complications. Compared with tracheostomies conducted after 14 days of intubation, tracheostomies within 14 days were associated with an increased mortality rate. Despite the results, further research and data from other institutions are warranted to more accurately verify these findings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Union Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

YT, YW, FZ, XY, CH, GH, WX, MH, LZ, AC, ZX, BL, SH, GZ, XF, XZh, YY, HF, LY, BW, ZL, YP, ZS, SF, YO, JX, and XZo collected the epidemiological and clinical data. YT, YW, and FZ summarized all the data. YT, YW, FZ, XY, CH, and GH drafted the manuscript. MF, ZY, BH, and YS revised the final manuscript. All authors read and approved the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
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COVID-19 Induced Acute Respiratory Distress Syndrome—A Multicenter Observational Study

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Background: Proportions of patients dying from the coronavirus disease-19 (COVID-19) vary between different countries. We report the characteristics; clinical course and outcome of patients requiring intensive care due to COVID-19 induced acute respiratory distress syndrome (ARDS).

Methods: This is a retrospective, observational multicentre study in five German secondary or tertiary care hospitals. All patients consecutively admitted to the intensive care unit (ICU) in any of the participating hospitals between March 12 and May 4, 2020 with a COVID-19 induced ARDS were included.

Results: A total of 106 ICU patients were treated for COVID-19 induced ARDS, whereas severe ARDS was present in the majority of cases. Survival of ICU treatment was 65.0%. Median duration of ICU treatment was 11 days; median duration of mechanical ventilation was 9 days. The majority of ICU treated patients (75.5%) did not receive any antiviral or anti-inflammatory therapies. Venovenous (vv) ECMO was utilized in 16.3%. ICU triage with population-level decision making was not necessary at any time. Univariate analysis associated older age, diabetes mellitus or a higher SOFA score on admission with non-survival during ICU stay.

Conclusions: A high level of care adhering to standard ARDS treatments lead to a good outcome in critically ill COVID-19 patients.

Keywords: COVID−19, ARDS (acute respiratory distress syndrome), intensive care medicine, pandemia, Germany

BACKGROUND

Following the first outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) in December 2019, the virus has spread worldwide. The coronavirus disease-19 (COVID-19) currently affects 188 countries and territories (1).

In Germany the first case of a SARS-CoV2 infection was diagnosed on February 27, 2020 (2). Although means of social distancing helped to contain virus transmission more than 175 000 people were infected (1). SARS-CoV2 was suggested to elicit a new ARDS-subphenotype, where hypoxemia often does not match lung compliance and ventilator responsiveness (3). The observed case-fatality ratios differ among countries, with the United States reporting 3.8% and Germany reporting 4.5%,respectively. This is lower compared to other European countries, for example, Italy (14.3%), United Kingdom (15.3%) or France (14.2%) (4). Understanding the specific characteristics of severe and fatal disease, as well as the therapeutic approaches to COVID-19 induced ARDS remains an urgent need to provide a basis for best practice models of standardized ARDS treatment.

In the current study, we report the epidemiologic features, clinical course, treatment patterns and outcome of patients requiring intensive care due to COVID-19 induced ARDS in five German centers.

METHODS

This is a retrospective, observational multicenter study at the University Hospital Würzburg and University Hospital Frankfurt, as well as the municipal hospitals of Kassel, Offenbach and Aschaffenburg. Würzburg, Frankfurt, and Kassel are referral centers for adult extracorporeal membrane oxygenation (ECMO) and part of the German ARDS network. To guarantee an individual high level of ICU care all participating hospitals immediately improved ICU infrastructure by adding extra ICU nurses, physicians, medical students and other support workers to the COVID-19 ICUs.

The institutional ethic boards of the University of Würzburg and Frankfurt, as well as the medical association of Bavaria ethics board (Aschaffenburg) and Hessen (Offenbach, Kassel), respectively, approved the study. The need for informed consent from individual patients was waived due to the context of sole retrospective chart review within standard care.

Patient Selection

We included all patients consecutively admitted to the ICU in any of the participating hospitals due to an acute respiratory distress syndrome between March 12 and May 4, 2020. All patients submitted to the ICU had received the diagnosis of a SARS-CoV2 infection or were tested positive for COVID-19 during ICU treatment. SARS-CoV2 infection was detected with real-time reverse transcriptase polymerase chain reaction (RT-PCR) testing based on the recommended World Health Organization standards. No patient tested positive for other respiratory viruses in primary diagnostics. All patients received venous thromboembolism (VTE) prophylaxis with pharmacologic anticoagulation according to the German guidelines on VTE (5). In case of contraindications against pharmacological anticoagulation, mechanical prophylaxis (intermittent pneumatic compression) was conducted. Follow-up ended with ICU discharge or death during ICU treatment, respectively.

Data Collection

Specific treatment protocols were not defined. Routine clinical data were continuously recorded using patient data management systems (PDMS) (University of Würzburg: COPRA6 RM1.0, COPRA System GmbH, Berlin, Germany; University of Frankfurt: Metavision 5.0, imd soft, Dusseldorf, Germany) or assessed via handwritten records (Aschaffenburg, Offenbach, Kassel). The data were retrieved according to the diagnostic standards of the individual centers. Demographic data, pre-existing medical conditions and medications were gathered from prior written records or discharge letters, questionnaires at the time of hospital admission, as well as personal communication with family members. Lung edema on chest radiographs was evaluated via the Radiographic Assessment of Lung Edema (RALE) score (6) in all patients admitted to the ICU in Würzburg. Severity of ARDS was categorized in line with the Berlin definition (mild: 200 mm Hg $<$ PaO_2/FIO_2 $\leq$ 300 mm Hg; moderate: 100 mm Hg $<$ PaO_2/FIO_2 $<$ 200 mm Hg and severe PaO_2/FIO_2 $<$ 100 mm Hg) (7). Since treatment and data acquisition were conducted according to the standard procedures of the respective hospital, diagnostics and reported parameters varied to some degree between the centers. Hence, if applicable the nominators and denominators are reported for each parameter separately, since not all parameters could be retrieved in the whole cohort of patients. All participating hospitals reported their data via a unified sheet (Microsoft® Excel 2019, Version 16.41, Microsoft® Corporation, Redmond, WA).

Statistical Analysis

Median and interquartile range (25–75%) were reported for continuous data, absolute and relative frequencies for categorical variables. Percentages are based on the total number of patients with complete information in the respective category. Continuous variables were tested for normality using histogram and QQ-plot. To compare differences between survivors and non-survivors in continuous variables the Mann-Whitney rank-sum test or the Wilcoxon matched-pairs signed rank test, respectively, was used as appropriate, as most of the variables were not normally distributed. The Chi^2-Test or Fisher exact test was used to assess the association of dichotomous variables and the outcome. Age-adjusted logistic regression analyses were

Abbreviations: COVID-19, coronavirus disease-19; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; vvECMO, venovenous extracorporeal membrane oxygenation; RT-PCR, real-time reverse transcriptase polymerase chain reaction; SOFA, sepsis-related organ failure assessment; F_iO_2, fraction of inspired oxygen; p_aO_2/F_iO_2, arterial partial pressure of oxygen/fraction of inspired oxygen oxygenation index; PEEP, positive end-expiratory pressure; P_{Plat}, maximum airway plateau pressure; P_{mean}, mean airway pressure; RALE, radiographic assessment of lung edema; IQR, interquartile range (25–75%); PCT, procalcitonin; IL-6, interleukin 6; VTE, venous thromboembolism.

performed to identify factors associated with death during ICU treatment. Wilson score method was used to estimate 95%-confidence intervals for the crude proportion of survival during ICU stay; Kaplan-Meier estimates were used for estimating survival probability. All tests were two-tailed, a p-value <0.05 was considered as statistically significant. The univariate p-values were based on Mann-Whitney U Test, Chir²-Test or Fisher's exact Test as appropriate. The adjusted p-values are based on a logistic regression adjusted for age.

Data were analyzed using SAS® Software, Version 9.4. Copyright© SAS Institute Inc. Cary, NC, USA, R, R Version 3.6.2., Prism 5 for Mac OS X (GraphPad Software, San Diego, CA), Stata version 14.2 (Stata Corp, College Station, TX) or SigmaPlot®, version 10.0 (Systat Software, Erkrath, Germany).

RESULTS

A total of 106 ICU patients were treated for COVID-19 induced ARDS. None of these patients remained in ICU care at the end of the study period. Three patients were transferred from Italy to the ICU in Würzburg. Two of these patients were excluded from the analysis due to an advanced clinical course at the time of their transfer, as well as incomplete records and short-term ICU stay.

Epidemiologic Characteristics and Outcome

Median age of the patients was 64 (IQR 54–76) years, 70.5% were males. Median time from hospital to ICU admission was 2 (IQR 1–4) days. Overall, 37 patients died during ICU stay, constituting an overall survival of 65.0% (95% CI 55.6–73.5) (**Figure 1**). Considering only severe ARDS (P_aO_2/F_iO_2 < 100) (7), survival in critical care was 59.7% (CI 46.7–71.4) (**Supplementary Table 1**). Median duration of ICU treatment was 11 (IQR 7–19) days. Reported comorbidities were present in 79.3% of the cases, with arterial hypertension as most common comorbidity followed by diabetes mellitus (**Table 1**). Patients surviving ICU treatment were significantly younger. Although the majority of patients were male, a gender difference with respect to survival was not observed. Diabetes mellitus [age-adjusted Odds Ratio (OR) 3.4; 95-CI 1.3–8.7] and a higher SOFA score on admission (age-adjusted OR 1.2; 95%-CI 1.1–1.4) were associated with non-survival in univariate and age-adjusted analyses.

Laboratory Findings

Laboratory findings are presented in **Table 2**. Patients who survived ICU treatment had lower levels of inflammatory markers on admission and during the course of therapy. A near

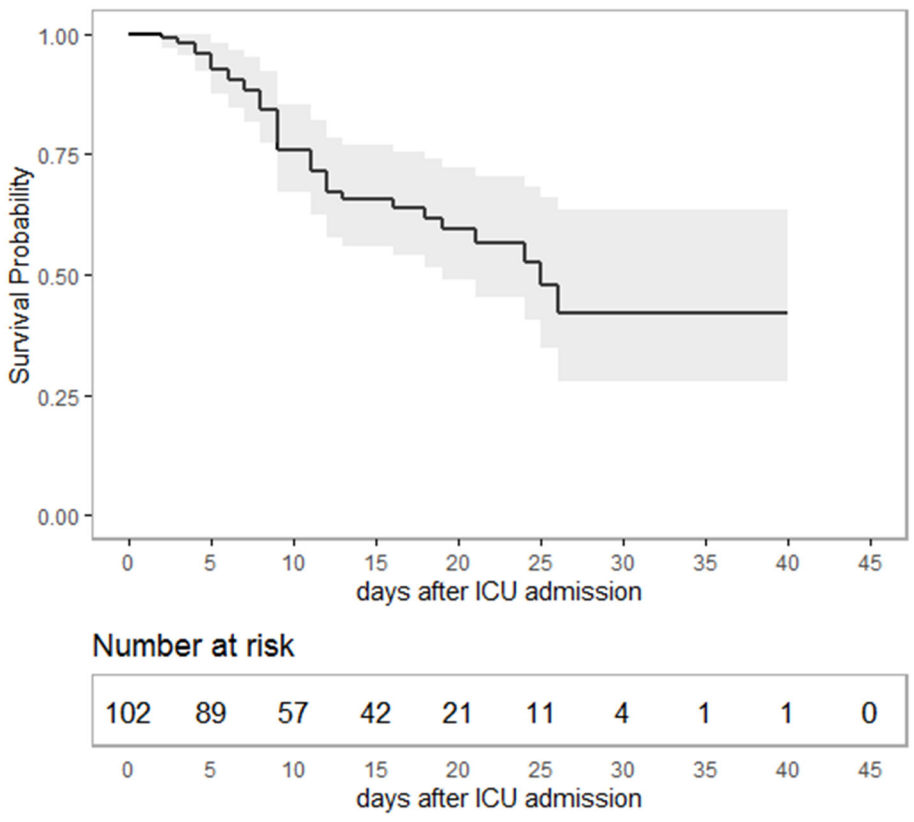

FIGURE 1 | Kaplan-Meier-plot showing survival probability as a function of time in intensive care. Overall, 65% (95%-CI 55.6–73.5) of the patients survived ICU treatment with a median duration of 11 (IQR: 7–19) days. The study period ended with ICU discharge or death, respectively. Hence, survival data are terminally censored resulting in a horizontal line on the far right.

TABLE 1 | Epidemiologic characteristics.

Characteristic	All patients (*N* = 106)	Survivors (*N* = 69)	Non-survivors (*N* = 37)	*P*-value*	Adjusted *p*-value**
Demographics					
Age (years)	64 (54–76)	61 (51–71)	70 (60–78)	0.0029	
Male—no. patients (%)	74(70.5)	50 (72.5)	24 (66.7)	0.5365	0.8194
BMI—median	27.8 (24.9–32.0)	27.8 (24.9–32.0)	27.4 (25.0–31.7)	0.9385	0.8029
Co-morbidities					
Arterial hypertension—no. patients (%)	71 (67.0)	44 (63.8)	27 (73.0)	0.3368	0.6103
Diabetes mellitus—no. patients (%)	26 (24.5)	11 (15.9)	115 (40.5)	0.0050	0.0133
COPD/asthma bronchiale—no. patients (%)	16 (15.1)	7 (10.1)	9 (24.3)	0.0519	0.1192
Coronary artery disease—no. patients (%)	20 (18.9)	9 (13.0)	11 (29.7)	0.0363	0.2236
Heart failure—No. patients (%)	15 (14.2)	7 (10.2)	8 (21.6)	0.1061	0.4755
Stroke—no. patients (%)	13 (12.3)	7 (10.1)	6 (16.2)	0.3637	0.6759
Chronic renal failure—no. patients (%)	16 (15.1)	8 (11.6)	8 (21.6)	0.1692	0.5348
Cancer—no. patients (%)	12 (11.3)	8 (11.6)	4 (10.8)	>0.900	0.3842
Duration prior to ICU admission—days in hospital	2 (0–4) (*N* = 51)	2 (0–4) (*N* = 33)	2 (1–4) (*N* = 18)	0.6519	0.9821
Body temp. > 37.5°C at time of ICU admission (%)	54 (71.0) (*N* = 76)	41 (68.9) (*N* = 52)	13 (54.2) (*N* = 24)	0.0274	0.0098
Scores					
SOFA at time of ICU admission	9 (4–14) (*N* = 78)	5 (4–11) (*N* = 49)	13 (9–16) (*N* = 29)	0.0002	0.0003
Highest SOFA	13 (7–18) (*N* = 69)	10 (5–15) (*N* = 45)	18 (14–21) (*N* = 24)	<0.0001	0.0010

**P-values based on Mann-Whitney, Chi²-Test or Fisher exact test as appropriate.*

***P-values adjusted for age in a logistic regression.*

ICU, intensive care unit; Covid-19, Corona virus disease 2019; No. patients, number of patients; BMI, body mass index; SOFA, Sepsis-related organ failure assessment score. Data are shown as median and interquartile range (25%-75%) or absolute numbers and percentage of patients, respectively. The data represent the analysis of 106 patients, unless otherwise specified via the n-number in the respective row.

three-fold difference in interleukin-6 (IL-6) was present between survivors and non-survivors at the time of ICU admission. 58.3% percent of the non-survivors had IL-6 levels >400 pg/ml. Bacterial specimens were found in 12.3% of the patients with no significantly differences between survivors or non-survivors. Nevertheless, a high percentage was already treated with antibiotics prior to ICU admission.

Respiratory Support

The median arterial oxygenation index (P_aO_2/F_iO_2) at the time of admission was 120 (IQR 88–164), indicating moderate to severe ARDS in the majority of patients. Overall, 55.6% had a moderate ARDS at admission; 35.8% of all patients and 63.8% of the non-survivors already suffered from a severe ARDS ($P_aO_2/F_iO_2 < 100$) at the time of ICU admission. Pulmonary gas exchange worsened in both populations. Prone positioning was performed in 78.9% of the cases. However, comparing the P_aO_2 at the time of ICU discharge or death, respectively, there was no significant difference. Median duration of mechanical ventilation was 9 (IQR 5.5–15.5) days and not significantly different between survivors and non-survivors. The same applies to lung mechanics or radiographic findings (**Table 3**). Chest X-ray pathologies were relatively minor compared to the degree of hypoxemia at admission. While deteriorating during the course of therapy, RALE scores were never significantly different between survivors and non-survivors. Moreover, RALE scores recovered in both groups toward the end of therapy.

Extracorporeal Membrane Oxygenation (ECMO)

Venovenous (vv) ECMO was utilized in 16.3% ($n = 17$) of the patients with a median age of 58 (IQR 51–63) years. Two patients received venoveno-arterial (vva) support due to acute cor pulmonale. ECMO patients had been on mechanical ventilation for a median of two (IQR 1–6) days. In three quarters of all cases, the use of ECMO was indicated due to refractory hypoxemia. Median P_aO_2/F_iO_2 at the time of ECMO commencement was 58 (IQR 51–66). Six patients (35.3%; 95%-CI 17.3–58.7) survived until ICU discharge.

TABLE 2 | Laboratory and microbiological findings.

	All patients (*N* = 106)	Survivors (*N* = 69)	Non-survivors (*N* = 37)	*P*-value*	Adjusted *p*-value**
Laboratory data					
Lactate on Admission (mmol/l)	1.3 (0.9–1.8) (*N* = 72)	1.2 (0.9–1.4) (*N* = 44)	1.7 (1.3–3.2) (*N* = 28)	0.0002	0.0025
Ferritin (μg/l) on Admission	1,917 (1,310–3,166) (*N* = 26)	1,563 (1,013–2,453) (*N* = 17)	2,794 (1,483–3,487) (*N* = 9)	0.1693	
Highest D-dimers (mg/l) during ICU stay	5.7 (2.1–15.6) (*N* = 74)	4.4 (1.4–15.6) (*N* = 51)	7.1 (3.6–15.7) (*N* = 23)	0.0768	0.0502
Infection analyses					
IL-6 (pg/ml) on admission	236.0 (80.3–608.0) (*N* = 64)	146 (49.8–374.5) (*N* = 40)	501.5 (236.0–1,019.5) (*N* = 24)	0.0004	0.0985
IL-6 > 400 pg/ml on Admission- No. patients (%)	23 (35.9)	9 (22.5)	14 (58.3)	0.0038	0.0046
IL-6 (pg/ml) at discharge or death	47 (18.8–447.5) (*N* = 72)	22.8 (11.0–44.8) (*N* = 43)	550.0 (200.0–2,957.0) (*N* = 29)	<0.0001	0.0440
White blood cell count (*n**1000/μl) on admission	9.2 (6.3–11.8) (*N* = 104)	8.1 (5.6–11.3) (*N* = 67)	10.0 (7.4–12.7) (*N* = 37)	0.0111	0.0290
Lymphocyte count (*n**1000/μl) at discharge or death	1.5 (0.8–8.4) (*N* = 76)	1.5 (0.8–9.0) (*N* = 53)	1.6 (0.8–6.0) (*N* = 23)	0.4386	0.1760
PCT (ng/ml) on admission	0.5 (0.3–2.0) (*N* = 99)	0.5 (0.2–0.9) (*N* = 65)	1.3 (0.5–5.5) (*N* = 34)	0.0029	0.1001
PCT (ng/ml) at discharge or death	0.8 (0.1–4.1) (*N* = 80)	0.2 (0.1–0.8) (*N* = 48)	3.9 (1.6–7.4) (*N* = 32)	<0.0001	0.0273
Pos. bacterial culture (all sources of culture)—no. patients (%)	13 (12.3)	5 (7.3)	8 (21.6)	0.0582	0.0741
Antibiotic treatment no. patients (%)	57 (64.8) (*N* = 88)	31 (56.4) (*N* = 55)	26 (78.8) (*N* = 33)	0.0397	
Antiviral therapy—no. patients (%)	26 (24.5)	17 (24.6)	9 (24.3)	0.9715	0.8392

**P-values based on Mann-Whitney,Chi²-Test or Fisher exact test as appropriate.*

***P-values adjusted for age in a logistic regression.*

IL-6, interleukin-6; PCT, procalcitonin; No. patients, number of patients.

Data are shown as median and interquartile range (25%-75%) or absolute numbers and percentage of patients, respectively. The data represent the analysis of 106 patients, unless otherwise specified via the n-number in the respective row.

Antiviral Therapies

The majority of patients (75.5%) did not receive any antiviral or anti-inflammatory therapy, while 24.5% received adjunct therapies including oseltamvir ($n = 10$), remdesivir ($n = 1$), chloroquins ($n = 10$) or tocilizumab ($n = 3$). However, as the choice and duration of therapy was purely at the discretion of the attending physicians, a large number of heterogeneous substances and protocols were used. Hence, no further analyses were performed due to the small sample sizes.

DISCUSSION

The current study focused on the characteristics and outcome of COVID-19 patients admitted to the ICU in five German centers. Our study population mainly consisted of high-risk patients, where ARDS mortality rates of 40 to 46% can be expected (8). Half of our patients suffered from severe ARDS. Major findings include the identification of age, diabetes mellitus and higher SOFA scores on admission as factors associated with non-survival during ICU treatment. Furthermore, our observations indicate that standard ARDS treatment resolves acute hypoxemia in the majority of cases.

The proportion of patients surviving ICU care was 65.0% with a corresponding 95% CI of 55.6–73.5. Survival rates of ICU patients varied substantially between previous studies and different countries, for example, between 22 to 84% in China (9–12), 50% in Seattle (13), 33% in Washington State (14) and 61% in New York (15). In a retrospective cohort study from Italy only 46.6% of the patients requiring hospital admission survived (16). The ICNARC currently reports a survival of 60% in intensive care from the United Kingdom (17). A recent analysis of COVID-19 patients via the claims of the German Local Health Care Funds revealed an overall mortality of 22% and a mortality of 53% in patients requiring invasive ventilation. However, ARDS subtypes were not classified and risk factors of non-survival were not identified (18). Differences between countries may be due to variations in patient characteristics, as well as ICU admission criteria, criteria for ECMO, or availability of ICU capacities. All of the participating hospitals had sufficient resources to provide the best available standard care at any time. The workforce on the ICU of the participating hospitals was actually increased

TABLE 3 | Characteristics of pulmonary function and outcome.

	All patients (*N* = 106)	Survivors (*N* = 69)	Non-survivors (*N* = 37)	*P*-value*	Adjusted p-value**
Pulmonary gas exchange (on admission)					
P_aO_2/F_iO_2	120 (88–164) (*N* = 83)	121 (88–167) (*N* = 56)	120 (88–156) (*N* = 27)	0.8269	0.5717
P_aO_2 (mmHg)	74.1 (61.0–90.0) (*N* = 103)	76.0 (61.0–88.1) (*N* = 69)	67.4 (59.4–104.0) (*N* = 34)	0.6259	0.2783
P_aCO_2 (mmHg)	39.0 (34.2–47.5) (*N* = 104)	38.1 (33–43.6) (*N* = 69)	44.8 (37–49.4) (*N* = 34)	0.0072	0.0287
s_aO_2 (%)	94.0 (91.1–97.1) (*N* = 102)	94.6 (91.7–97.0) (*N* = 68)	93.6 (89.0–98.0) (*N* = 34)	0.8230	0.1693
Lung compliance (ml/cmH_2O)	43.1 (32.0–59.8) (*N* = 42)	43.2 (36.4–55.4) (*N* = 21)	41.2 (30.7–59.8) (*N* = 21)	0.6781	0.7680
RALE score	12.0 (5.5–28.5) (*N* = 28)	12.5 (8.0–28.0) (*N* = 18)	8.5 (4.0–29.0) (*N* = 10)	0.3368	0.9313
Pulmonary gas exchange (during ICU stay)					
Lowest P_aO_2/F_iO_2	100. (75–131.) (*N* = 61)	110 (81–142) (*N* = 42)	89 (60–111) (*N* = 19)	0.0437	0.0256
Lowest p_aO_2 (mmHg)	57 (49.8–66.5) (*N* = 72)	61.9 (53.8–68.0) (*N* = 46)	51.7 (45.0–59.0) (*N* = 26)	0.0082	0.0064
P_aO_2 (mmHg)—at ICU-Discharge/Death	73.0 (66.0–89.8) (*N* = 95)	73.0 (67.0–92.0) (*N* = 62)	75.0 (66.0–86.5) (*N* = 33)	0.7337	0.5492
Highest p_aCO_2 (mmHg)	56.0 (45.0–72.0) (*N* = 98)	52.0 (41.0–62.8) (*N* = 67)	71.4 (53.1–81.5) (*N* = 31)	0.0005	0.0045
RALE score day 7	16 (5–36) (*N* = 27)	16 (7–36) (*N* = 17)	13 (2–33) (*N* = 10)	0.4204	0.6911
RALE score at time of discharge/death	6 (3–18) (*N* = 28)	7 (4–12) (*N* = 18)	4.5 (2.0–33.0) (*N* = 10)	0.8101	
Mechanical ventilation					
Highest F_iO_2 (%)	90 (65.0–100) (*N* = 103)	85 (60–100) (*N* = 67)	100 (90–100) (*N* = 36)	0.0012	0.0018
Highest peep (cmH_2O)	15 (11–16) (*N* = 95)	12 (10–15) (*N* = 59)	15 (14–17) (*N* = 36)	0.0016	0.0058
Highest P_{Plat} (cmH_2O)	31 (26–34) (*N* = 92)	29.5 (24.0–33) (*N* = 58)	32 (31–36) (*N* = 34)	0.0013	0.0054
Prone positioning—no. patients (%)	76 (71.7) (*N* = 104)	45 (65.2) (*N* = 69)	31 (88.6) (*N* = 35)	0.0111	
ECMO (*N* = 17)					
Age	58 (51–63)	50 (47–52)	62 (57–67)	0.0137	
Mode—no. patients (%)					
vvECMO	17 (16.0)	6 (8.7)	11 (29.7)		
vvaECMO	2 (1.9)	0 (0.0)	2 (5.4)		
P_aO_2/F_iO_2–prior to ECMO start	58 (51–66)	58.0 (56.3–69)	59.6 (55–80)	0.8548	
P_aCO_2–prior to ECMO start	70.5 (60.5–77.7)	71.3 (60.5–77.7)	67.3 (60.5–76.5)	0.7963	
Duration—hours	164.5 (126.7–369.3)	164.5 (126.7–225.4)	217.7 (126.5–444.6)	0.6605	
Duration mechanical ventilation prior to ECMO—days	2 (1–6)	1.5 (1.0–2.0)	5 (2–6)	0.0961	
Survival (%)	35.3 (95%-CI 17.3–58.7)				
Outcome					
Duration of ICU treatment–days	11 (7–19) (*N* = 102)	15 (7–20) (*N* = 67)	9 (6.5–12) (*N* = 35)	0.0540	
Duration of mechanical ventilation—days	9 (4.5–15.5) (*N* = 100)	9 (4–17) (*N* = 65)	9 (5–15) (*N* = 35)	0.6795	
Survival—(%)	65 (95%-CI 55.6–73.5)				

**P-values based on Mann-Whitney,Chi²-Test or Fisher exact test as appropriate.*

***P-values adjusted for age in a logistic regression.*

P_aO_2, arterial partial pressure of oxygen; F_iO_2, fraction of inspired oxygen; s_aO_2, arterial saturation of hemoglobin; PEEP, positive end-expiratory pressure, P_{Plat}, plateau airway pressure; SOFA, sepsis-related organ failure assessment score; vvECMO, venovenous extracorporeal membrane oxygenation; vaECMO, venoarterial extracorporeal membrane oxygenation; ICU, intensive care unit; No. patients, number of patients.

Data are shown as median and interquartile range (25%-75%) or absolute numbers and percentage of patients, respectively. The data represent the analysis of 106 patients, unless otherwise specified via the n-number in the respective row.

to counteract the big challenges associated with COVID-19, including a high number of patients requiring prone positioning, as well as time and effort associated with the use of personal protective equipment.

Advanced age has been uniformly reported as a risk factor for severe disease (12, 19) and was also associated with a worse outcome in our study. Diabetes mellitus was also reported as a factor associated with death from COVID-19 in critically ill in New York City and Lombardy (15, 16). It was associated with an approximately three-fold increased risk of death in our study. Arterial hypertension on the other hand was the most frequent comorbidity. Nevertheless its presence was not associated with a worse outcome and likely only represents the overall disease frequency (20). Although previously reported as a predictor of sepsis mortality (21), lymphocytopenia was not a distinctive feature in our ICU population. We did observe differences in SOFA scores and IL-6. IL-6 is perceived to be the central mediator of a cytokine release syndrome (22) and survivors had significantly lower IL-6 levels at the time of ICU admission. In this regard, preliminary data indicate that the administration of dexamethasone could improve survival in patients receiving respiratory support (23). Nevertheless, in our study treatment protocols for the use of glucocorticoids were not defined and dexamethasone was not utilized in any of the patients. Moreover, due to the small sample size, no multivariable prediction model to identify potential predictors of survival could be build.

The standards of ARDS treatment consist of prone positioning and protective mechanical ventilation with higher PEEP levels. All centers adhered to these guideline recommended therapies (24), although P_{Plat} values indicate difficulties in maintaining lung protective ventilation at all times. Both survivors and non-survivors had worsening lung injury during the course of treatment with a high percentage of prone positioning. Patients dying during ICU treatment suffered from a worse pulmonary function at time of ICU admission, however, interestingly the duration of mechanical ventilation was not significantly different to patients surviving ICU care. Furthermore, p_aO_2 values do not indicate hypoxemia at the time of death. The same applies to the RALE score or lung compliance, emphasizing that radiographic findings and lung mechanics often do not match the severity of disease (3). Antiviral or anti-inflammatory treatments were only utilized in a minority of the patients. The use of remdesivir was recently associated with faster COVID-19 recovery times, whereupon beneficial effects could not be shown in patients receiving mechanical ventilation or ECMO (25). In our cohort, approximately one fourth received antiviral treatment, whereas no significant difference in survival was observed.

Seventeen patients (16.3%) received vvECMO therapy. The overall rate of vvECMO treatment was higher compared to what has been reported from China (11, 12), the United States (15) and Italy (26). German Local Health Care Fund data recorded ECMO treatment in 7% of all ventilated patients in 920 German hospitals (18). The high ECMO rate in our study population emphasizes the severity of disease and that mainly specialized centers participated in the study. Nevertheless, the survival rate was lower in these patients and worse compared to other causes of ARDS.

Taken together, standard ARDS treatment according to published guidelines resolved acute hypoxemia in the majority of cases. Advanced age and diabetes mellitus increased the risk of non-survival. ICU triage with population-level decision making was not necessary and sufficient ICU equipment and personnel resources were available at any time. If the number of COVID-19 ICU patients re-increases, standard ARDS treatment provides a strong basis to ensure a good outcome in critically ill COVID-19 ARDS patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Würzburg and Frankfurt, as well as the medical association of Bavaria ethics board (Aschaffenburg) and Hessen (Offenbach, Kassel). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JH, EA, KZ, and CL contributed substantially to the conception and design of the study, the acquisition, analysis, interpretation of the data, and drafted the article. PM, QN, PHel, MS, PU-P, AS, IT, CaR, ChR, MK, JS, and DG-S contributed substantially to the acquisition and analysis of the data. PK, AB, ToS, BS, DW, HK, TW, SF, GE, RM, HM, and YZ contributed substantially to the acquisition of data, the interpretation of the data and provided critical revision of the article. ThS contributed substantially to the critical revision of the article. PHeu contributed substantially to the analysis, interpretation of the data and provided critical revision of the article. VR contributed substantially to the analysis of the data. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Effect of Early vs. Delayed or No Intubation on Clinical Outcomes of Patients With COVID-19: An Observational Study

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Background: Optimal timing of initiation of invasive mechanical ventilation in patients with acute hypoxemic respiratory failure due to COVID-19 is unknown. Thanks to early flattening of the epidemiological curve, ventilator demand in Greece was kept lower than supply throughout the pandemic, allowing for unbiased comparison of the outcomes of patients undergoing early intubation vs. delayed or no intubation.

Methods: We conducted an observational study including all adult patients with laboratory-confirmed COVID-19 consecutively admitted in Evangelismos Hospital, Athens, Greece between March 11, 2020 and April 15, 2020. Patients subsequently admitted in the intensive care unit (ICU) were categorized into the "early intubation" vs. the "delayed or no intubation" group. The "delayed or no intubation" group included patients receiving non-rebreather mask for equal to or more than 24 h or high-flow nasal oxygen for any period of time or non-invasive mechanical ventilation for any period of time in an attempt to avoid intubation. The remaining intubated patients comprised the "early intubation" group.

Results: During the study period, a total of 101 patients (37% female, median age 65 years) were admitted in the hospital. Fifty-nine patients (58% of the entire cohort) were exclusively hospitalized in general wards with a mortality of 3% and median length of stay of 7 days. Forty-two patients (19% female, median age 65 years) were admitted in the ICU; all with acute hypoxemic respiratory failure. Of those admitted in the ICU, 62% had at least one comorbidity and 14% were never intubated. Early intubation was not associated with higher ICU-mortality (21 vs. 33%), fewer ventilator-free days (3 vs. 2 days) or fewer ICU-free days than delayed or no intubation.

Conclusions: A strategy of early intubation was not associated with worse clinical outcomes compared to delayed or no intubation. Given that early intubation may presumably reduce virus aerosolization, these results may justify further research with a randomized controlled trial.

Keywords: acute respiratory distress syndrome, ARDS, acute respiratory failure, coronavirus, viral pneumonia, critically ill

BACKGROUND

Management of acute hypoxemic respiratory failure associated with coronavirus disease 2019 (COVID-19) often includes mechanical ventilation (1, 2). Optimal timing of initiation of invasive mechanical ventilation remains unknown. On the one hand, early initiation of invasive mechanical ventilation (i.e., early endotracheal intubation) has been advocated to avoid alternate means of oxygenation (such as high-flow nasal oxygen or non-invasive mechanical ventilation) associated with aerosolization of virus (3). Also, early intubation may prevent induction of harmful self-inflicting lung injury in patients who breath spontaneously and have large transpulmonary pressure swings (4). On the other hand, skeptics of early intubation may retort that intubation itself may generate viral aerosols (5), while the concept of self-inflicting lung injury (which could presumably be prevented by early intubation) may not yet be sufficiently supported by solid scientific data (6, 7). Furthermore, delaying intubation, by trying alternate means of oxygenation, may mean that some patients may not be intubated at all and therefore will be protected from the adverse events of invasive mechanical ventilation. The latter strategy may also address the shortage of ventilators to meet the increased demand of treating patients with COVID-19.

Ventilator supply-demand mismatch could have affected clinical decision-making regarding application of early vs. delayed or no intubation in several epicenters of the pandemic (8), i.e., the possibility could not be precluded that physicians might be forced not to intubate as part of a triage if ventilators were missing. Accordingly, ventilator supply-demand mismatch could also have affected clinical outcomes (9) and may therefore have acted as a confounder when attempting to estimate the effect of early vs. delayed or no intubation on clinical outcomes of patients with COVID-19 in several epicenters of the pandemic. This might not be the case for Greece where early implementation of social distancing measures and flattening of the epidemiological curve reduced burden of health-care system, constantly maintaining ventilator demand lower than supply. This fact allowed for an unbiased estimation as to whether early intubation as opposed to delayed or no intubation affects prognosis of patients with COVID-19. We hypothesized that early intubation is not associated with worse clinical outcomes, including mortality, than delayed or no intubation among patients with acute hypoxemic respiratory failure due to COVID-19.

METHODS

Study Design

We conducted an observational cohort study including all adult (≥18 years old) patients with laboratory-confirmed COVID-19, consecutively admitted in Evangelismos Hospital (Athens, Greece) between March 11, 2020 (the day of hospital admission of the first patient with COVID-19) and April 15, 2020. Evangelismos, the biggest tertiary-care hospital in Greece, serves as one of the three reference medical centers for treating patients with COVID-19 in Athens. In response to the pandemic, 72 ICU beds (from the initially available 30), never concomitantly occupied during the study period, were made available for inpatients.

Compared Groups

Following collection of demographic and clinical data for the complete patient population through review of charts, patients with acute hypoxemic respiratory failure admitted in the ICU were categorized into the "early intubation" and the "delayed or no intubation" group. Acute hypoxemic respiratory failure was defined as the requirement for more than 5 L/min nasal oxygen (or Venturi mask more than 40%) to keep a pulse oximeter measured arterial blood oxygen saturation (SpO2) of equal to or more than 95%. "Delayed or no intubation" group consisted of patients receiving non-rebreather mask for equal to or more than 24 h or high-flow nasal oxygen for any period of time or non-invasive mechanical ventilation for any period of time in an attempt to avoid intubation. The remaining intubated patients comprised the "early intubation" group. The decision of early vs. delayed or no intubation rested with the treating clinicians. Clinicians of our department decided intubation in case of hemodynamic instability, altered mentation and respiratory distress (as evidenced by the usage of accessory respiratory muscles or inability to speak). Rather, hypoxemia without respiratory distress or dyspnea (i.e., the silent hypoxemia, which may be commonly seen of patients with COVID-19) was not usually considered enough to trigger intubation in accordance to relevant reports highlighting both the confounders affecting the quantification of hypoxemia and its association with the physiologic state of patients with COVID-19 (10).

Study Outcomes

ICU-mortality, ventilator-free days and ICU-free days were the outcomes of the study. ICU-mortality was censored at 28 days after the occurrence of acute hypoxemic respiratory failure. Ventilator-free days were calculated starting at the first 24 continuous hours without invasive mechanical ventilation. The day of acute hypoxemic respiratory failure occurrence was considered as day 0 of the 28-day period for which ventilator-free days were calculated. Periods of extubation lasting for equal to or <48 h before re-intubation were not calculated in the sum of ventilator-free days (11). ICU-free days were calculated starting at the first 24 continuous hours outside the ICU in the post-ICU discharge period. The day of ICU admission was considered as day 0 of the 28-day period for which ICU-free days were calculated. Occurrence of septic shock (defined according to Sepsis-3) (12) and need of continuous renal replacement therapy also served as secondary outcomes of the study.

Statistical Analysis

Study population included all patients treated during the study period. Continuous variables are presented as median and interquartile range (IQR). Mann-Whitney rank sum-test was

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range; SOFA, sequential organ failure assessment.

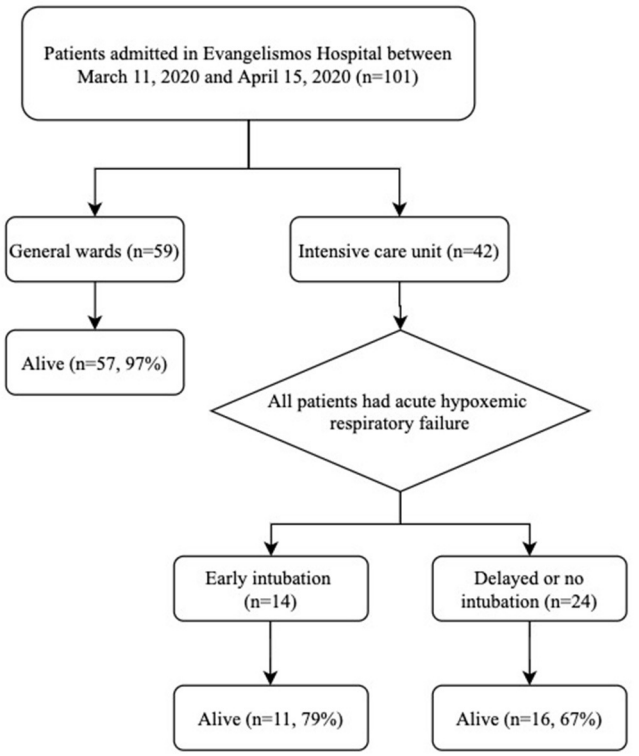

FIGURE 1 | Patient flow diagram. Six patients admitted in the intensive care unit were not intubated and therefore were included in the delayed or no intubation group. Four patients (transferred intubated from another hospital) were not categorized into the early vs. delayed or no intubation group due to unavailability of relevant data.

used to compare continuous variables. Categorical variables are presented as number of patients (percentage). X^2 or Fisher exact-test was used to compare categorical variables. A binary logistic regression analysis was carried out to isolate the contribution of early intubation and sex (independent variables) to mortality (categorical dependent variable). All statistical tests were 2-tailed and statistical significance was defined as $p < 0.05$. Statistical analyses were performed using SPSS software ver. 22.0 (IBM, Armonk, NY, USA).

RESULTS

During the study period, a total of 101 patients [37% female, median age 65 (IQR 53-73) years] were admitted in the hospital (**Figure 1**). Fifty-nine patients (58% of the entire cohort) were exclusively hospitalized in general wards. Their mortality rate was 3% (only two patients, who opted out ICU admission, died) and median length of stay was 7 days (IQR 5-13). None of the healthcare-workers of the hospital tested positive for COVID-19.

Table 1 summarizes the baseline characteristics and outcomes of 42 patients admitted in the ICU (all with acute hypoxemic respiratory failure) during the study period. The median time from hospital to ICU admission was 0 (IQR 0-3) days. Of those admitted in the ICU, 19% were female and 62% had at least one comorbidity. Their median age was 65 (IQR 58-71) years. None of those had a do-not-intubate order and 36 (86%) patients were indeed intubated. ICU-mortality among patients admitted in the ICU was 26%. Data for 13 of those patients have been included in a previous report focusing on the application of positive end-expiratory pressure (13).

Table 1 also summarizes the baseline characteristics and outcomes of patients undergoing early vs. delayed or no intubation. Four patients (all transferred intubated from another hospital) were not categorized into the early vs. delayed or no intubation group due to unavailability of relevant data. Baseline characteristics [including age, comorbidities and organ failure, as assessed by the Sequential Organ Failure Assessment (SOFA) scores, on the day of occurrence of acute hypoxemic respiratory failure] were comparable between the two groups with the exemption of sex. Regarding means of oxygenation, non-rebreather mask was used by all but one patient (who belonged in the delayed or no intubation group), while high-flow nasal oxygen and non-invasive mechanical ventilation was used by 11 and two patients, respectively. Regarding outcomes, early intubation was not associated with higher ICU-mortality, (21 vs. 33%), fewer ventilator-free days (3 vs. 2 days) or fewer ICU-free days (0 vs. 0 days) than delayed or no intubation. Early intubation was associated with lower (albeit statistically non-significant) need for continuous renal replacement therapy (29 vs. 50%) than delayed or no intubation. The above findings persisted when comparing the baseline characteristics and outcomes of patients undergoing early vs. delayed intubation, i.e., after exclusion of six ICU patients who were not intubated (**Supplementary Table**). Time from acute respiratory failure to intubation was shorter for the early intubation compared to the delayed intubation group (0 vs. 2 days) (**Supplementary Table**).

Early intubation (as opposed to delayed or no intubation) was not associated with mortality even after adjustment for sex (i.e., a baseline characteristic which differed between the two groups).

DISCUSSION

We found that approximately one-fourth of patients admitted in the ICU with acute hypoxemic respiratory failure due to laboratory confirmed COVID-19 in Athens, Greece died during their ICU stay. We also found that early intubation was not associated with worse clinical outcomes, such as mortality, ICU-free days and ventilator-free days, compared to delayed or no intubation among those patients.

The observed mortality rate of 26% for patients with COVID-19 admitted in our ICU seems lower than the mortality rates of 62 and 51% reported by early studies from Wuhan, China and Washington State, USA, respectively (14, 15). Although the latter mortality rates might be exaggerated (16) and subsequent studies reported outcomes similar to ours (17), this finding is intriguing. It could be explained by the fact that the health-care system of Greece was not substantially burdened throughout the course of the COVID-19 outbreak. Indeed, a substantially burdened health-care system might lead to worse outcomes (9). Thus,

TABLE 1 | Baseline characteristics and outcomes of patients admitted in the intensive care unit.

	All ($n = 42$)	Early intubation ($n = 14$)	Delayed or no intubation ($n = 24$)	p-value
Age, years (IQR)	65 (58–71)	63 (57–69)	64 (57–74)	0.68
Sex, female, *n* (%)	8 (19)	6 (43)	2 (8)	0.03
Race, *n* (%)				0.69
Caucasian	39 (93)	14 (100)	21 (85)	
Asian	2 (5)	0 (0)	2 (8)	
Middle Eastern	1 (2)	0 (0)	1 (4)	
Comorbidity, *n* (%)	26 (62)	8 (57)	15 (63)	0.74
Cardiovascular	20 (48)	7 (50)	11 (46)	0.80
Diabetes Mellitus	7 (17)	2 (14)	5 (21)	1
Chronic lung disease	4 (10)	1 (7)	3 (13)	1
Renal failure	1 (2)	0 (0)	1 (4)	1
Malignancy	5 (12)	0 (0)	4 (17)	0.27
SOFA score (IQR)	4 (4–6)	4 (4–5)	4 (4–6)	0.8
Respiratory	4 (3–4)	4 (4–4)	4 (3–4)	0.11
Coagulation	0 (0–0)	0 (0–0)	0 (0–1)	0.16
Hepatic	0 (0–0)	0 (0–0)	0 (0–0)	0.3
Neurologic	0 (0–0)	0 (0–0)	0 (0–0)	0.97
Cardiovascular	0 (0–0)	0 (0–0)	0 (0–0)	0.2
Renal	0 (0–0)	0 (0–0)	0 (0–0)	0.77
Usage of non-rebreather mask, *n* (%)	41 (98)	14 (100)	23 (96)	1
Usage of high-flow nasal oxygen, *n* (%)	11 (26)	0 (0)	11 (46)	0.003
Usage of non-invasive mechanical ventilation, *n* (%)	2 (5)	0 (0)	2 (8)	0.52
Lung mechanics at day of intubation, (IQR)				
Ppeak	NA	39 (36–41)	37 (32–42)	0.6
Pplateau	NA	28 (28–31)	28 (25–32)	0.45
PEEPtotal	NA	17 (13–19)	14 (11–19)	0.2
Pdriving	NA	13 (10–15)	13 (12–17)	0.27
Transferred intubated from another hospital, *n* (%)	19 (45)	12 (86)	3 (13)	<0.001
Outcomes within 28 days				
Intubation, *n* (%)	36 (86)	14 (100)	18 (75)	0.06
Intubation outside ICU, *n* (%)	21 (50)	12 (86)	6 (25)	0.004
Septic shock, *n* (%)	18 (43)	6 (43)	11 (46)	1
Continuous renal replacement therapy, *n* (%)	17 (41)	4 (29)	12 (50)	0.19
Ventilator-free days, days (IQR)	NA	3 (0–17)	2 (1–13)	0.57
ICU-free days, days (IQR)	0 (0–15)	0 (0–16)	0 (0–12)	0.59
Time from acute respiratory failure to ICU admission, days (IQR)	1 (0–1)	1 (0–1)	1 (0–2)	0.87
ICU-mortality, *n* (%)	11 (26)	3 (21)	8 (33)	0.48

IQR, interquartile range; SOFA, sequential organ failure assessment; NA, not applicable; ICU, intensive care unit.
"Delayed or no intubation" group consisted of patients receiving non-rebreather mask for equal to or more than 24 h or high-flow nasal oxygen for any period of time or non-invasive mechanical ventilation for any period of time in an attempt to avoid intubation. The remaining intubated patients comprised the "early intubation" group.
Six patients admitted in the ICU were not intubated and therefore were included in the delayed or no intubation group. Four patients (transferred intubated from another hospital) were not categorized into the early vs. delayed or no intubation group due to unavailability of relevant data.
Cardiovascular comorbidities included congestive heart failure, hypertension, coronary artery disease, dyslipidemia and valvular dysfunction.

our finding regarding mortality rate may highlight the beneficial effect of protecting health-care care systems (e.g., through early flattening of the epidemiological curve) from overwhelming on outcomes of critically ill patients with COVID-19.

We found that a strategy of early intubation, as opposed to delayed or no intubation, was not associated with worse clinical outcomes, such as mortality, ventilator-free days and ICU-free days. Rather, it seems that the difference in terms of mortality (early: 21% vs. delayed or no: 33%) and ventilator-free days (early: 3 vs. delayed or no: 2 days) was in favor of the early than the delayed or no intubation strategy. Especially, the observed 12% absolute reduction in mortality with early intubation (which did not reach statistical significance, presumably due to small sample size) may indeed be clinically significant. This finding does not seem to justify the hesitance of clinicians to perform early intubation in concern that it may inadvertently lead to

otherwise preventable intubations. In the light of our finding that an early intubation strategy might not be associated with increased mortality and morbidity, one could advocate this approach when taking into consideration its potential benefit of reduced viral aerosolization. To this end, early intubation and avoidance of prolonged use of high-flow nasal oxygen and non-invasive mechanical ventilation (although a short trial should not be precluded) has been advised by various societies' guidelines to prevent risks for patients and healthcare workers (18, 19).

In addition to its usage as an infection control measure, early intubation could also serve as a means to prevent both emergent intubation and patient self-inflicting lung injury. Regarding emergent intubation, its avoidance could improve outcomes, including mortality (20), by reducing incidence of hypoxemia (21). Regarding patient self-inflicting lung injury, its prevention and the subsequent pulmonary-renal crosstalk (with or without the effect of intrathoracic pressures and positive end-expiratory pressure) might explain our finding that need for continuous renal replacement therapy was lower (albeit statistically non-significant) in the early vs. the delayed or no intubation group (29 vs. 50%) (22, 23). The latter finding could also be explained by the relative dehydration of patients struggling to maintain normoxemia and avoid intubation through the prolonged usage of non-rebreather mask or high-flow nasal oxygen or non-invasive mechanical ventilation.

Our study has limitations. Firstly, although we included all consecutive patients admitted in our hospital, our retrospective single-center study still has a moderate sample size. However, this is the case for several other studies involving critically ill patients with COVID-19 (17, 24). Also, the moderate sample size is the fortunate outcome of the early flattening of the epidemiological curve in Greece and eventually the reason we were able to estimate the effect of early vs. delayed or no intubation on outcomes of patients with COVID-19 without the major confounding factor of the shortage of ventilators. Secondly, similar to the vast majority of studies in the field of COVID-19 (1, 8, 25), our study is observational and therefore subject to confounding. Even though there was no difference at baseline between the compared groups in terms of variables known to affect prognosis of patients with COVID-19, such as age, comorbidities and severity of illness (as assessed by SOFA) (1), we cannot preclude potential residual confounding, which could only be eliminated if the study was designed as a randomized controlled trial. Besides, our main finding persisted even after adjusting for sex. Thirdly, although we presented data on pulmonary and circulatory SOFA at baseline (**Table 1**), we did not collect specific data on respiratory rate and heart rate, which could further inform readers regarding the decision for intubation. Finally, one could argue that the comparison of early vs. delayed intubation (i.e., after exclusion of ICU patients who were not intubated) should be the primary analysis of our report. To that end, we presented the aforementioned analysis in the **Supplementary Table** and found similar results as in our main analysis. Moreover, the fact that an early intubation strategy was not associated with worse outcomes even when the comparator included never intubated patients may further strengthens the findings of our study.

CONCLUSIONS

The findings of our study suggest that early intubation, as opposed to delayed or no intubation, may not be associated with worse outcomes among critically ill patients with COVID-19. Given the observed lack of a negative effect of early intubation on mortality and morbidity of critically ill patients, such a therapeutic approach could be considered to avoid viral cross-contamination and to prevent self-inflicting lung injury. Thus, our study may justify further research with a prospective, randomized controlled trial.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Institutional Review Board of Evangelismos approved of this study (#212, 2020) and waived the need for informed patient consent. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

IS, EX, CR, and SZ study concept and design. IS, TN, DZ, and EM acquisition of data. EX and IS first drafting of the manuscript. EX statistical analysis. IS and SZ obtained funding and study supervision. AK and SZ administrative, technical, and material support. IS had full access to all the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis, and data access and responsibility. All authors read and approved the final manuscript, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2020.614152/full#supplementary-material

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Room to Breathe: The Impact of Oxygen Rationing on Health Outcomes in SARS-CoV2

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As the primary surge of coronavirus disease 2019 (COVID-19) wanes in many countries, it is important to reconsider best practice. More cases, probably the majority of cases, are yet to come. Hopefully, during this next phase, we will have more time, more resources, and more experience from which to affect better outcomes. Here, we examine the compromised oxygen strategy that many nations followed. We explore the evidence related to such strategies and discuss the potential mortality impact of delaying oxygen treatment in COVID-19 pneumonia.

Keywords: guidelines, hypoxia, SARS - CoV-2, treatment, oxygen, COVID-19, healthcare, rationing

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) is a new viral infection in humans, causing what has been termed COVID-19 (coronavirus disease 2019). For many, the illness is mild, often causing an upper respiratory tract infection (URTI). For a few, the disease progresses to a lower respiratory tract infection, and invariably, chest imaging shows this as a viral pneumonia (1). Again, most recover, but for some, the disease does not abate, and they go on to develop acute respiratory distress syndrome (ARDS) (2).

The rate of progression from mild (URTI or other viral constellation) to severe (pneumonia) to critical (ARDS) is not entirely clear. Estimates range between 76 and 99% for mild disease, 1 and 24% for progressive pneumonic illness, and 0.6 and 13% for further progression to ARDS. The true mortality rate also remains relatively unclear with estimates of <1% to over 10% and is likely to depend in part on access to appropriate health care (3–5).

Wuhan (China), Lombardy (Italy), Madrid (Spain), London (UK), and New York (USA) each experienced a surge of cases to the point where the local health services struggled to provide optimal care to all patients (6). During this "surge" period, the decision was made by some healthcare systems to ration oxygen, i.e., to delay the initiation of oxygen and to permit patients to maintain lower oxygen levels than would normally be accepted (7).

Such "conservative" oxygen strategies continue in many parts of the world despite adequate healthcare capacity and resources (8–12). The concern then is that patients are going without optimal treatment not due to excess demand on the health service but due to a practice established during actual or feared resource limitations.

To appreciate the impact of oxygen rationing on health outcomes during the COVID-19 pandemic, the evidence behind the "conservative" oxygen approach was examined, specifically for mortality outcomes.

THE GUIDELINES

The normal, mean oxygen saturations (SpO2) across an adult population has been reported as 97.5% (±1.5%) within a mean age of 63 years (range, 38–83 years). Approximately 7% of the population is classified as hypoxic at baseline (SpO2 <95%) (13).

Current treatment guidelines for community acquired pneumonia, including viral pneumonia, recommend commencement of supplemental oxygen when SpO2 falls below 95% and recommend a maintenance target SpO2 of 94–98% in the majority of patients (14).

The recent World Health Organization (WHO) COVID-19 treatment guidelines recommend to maintain target SpO2 of >90% in adults and between 92 and 95% in pregnant women (15).

The COVID-19 guidelines produced by the Surviving Sepsis Campaign (SSC) suggest (at recommendation 23) that supplemental oxygen should be commenced when a patient's SpO2 is <92%. The guidelines also recommend a "conservative oxygen" strategy for all patients with COVID-19 aiming for target SpO2 between 92 and 96%. The panel go on to explain how their concern for potential resource limitations influenced the clinical recommendations (16):

"Considering the associated patient harm at the extremes of SpO2 targets and the increased cost of liberal oxygen use, as well as the potential to reduce equity if oxygen resources are depleted, the panel issued a strong recommendation against using oxygen to target SpO2 >96%, and a strong recommendation to avoid lower values (SpO2 <90%)" (16).

THE EVIDENCE BEHIND THE "CONSERVATIVE OXYGEN" STRATEGY

The WHO references its own general pediatric guidelines. The SSC guidelines reference the five most pertinent publications, reviewed below (17–21).

The first was a retrospective analysis published in March 2020, investigating the optimal oxygen saturations (SpO2) for patients admitted to Intensive Care Units (ICU). The investigators analyzed over 35,000 patients and concluded that the optimum oxygen range for patients in ICUs was 94–98%. Patients who spent only 40% in the optimal range had a 50% increased mortality than those who spent 80% in the optimal range of SpO2 94–98% (17). The investigators corrected for a number of confounders, including disease severity.

The second study referenced by the SSC guidelines is the Improving Oxygen Therapy in Acute Illness (IOTA) meta-analysis examining liberal vs. conservative oxygen use in patients with a variety of conditions [stroke ($n = 8$), myocardial infarction ($n = 6$), cardiac arrest ($n = 2$), acute appendicitis ($n = 2$), critical care ($n = 2$), sepsis ($n = 1$), septic shock ($n = 1$), perforated viscus ($n = 1$), limb ischemia ($n = 1$), and traumatic brain injury ($n = 1$)] (18).

None of the studies reviewed in the IOTA meta-analysis examined pneumonia. Perhaps of some relevance are the two critical care studies analyzed (22, 23).

The first was a randomized controlled trial (RCT) examining the effect of conservative oxygen (defined in this study as SpO2 of 94–98%) and liberal oxygen (97–100%) on mortality in an ICU. The supplementary data suggest that the liberal group was significantly more acutely unwell *on admission* than the conservative group (for example, respiratory failure of 30.2 vs. 17.4%; mechanical ventilation at admission of 27 vs. 16.1%; liver failure of 33.3 vs. 22.5%; and renal failure of 45.7 vs. 25%). This RCT reported improved mortality in the conservative, SpO2 94–98% group (22).

The second critical care study examined in the IOTA meta-analysis was a pilot RCT study examining conservative oxygen targets (88–92%) vs. liberal oxygen targets (>96%) in patients on mechanical ventilation ($n = 103$). It is of note that 21% of the conservative arm were chronic obstructive pulmonary disease (COPD) patients vs. only 10% of patients in the liberal oxygen arm. The mean oxygen levels in each group over the study period were 93.4% in the conservative arm and 97% in the liberal arm. The study did not identify any difference in mortality between the two groups (23).

All of the other trials analyzed in the IOTA meta-analysis had little relevance to optimum oxygen saturations in patients with pneumonia or ARDS. Most of the studies were testing supplemental oxygen as a potential treatment (for example in stroke or myocardial infarction). Further, patients who were hypoxic were excluded from almost half the trials analyzed. The mean oxygen saturation (where the data was available) in the liberal group was 96.4%, and in the conservative group was 96.7%. Following trial sequential analysis, the authors concluded that hyperoxemia carried an increased 1-year mortality risk [hazard ratio (HR), 1.11 (95% CI 1.00–1.24), $p = 0.05$]. The authors go on to suggest that the ideal target SpO2 for all admissions *might* be 94–96%. With the regression analysis likely powered by the true hyperoxemic trials and the marked heterogeneity within the studies analyzed, the reason for the authors equivocation seems justified (18).

The third paper referenced in the SSC guidelines was an opinion paper making recommendations based on the IOTA meta-analysis (19).

The fourth paper was an RCT examining conservative (90–96%) vs. normal oxygen targets during mechanical ventilation in the ICU ($n = 1{,}000$). Over 22 days, the conservative group spent 28 h more with an Fio2 of <0.21 than the usual group, and a total of 22 h less time above SpO2 of 96% than the usual group. The mean oxygen level range over the course of the study were PaO2 of 80–85 mmHg (∼SpO2 of 95–96%) in the conservative group and PaO2 of 90–95 mmHg (∼SpO2 of 96–97%) in the normal group. There was no significant mortality difference noted (20).

The final paper referenced was an RCT into the use of conservative oxygen levels (sats 88–92%) vs. liberal oxygen use (sats >96%) in ARDS ($n = 205$). Relatively strict adherence to target saturations were observed with a mean range of SpO2 of 92–93% in the conservative group vs. 95–97% in the liberal group. The study was halted due to excessive death in the conservative oxygen arm vs. the liberal arm (44.4 vs. 30.4% 90-day mortality). As well as the 23% increased ICU mortality, 27% increased 28-day mortality, and the 50% higher 90-day mortality,

TABLE 1 | Relevant studies comparing conservative vs. liberal oxygen strategies in acute illness.

Study	Methods	Findings	Comment	Suggestions
Chu et al. (18)	Meta-analysis (up to Oct 2017) of trials comparing liberal vs. conservative oxygen strategies in a variety of conditions(n = 16,037)	"hyperoxemia" carries an increased 1-year mortality risk [HR 1.11 (95% CI 1.00–1.24), p = 0.05)	Heterogenous studies, examining oxygen therapy mainly in ischemic conditions. Unreliable in relation to oxygen targets in acute nonischemic illness.	Optimum target saturations *might* become unfavorable above SpO2 of 94–96%
Girardis et al. (22)	Single-centered, open-labeled RCT Conservative (SpO2 of 94–95%) vs. liberal (SPO2 of 97–100%) in ICU admissions of any cause (n = 434)	Improved mortality in conservative group (SpO2 of 94–98%): RR 0.57 (95% CI 0.37–0.9, p = 0.01)	Liberal group had significantly more medical problems at enrolment.	Target sats of 94–98%
Panwar et al. (23)	Pilot multicenter RCT SpO2 of 88–92% vs. 96%in patients requiring MV of any cause (n = 103)	No difference in mortality or length of ICU stay	21% of the conservative group had COPD vs. only 10% of the liberal. Actual comparison was SpO2 of 93.4 vs. 97%	Larger trial needed
Schernthaner et al. (24)	Retrospective observational studies comparing arterial blood gases and mortality in pulmonary edema and heart failure (n = 475)	Increased mortality in patients with pneumonia with arterial PO2 of 150 vs. 117 mmHG (HR = 1.02; 95% CI: 1–1.4, p = 0.02)	Pneumonia related Nontrial data Potentially measuring true hyperoxemia effects.	Optimal PO2 calculated as 98 mmHg (or ∼SpO2 of 97.3%)
van den Boom et al. (17)	Multicenter, retrospective observational analysis of SpO2 and mortality in ICU patients of any cause (n = 35,000)	Increased mortality with mean SpO2 92 vs. 96% [OR, 3.2 (2.9–3.5)]. Increased mortality with mean SpO2 100 vs. 96% [OR 1.6 (1.5–1.6)] (n = 26,723).	Large patient numbers utilizing shared datasets. Not a clinical trial.	Optimum target SpO2 is 94–98%
IICU-ROX Investigators the Australian New Zealand Intensive Care Society Clinical Trials Group et al. (20)	Multicenter, RCT SpO2 of 92–96% vs. normal in patients requiring MV of any cause (n = 1,000)	No difference in mortality or length of ICU stay	Actual Comparison was mean SpO2 of 95–96% vs. 96–97%	None made
Barrot et al. (21)	Multicenter, RCT SpO2 of 88–92% vs. >96%in patients with ARDS of any cause (n = 205)	Study halted due to safety. Significantly higher mortality in the conservative oxygen group. Ninety-day mortality was 44% in conservative arm vs. 30.4% in liberal arm.	Actual Comparison was mean SpO2 of 92–93% vs. 95–97%	None made

RCT, randomized controlled trial; SpO2, oxygen saturations; HR, hazard ratio; RR, relative risk; OR, odds ratio (adjusted); ICU, intensive care unit; MV, mechanical ventilation.

the complications in the conservative arm included mesenteric ischemia (5 vs. 0%) and cardiac arrhythmias (44 vs. 28%). Target oxygen saturations lower than that currently recommended were shown to substantially increase mortality (21).

DISCUSSION

Instigating a "conservative oxygen" strategy as a means of healthcare rationing is likely to contribute to the higher mortality experienced during a COVID-19 "surge." The evidence for a significant increase to mortality rate was particular strong for targeting lower oxygen saturations (<94%). The evidence of harm when restricting the upper limit of oxygen saturations (98–96%) was less convincing (**Table 1**). It is of note that the recent British Thoracic Society (BTS) guidelines specifically for COVID-19 advises a target SpO2 of 94–98% (25).

Hypoxia (SpO2 < 95%) has numerous adverse health effects. In the acute setting, hypoxia increases the risk of fatal arrhythmia and end-organ damage (26). In a subacute setting, hypoxia has been shown to drive pulmonary inflammation and the systemic inflammatory response (27, 28) and to promote coagulation leading to an increase in thromboembolic events (29, 30). Long-term effects of hypoxia include ongoing cognitive impairment (31).

In relation to pneumonia specifically, delayed correction of hypoxia has been shown to lead to a more protracted and severe pneumonia, an increase in the rate of mechanical ventilation, and an increase in actual mortality (32, 33).

There is no evidence to suggest that the pathophysiology of COVID-19 pneumonia is exempt from these established detrimental effects of hypoxia. Indeed, there is evidence to suggest earlier correction of hypoxia in COVID-19 pneumonia may lead to improved outcomes. Shenoy et al. highlight the exacerbation of hypoxia on angiotensin-converting enzyme 2 (ACE2) upregulation and pulmonary vasoconstriction in COVID-19 pneumonia, suggesting that "permitted hypoxia" may be leading to more severe disease (34). Ackermann et al. examined autopsy specimens from influenza (H1N1) and COVID-19 cases and found a greater level of intussusceptive angiogenesis and alveolar microthrombi in COVID-19—both of which can be caused/exacerbated by hypoxia (35). It is of note that the H1N1 outbreak did not incur oxygen rationing.

Of the large postmortem cohort studies, an Italian cohort ($n = 38$) and a US cohort ($n = 67$) both report a hypercoaguable state with pulmonary thromboembolism in medium or small arteries in over 80% of COVID-19 lung specimens examined (36, 37). Both the US and Italy adopt a conservative oxygen strategy [SpO2 <92% prior to the commencement of oxygen (10, 11)]. The largest Swiss postmortem cohort ($n = 21$), where standards of oxygen targets have been maintained (SpO2 of 94–98%) (38), found that only 19% had evidence of peripheral or central pulmonary thromboembolism (39). There are inadequate numbers of postmortem studies globally to generate any form of conclusions, but given that hypoxia is known to cause a hypercoaguable state, likely to be exacerbated under proinflammatory conditions, and hypoxia itself further promotes pulmonary inflammation, we should be mindful of the likelihood that delayed correction of hypoxia in COVID-19 patients increase the propensity for, and therefore damage caused by, thromboembolism of the pulmonary vasculature.

In-keeping with this, Sun et al. reported a reduction in ICU admissions and mechanical ventilation by early identification and correction of hypoxia in patients with COVID-19 (40).

While such evidence is welcomed, we must be clear that it is not a requirement for the established pneumonia guidelines to prove efficacy in COVID-19 pneumonia. Target oxygen saturations in acute illness, pneumonia, and COVID-19 pneumonia remain at SpO2 of 94–98% (14, 25, 41). In the complete absence of any evidence to support an improved outcome—or even convincing evidence of the same outcomes—for lower target oxygen saturations in COVID-19 pneumonia, and with the more recent trials showing a convincing increase in mortality of conservative oxygen strategies, clinicians must continue to advocate for improved access to care and must not accept suboptimal or harmful amendments to established standards of care, certainly not based on an evidential argument.

While the scientific evidence provides no defense for lowering target oxygen saturations in COVID-19 pneumonia, there may be local civil contingency or procurement rationale for implementing such policies. The UK-wide directive to ration oxygen to patients, issued by the National Health Service (NHS) England in April 2020, may have been such a resource-related recommendation (7). Such a directive—where the evidence for harm is substantial—poses a considerable challenge to healthcare providers. The evidence is quite clear that a delay in the initiation of oxygen to the hypoxic, pneumonic patient leads to higher rates of mechanical ventilation, prolonged hospital stays, higher mortality, and, crucially, from a civil contingency standpoint, the real possibility of an overall increased consumption of oxygen supplies. There is also no evidence to suggest that COVID-19 pneumonia will differ in this regard. As such, and while we appreciate the challenging decisions relating to resource allocations, we must continue to advocate for improved access to treatment. That is, the decision to conserve oxygen and reduce target oxygen saturations in COVID-19 patients may well be made on a resource-limitation perspective, but it is done so within the fully transparent evidence that such compromise will cost lives.

The identification of the COVID-19 phenomenon of "silent hypoxia" adds further levels of complexity to frontline healthcare providers. The evidence already alluded to clearly support efforts to maintain the standards of care of COVID-19 patients to at least that afforded patients with other forms of viral pneumonia. Given that there are these "silent hypoxic" COVID-19 patients who do not complain of shortness of breath yet suffer marked hypoxia at rest, then—if the aim is to reduce mortality—we cannot rely on the self-reported symptom of breathlessness to identify those requiring further assessment and/or supplemental oxygen (42). Lower thresholds for measuring oxygen levels in patients suspected or confirmed to have COVID-19 may be prudent. This of course challenges the "stay home" approach adopted by a number of nations in favor of an "early assessment and ongoing vigilance" approach as adopted by the likes of Singapore, Australia, and Japan.

Similar to Middle East respiratory syndrome (MERS) and SARS, evidence is growing of a prolonged recovery time, and disability, following COVID-19 pneumonia (43). The largest study to date examined 548 patients more than 3 months after discharge from hospital and compared them to local controls. Half of the patients suffered prolonged symptoms (fatigue/physical decline, dyspnea, tachycardia, and alopecia), but <10% had persistence of these symptoms at 3 months. Of considerable note is that the only acute symptom present on initial admission to hospital that was associated with persistent symptoms (fatigue/physical decline, dyspnea, and tachycardia) was shortness of breath. A further UK cohort revealed a startling 85% of patients suffering prolonged symptoms who stayed home during the initial infection suffered breathlessness ($n = 164$) (38). Prolonged hypoxia during the active infection may account for some of the more prolonged disability following COVID-19.

Many countries have not taken a "conservative" oxygen approach to COVID-19. Most notably, Singapore, Switzerland, and Austria have maintained target SpO2 of >94% throughout the outbreak (24, 44); (45). Other countries with similar population burdens of total COVID-19 cases have taken a conservative oxygen approach. Most notably, the US, UK, Italy, France, and Spain have all maintained guidelines permitting a delay in the initiation of oxygen until oxygen saturations are ≤92% (8–12). Within the context of reduced vigilance and an overexuberant "stay home" message, the excess mortality caused by such conservative oxygen strategies are likely to be compounded further. Most certainly, patients with COVID-19 require more care and attention, not less.

The reason some nations have employed a "conservative oxygen strategy" remains largely unknown. The UK, and perhaps the US, was concerned about oxygen provisions (7, 10). The UK specifically was concerned with the "rate of flow" (not the actual oxygen supply). Would the system (pipes and valves) handle the increased draw? There is also the possibility that the implementation of a conservative oxygen strategy was motivated to permit more patients to be managed at home or indeed to remove them from healthcare follow-up altogether and, as such, relieve the healthcare system. No modeling regarding such an approach has been published. Indeed, failing to correct hypoxia earlier is likely to compound the pressures on the high-intensity,

high-skilled clinical care areas (e.g., Respiratory and Intensive Care Wards).

CONCLUSION

During a surge of cases that overwhelms a local healthcare system, there will be many compromises. It is likely that some of these compromises will have an impact on morbidity and mortality. It is then important to readjust quality and standards back to optimum when a healthcare system begins to recover or, where the healthcare system continues to struggle, place greater emphasis and effort into building healthcare capacity.

A conservative oxygen approach is a compromise that carries a significant mortality impact in COVID-19 pneumonia. Just as in other pneumonias, the time taken to correct hypoxia relates to disease severity, disease burden, and mortality. As the focus shifts to re-establishing healthcare capacity, improving the identification of the hypoxic patient and improving access to supplemental oxygen—delivered optimally—likely represent an appreciable modifiable factor in the bid to reduce the morbidity and mortality associated with the COVID-19 pandemic.

With regard to target oxygen saturations specifically, the evidence is clear: target oxygen saturations for the majority of people with COVID-19 remain at 94–98% [for acidotic type 2 respiratory failure see specific guidelines (25)].

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

DG, FM, and SB contributed to the conception and writing of the article.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
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Acute Functional Outcomes in Critically Ill COVID-19 Patients

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Background: COVID-19 (Coronavirus Disease 2019) is a global cause of morbidity and mortality currently. We aim to describe the acute functional outcomes of critically ill coronavirus disease 2019 (COVID-19) patients after transferring out of the intensive care unit (ICU).

Methods: 51 consecutive critically ill COVID-19 patients at a national designated center for COVID-19 were included in this exploratory, retrospective observational cohort study from January 1 to May 31, 2020. Demographic and clinical data were collected and analyzed. Functional outcomes were measured primarily with the Functional Ambulation Category (FAC), and divided into 2 categories: dependent ambulators (FAC 0–3) and independent ambulators (FAC 4–5). Multivariate analysis was performed to determine associations.

Results: Many patients were dependent ambulators (47.1%) upon transferring out of ICU, although 92.2% regained independent ambulation at discharge. On multivariate analysis, we found that a Charlson Comorbidity Index of 1 or more (odds ratio 14.02, 95% CI 1.15–171.28, $P = 0.039$) and a longer length of ICU stay (odds ratio 1.50, 95% CI 1.04–2.16, $P = 0.029$) were associated with dependent ambulation upon discharge from ICU.

Conclusions: Critically ill COVID-19 survivors have a high level of impairment following discharge from ICU. Such patients should be screened for impairment and managed appropriately by rehabilitation professionals, so as to achieve good functional outcomes on discharge.

Keywords: SARS-CoV-2, critical illness, coronavirus, acute respiratory distress syndrome, dependent ambulation, intensive care units, dyspnea, muscle weakness

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INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) presents with various degrees of severity, with a significant proportion developing critical illness (1, 2). In these patients, acute respiratory distress syndrome (ARDS) is the most common complication, though encephalopathy, shock, myocardial injury, thromboembolism, and acute kidney injury can also co-exist (3–5). Although it is estimated that many critically ill COVID-19 patients survive (6), it is likely that mechanical ventilation and prolonged bed rest or immobilization can lead to detrimental neuromuscular and cardiorespiratory impairments after critical care, as part of the post-intensive care syndrome (7, 8). Critically ill COVID-19 patients tend to be older and may have comorbid conditions, including hypertension,

diabetes mellitus, and cardiac disease (9), which can exacerbate physical function deterioration during critical care.

The surging number of critically ill COVID-19 survivors with widespread disability after discharge from intensive care unit (ICU) is hence expected to present a major rehabilitation need (10). Despite discharge from ICU, these patients may still be functionally dependent due to cardiopulmonary and neuromuscular sequelae of critical illness, such as exertional desaturation (11), platypnea-orthodeoxia (12) and ICU-acquired weakness (ICUAW) (13). Despite the need for acute rehabilitation after ICU, there has been a scarcity of reports on the prevalence and associations of functional dependence in critically ill COVID-19 survivors after ICU stay.

We therefore aim to describe the acute functional outcomes and associations of dependence in walking in critically ill COVID-19 patients after ICU stay. We also describe the cardiopulmonary and neurological sequelae of critical illness contributing to functional dependence.

MATERIALS AND METHODS

Study Design and Participants

We retrospectively reviewed medical records of 62 consecutive critically ill COVID-19 patients admitted to the Intensive Care Unit (ICU) of the National Center for Infectious Diseases, Singapore, between January 1, 2020 to May 31, 2020. The 330-bed National Center for Infectious Diseases, Singapore is the national designated center for COVID-19 patients.

Patients were included if they had laboratory-confirmed COVID-19 and had critical illness as defined by the development of ARDS (14). All patients either required mechanical ventilation or had a fraction of inspired oxygen (FiO_2) of at least 60% or more (2). All critically ill patients were admitted to the ICU. Laboratory testing for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection was done using SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) of nasopharyngeal, oropharyngeal, or endotracheal aspirate swab samples. There were 2 patients who were admitted to ICU for non-respiratory complications and nine patients who had died during ICU stay. These patients were excluded from this study. The present study was approved by the ethics committee at our institution (NHG DSRB 2020/00639). The requirement for informed consent was waived by the hospital's ethics commission. No sample size calculation was performed due to the exploratory nature of the study. This manuscript adheres to the applicable STROBE guidelines.

Data Collection

Baseline demographic and clinical characteristics of the patients, including age, sex, ethnicity, body mass index (BMI), premorbid function, comorbidities, and chest radiography findings on admission were extracted from inpatient hospital electronic medical records. In addition to studying individual preadmission comorbidities, comorbidities were also represented using the Charlson Comorbidity Index (CCI), a validated tool for comorbidity adjustment (15). Details of the patient's ICU stay were recorded, including the PaO_2/FiO_2 (PF) ratio at admission to ICU, length of ICU stay and the ICU therapies received (high flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, prone positioning, neuromuscular blockade, extracorporeal membrane oxygenation, vasopressors, and tracheostomy creation). Complications during the ICU stay, namely, ARDS, hospital acquired pneumonia, pneumothorax, myocardial infarction, thromboembolic event, acute renal failure requiring renal replacement therapy (RRT), and the presence of encephalopathy, were also recorded.

Outcome Measures

The primary functional outcome of patients was measured using the Functional Ambulation Category (FAC) score, which ranges from 0 to 5. This is an observer-assessed score, and we categorized patients into whether they were dependent or independent walkers (16, 17). Dependent walkers required varying degrees of support from another person and were represented by FAC scores of 0 (unable to walk or require 2 or more persons), 1 (requires continuous manual contact), 2 (requires intermittent or continuous light touch) or 3 (requires standby guarding of one person for safety or verbal cueing). An independent walker was represented by an FAC score of 4 and 5, meaning a person who could walk only on level surface or any surfaces including stairs, respectively. A secondary outcome measured was ADL dependence of patients, as defined by being unable or needing help bathing, dressing, toileting, transferring, or eating (18, 19). Another secondary functional outcome was whether patients required supplemental oxygen at rest to achieve a target oxygen saturation of >90% (20). The FAC score, dependence in ADLs and requirement for supplemental oxygen at rest were obtained prior to ICU admission, on the day of transfer out of ICU and the day of hospital discharge based on medical records.

Physical Sequelae After Critical Illness Contributing to Functional Impairments

Patients were referred for physical therapy after transferring out from ICU if they had functional impairments. These patients were assessed for respiratory or cardiac symptoms. Their heart rate, blood pressure, SpO_2 (oxygen saturation by pulse oximetry) and muscle strength of the shoulder, elbow, wrist, hip, knee and ankle using the Medical Research Council scale were recorded. These patients also had continuous SpO_2 and heart rate monitoring if they had respiratory or cardiac symptoms. The cardiopulmonary and neuromuscular sequelae of these patients undergoing physical therapy were then classified into one or more of the following: Orthostatic hypotension (defined as a drop in systolic blood pressure of at least 20 mmHg and/or diastolic blood pressure of at least 10 mmHg within 3 min of standing) (21), presence of exertional dyspnea, exertional desaturation (defined as reduction of SpO_2 $\leq$90% or relative reduction of 5% during exercise, lasting for 0.5–5.0 min) (11), platypnea-orthodeoxia syndrome (defined as a orthostatic dyspnea and a drop in >5% SpO_2 or a PaO_2 > 4 mmHg) (22) or ICUAW (defined as a summed score of <48 with 12 muscle groups being assessed on the Medical Research Council scale or a mean score of <4 in all testable muscle groups) (23, 24). These physical sequelae of critical illness were then compared between

patients receiving invasive mechanical ventilation against those that did not have invasive mechanical ventilation. If the patients were not functionally independent for discharge, they were then transferred to an inpatient rehabilitation facility.

Statistical Analysis

Descriptive statistics were utilized to illustrate patient demographics and clinical characteristics. There were no missing data. The distribution of categorical variables was compared using chi-square or Fisher's exact test. Variables were subjected to univariate analysis investigating their relationship with the primary outcome of independent ambulation upon transfer out of ICU as defined by a FAC score of 4 or 5. These variables analyzed were age, sex, ethnicity, BMI, comorbidities, CCI of 1 or more (25), hospital acquired pneumonia, pneumothorax, myocardial infarction, thromboembolic event, acute renal failure requiring RRT, encephalopathy, PF ratio, prone position, neuromuscular blockade, extracorporeal membrane oxygenation, vasopressors, tracheostomy creation, and length of stay in ICU. Variables which were significant on univariate analysis (age, chronic kidney disease, CCI of 1 or more, hospital acquired pneumonia, thromboembolic event, acute renal failure requiring RRT, tracheostomy, length of stay in ICU) were then subjected to logistic regression analysis. A $P < 0.05$ was considered statistically significant for a two-tailed test. Statistical analyses were generated using SPSS Version 25.0 (IBM Corp., Armonk, New York, USA).

RESULTS

There were 51 consecutive patients with critically ill COVID-19 enrolled in the study, with the majority being of male gender and Chinese ethnicity. All patients were premorbidly independent in walking and in basic ADLs, and none required supplementary oxygen at rest. The most common preadmission comorbidities were hypertension (41.2%), diabetes (27.5%) chronic cardiac disease (11.8%) and chronic kidney disease (9.8%). Most of the patients had a CCI of 0 (60.8%). All patients had abnormal chest radiography findings on admission, and all had ARDS, with a mean PF ratio (SD) at admission to ICU of 170.1 (55.9). The most common complications in the ICU apart from ARDS were hospital-acquired pneumonia (27.5%), followed by myocardial infarction (15.7%), thromboembolic events (9.8%), acute renal failure requiring RRT (9.8%), pneumothorax (5.9%), and encephalopathy (3.9%). None of the patients had pre-existing neuromuscular disorders or received corticosteroids during ICU admission, and no patients developed stroke as a complication during their hospital stay (which might have impacted their FAC score). There were 28 patients (54.9%) who required invasive mechanical ventilation, with a mean duration (SD) of invasive mechanical ventilation of 15.6 (16.1) days (**Table 1**).

Upon transfer out of ICU, there were 24 patients (47.1%) who were dependent walkers (defined as FAC of 0–3) with 22 patients (43.1%) who were dependent in 1 or more basic ADLs. However, upon discharge, a majority achieved independence in ambulation and basic ADLs (92.2 and 90.2%, respectively). All 41 patients (80.4%) who required continuous supplementary oxygen upon transferring out of ICU did not require supplementary oxygen on discharge (**Table 2**).

TABLE 1 | Clinical characteristics of study population.

Characteristics	*N* = 51
Age, years, mean (SD)	56.3 (13.1)
Sex, male/female	37/14
Ethnicity, *n* (%)	
- Chinese	31 (60.8)
- Malay	9 (17.6)
- Indian	3 (5.9)
- Others	8 (15.7)
Body mass index, mean (SD)	27.0 (5.38)
Premorbid independent in walking, *n* (%)	51 (100)
Premorbid independent in basic ADLs, *n* (%)	51 (100)
Preadmission comorbidities	
- Hypertension	21 (41.2)
- Diabetes mellitus	14 (27.5)
- Chronic cardiac disease	6 (11.8)
- Chronic kidney disease	5 (9.8)
- Chronic obstructive pulmonary disease	1 (2.0)
- Asthma	1 (2.0)
- Chronic neurological disease or dementia	1 (2.0)
- HIV infection	1 (2.0)
- Liver cirrhosis of any Child-Pugh class	1 (2.0)
Charlson Comorbidity Index, *n* (%)	
- 0	31 (60.8)
- 1	11 (21.6)
- >1	9 (17.6)
Abnormal chest radiography findings on admission, *n* (%)	51 (100)
PF ratio at admission to ICU, mean (SD)	170.1 (55.9)
Complications during ICU stay, *n* (%)	
- ARDS	51 (100)
- Hospital acquired pneumonia	14 (27.5)
- Pneumothorax	3 (5.9)
- Myocardial infarction	8 (15.7)
- Thromboembolic event	5 (9.8)
- Acute renal failure requiring RRT	5 (9.8)
- Encephalopathy	2 (3.9)
ICU therapy, *n* (%)	
- High flow nasal cannula	23 (45.1)
- Non-invasive mechanical ventilation	0 (0)
- Invasive mechanical ventilation	28 (54.9)
- Prone position	30 (58.8)
- Neuromuscular blockade	18 (35.3)
- Extracorporealmembrane oxygenation	1 (2.0)
- Vasopressors	19 (37.3)
- Corticosteroids	0 (0)
- Tracheostomy	5 (9.8)
Length of stay in ICU, days, mean (SD)	14.3 (16.2)

Data are mean (SD) or n (%). PF ratio, PaO_2/FiO_2 ratio; ICU, intensive care unit; RRT, renal replacement therapy; ARDS, acute respiratory distress syndrome.

TABLE 2 | Functional outcomes of study population.

Characteristics	*N* = 51
Outcomes after transferring out of ICU, *n* (%)	
- Continuous supplementary oxygen required	41 (80.4)
- Dependent in walking	24 (47.1)
- Dependent in 1 or more basic ADLs	22 (43.1)
Outcomes on discharge, *n* (%)	
- Continuous supplementary oxygen required	0 (0)
- Dependent in walking	4 (7.8)
- Dependent in 1 or more basic ADLs	5 (9.8)
Require discharge to inpatient rehabilitation facility, *n* (%)	7 (13.7)
Length of stay in acute medical ward, days, mean (SD)	21.9 (17.1)
Total length of stay, days, mean (SD)	36.2 (31.3)

Data are mean (SD) or n (%). ICU, intensive care unit, ADL, activities of daily living.

On univariate analysis, we found that an older age, premorbid comorbidity of chronic kidney disease, a CCI of 1 or more, hospital acquired pneumonia, thromboembolic event, acute renal failure requiring RRT, having undergone a tracheostomy and a longer length of ICU stay were significantly associated with dependence in walking as defined by an FAC score of 0–3. However, on multivariate analysis, only a CCI of 1 or more (odds ratio 21.54, 95% CI 2.92–158.84, $P = 0.003$) and a longer length of ICU stay (odds ratio 1.33, 95% CI 1.06–1.66, $P = 0.013$) were identified as significant factors for dependence in walking (**Table 3**).

Table 4 describes the cardiopulmonary and neuromuscular sequelae of critical illness faced during physical therapy, comparing patients with invasive and non-invasive mechanical ventilation. Most of these sequelae were in patients who received invasive mechanical ventilation, with two patients (7.1%) experiencing orthostatic hypotension, eight patients (28.6%) experiencing exertional dyspnea, 12 patients (42.9%) experiencing exertional desaturation, four patients (14.3%) experiencing platypnea-orthodeoxia syndrome, and five patients (17.9%) experiencing ICUAW. Fewer complications were present in patients receiving non-invasive mechanical ventilation, although there were no statistical differences between both groups.

DISCUSSION

This study found that nearly half of our critically ill COVID-19 patients had impairments in physical function after ICU care, which were attributable to cardiopulmonary limitations or neuromuscular weakness. This is unsurprising, given that the duration of ICU stay has been reported to be substantially longer in COVID-19 infection at 2 weeks or longer compared to typical ICU populations (26, 27). Our study, similarly, reported an average ICU stay of 14.3 days. The significant functional impairments faced by critically ill COVID-19 survivors are further reflected in the finding that 13.7% of the study's patients were unsuitable for immediate discharge home and required further rehabilitation at an inpatient rehabilitation facility.

We also found significant physical sequelae of critical illness in our study population during physical therapy, especially in patients receiving invasive mechanical ventilation. The significant number of patients (17.9%) who had ICUAW in our study after receiving invasive mechanical ventilation is consistent with the intensive care literature for ARDS patients (23, 28, 29). ARDS survivors have also been reported to have dyspnea and exertion-related desaturation despite not requiring supplementary oxygen at rest, with similar findings reported in critically ill COVID-19 patients (11). A prospective study also found that patients with severe disease had poorer exercise intolerance reflected in lower 6 min walk distance and a higher incidence of diffusing capacity for carbon monoxide impairment compared to patients without severe disease during the early convalescence phase (30). These findings indicate that rehabilitation providers should have a high degree of suspicion for these neuromuscular and cardiopulmonary complications in critically ill COVID-19 survivors.

A unique cardiopulmonary sequelae in our study was COVID-19 associated platypnea-orthodeoxia syndrome, which has been hypothesized to be secondary to alveolar hypoventilation and microangiopathy resulting in gravitational exacerbation of intra-pulmonary shunt in ARDS (12). Additionally, in our cohort of patients receiving invasive mechanical ventilation, nearly half (42.9%) of the patients had exertional desaturation, although only 8 (28.6%) patients had subjective complaints of exertional dyspnea. We suspect that silent hypoxemia, which have been described in patients suffering from COVID-19 pneumonia, persists after the acute phase, explaining the hypoxemic and dyspneic events experienced by the patients (31). This represents a population of patients which will likely benefit from close monitoring during rehabilitation after recovering from the critical phase of the illness.

Apart from close monitoring of patient-reported symptoms and respiratory rate, we found that continuous pulse oximetry and heart rate monitoring during initial rehabilitation was essential in detecting and monitoring for cardiopulmonary rehabilitative complications in critically ill COVID-19 patients, especially given the high prevalence of exertional desaturation. Successful cardiopulmonary rehabilitation strategies that were employed included stepwise mobilization from bed exercises, pre-emptive increases in supplementary oxygen during physical therapy, and interval training sessions (12). A majority of patients were still able to progress to functional independence with none requiring supplementary oxygen on discharge, highlighting the importance of rehabilitation in facilitating discharge planning.

An increased length of stay in ICU and having one or more co-morbidity on the CCI in critical COVID-19 patients were found to be associated with increased dependency upon transfer out of the ICU. This is in keeping with studies in critically ill patients, where length of stay in ICU and the presence of co-morbidities have also been found to be poor prognostic factors (32, 33); similarly, a longer length of stay has been found to be associated with ICUAW in critically ill COVID-19 patients

TABLE 3 | Associations with dependence in walking (defined by FAC 0–3) upon transfer out of ICU.

	Univariate analysis	Multivariate analysis		
Characteristics	***P*-value**	**Odds ratio**	**95% CI**	***P*-value**
Patient factors				
Age, years	0.023	0.994	0.880–1.123	0.929
Sex	0.318	–	–	–
Ethnicity	0.720	–	–	–
Body mass index	0.324	–	–	–
Hypertension	0.183	–	–	–
Diabetes mellitus	0.375	–	–	–
Chronic cardiac disease	0.088	–	–	–
Chronic kidney disease	0.013	0	–	1.000
Chronic obstructive pulmonary disease	1.00	–	–	–
Asthma	1.00	–	–	–
Chronic neurological disease or dementia	1.00	–	–	–
HIV infection	0.471	–	–	–
Liver cirrhosis of any Child-Pugh class	1.00	–	–	–
Charlson Comorbidity Index (1 or more vs. 0)	0.008	21.54	2.92–158.84	0.003
ICU factors				
Hospital acquired pneumonia	0.005	1.85	0.145–23.51	0.636
Pneumothorax	0.060	–	–	–
Myocardial infarction	0.088	–	–	–
Thromboembolic event	0.012	0	0	1.000
Acute renal failure requiring RRT	0.012	0	0	1.000
Encephalopathy	0.131	–	–	–
PF ratio	0.277	–	–	–
Prone position	0.227	–	–	
Neuromuscular blockade	0.138	–	–	–
Extracorporeal membrane oxygenation	0.284	–	–	–
Vasopressors	0.076	–	–	–
Tracheostomy	0.013	0	0	1.000
Length of stay in ICU, days	<0.001	1.33	1.06–1.66	0.013

P < 0.05 was considered statistically significant. ICU, Intensive Care Unit; PF ratio, PaO_2/FiO_2 ratio.

TABLE 4 | Comparison of physical sequelae of critical illness upon transfer out of ICU between patients receiving non-invasive and invasive mechanical ventilation.

Characteristics	**Total (*N* = 51)**	**Non-invasive mechanical ventilation (*N* = 23)**	**Invasive mechanical ventilation (*N* = 28)**	***P*-value**
Orthostatic hypotension, *n* (%)	2 (3.9)	0 (0)	2 (7.1)	0.495
Exertional dyspnea, *n* (%)	10 (19.6)	2 (8.7)	8 (28.6)	0.091
Exertional desaturation, *n* (%)	16 (31.4)	4 (17.4)	12 (42.9)	0.051
Platypnea-orthodeoxia syndrome, *n* (%)	5 (9.8)	1 (4.3)	4 (14.3)	0.362
ICU-acquired weakness, *n* (%)	5 (9.8)	0 (0)	5 (17.9)	0.056

Data are n (%). ICU, intensive care unit. Variables were analyzed with the chi-square or Fisher's exact test.

(13). Post-ICU rehabilitation of critically ill COVID-19 patients, though beneficial, may not be feasible for all patients in a resource-constrained setting superimposed with cross-infection risks (34). We believe our study may be useful to identify a subset of patients, especially those with pre-existing health conditions or have a longer length of ICU stay, who may be more susceptible to critical illness sequelae and hence benefit from targeted rehabilitation screening and intervention (35).

There are several limitations in our study. Firstly, we did not utilize other functional measures of impairment or activity limitation such as the 6 min walk test, Functional Independence Measure, or instrumental ADL assessments due to manpower constraints, which might have led to our study underestimating the degree of functional dependence in this population. Secondly, a larger study population will be required to confirm the findings of this exploratory study. Thirdly, patients who died in ICU were excluded from this study. With emerging evidenced-based management guidelines leading to increased survival rates of critically ill COVID-19 patients, it is possible that functional impairments may become more prevalent in this population (36). Fourthly, we only reported acute functional outcomes after ICU stay and hospital discharge. Survivorship issues with regard to long-term mortality, physical function, cognitive function, psychological outcomes and health-related quality of life is likely to be significantly affected in this population, and further study is urgently needed.

CONCLUSIONS

We report a high prevalence of functional impairment and physical sequelae of critical illness in a cohort of critically ill COVID-19 patients. Targeted rehabilitative assessment and management in these patients are crucial in addressing the physical repercussions of COVID-19 related critical illness. Although larger studies are required to confirm the subtypes of patients who are most likely to benefit from targeted rehabilitative assessment, we believe our findings indicate that an individualized rehabilitative approach is vital in the acute convalescent phase to optimize survivorship after critical COVID-19 illness.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the National Healthcare Group Domain Specific Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MT, PO, and ST: contributed to the conception and design of the manuscript and drafting of the manuscript. MT and PO: acquisition, analysis, and interpretation of data. MT, PO, SP, and SL: performed final manuscript review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Short-Term Variations in Neutrophil-to-Lymphocyte and Urea-to-Creatinine Ratios Anticipate Intensive Care Unit Admission of COVID-19 Patients in the Emergency Department

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Background: Timely assessment of COVID-19 severity is crucial for the rapid provision of appropriate treatments. Definitive criteria for the early identification of severe COVID-19 cases that require intensive care unit admission are lacking.

Methods: This was a single-center, retrospective case-control study of 95 consecutive adults admitted to the intensive care unit (cases) or a medical ward (controls) for laboratory-confirmed COVID-19. Clinical data were collected and changes in laboratory test results were calculated between presentation at the emergency department and admission. Univariate and multivariable logistic regression was performed to calculate odds ratios for intensive care unit admission according to changes in laboratory variables.

Results: Of the 95 adults with COVID-19, 25 were admitted to intensive care and 70 to a medical ward after a median 6 h stay in the emergency department. During this interval, neutrophil counts increased in cases and decreased in controls (median, 934 vs. -295×10^6/L; $P = 0.006$), while lymphocyte counts decreased in cases and increased in controls (median, -184 vs. 109×10^6/L; $P < 0.001$). In cases, the neutrophil-to-lymphocyte ratio increased 6-fold and the urea-to-creatinine ratio increased 20-fold during the emergency department stay, but these ratios did not change in controls ($P < 0.001$ for both comparisons). By multivariable logistic regression, short-term increases in the neutrophil-to-lymphocyte ratio (OR = 1.43; 95% CI, 1.16–1.76) and urea-to-creatinine

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ratio (OR = 1.72; 95% CI, 1.20–2.66) were independent predictors of intensive care unit admission.

Conclusion: Short-time changes in neutrophil-to-lymphocyte ratio and urea-to-creatinine ratio emerged as stand-alone parameters able to identify patients with aggressive disease at an early stage.

Keywords: COVID-19, disease severity, intensive care unit, neutrophil-to-lymphocyte ratio, urea-to-creatinine ratio

INTRODUCTION

The first case of coronavirus disease 2019 (COVID-19) in Italy was reported on February 20, 2020. Shortly after, the number of cases registered throughout the country exceeded those in China (1), and today Italy ranks as one of the most affected countries (2) in terms of both total cases per 10,000 population and case-fatality rate (https://covid19.who.int/). The clinical spectrum of COVID-19 appears to be wide, including asymptomatic infection, mild upper respiratory tract illness, and severe pneumonia with respiratory failure and even death (3–6). Even patients with initially mild illness without radiographic abnormalities may suddenly worsen and require intensive care (1, 7–9), making it challenging to estimate disease severity in the early phase. Patients who present to the emergency department with suspected COVID-19 need to be monitored, to anticipate clinical deterioration and initiate appropriate clinical management and treatments as needed.

The course of infection with the virus that causes COVID-19, namely severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is just beginning to be studied, and early indicators of severe disease are lacking. An accurate model of disease progression would help physicians assess each patient's risks and choose the required intensity of care at the moment of admission. So far, various prognostic factors have been identified (10, 11), but all of them are static indicators that provide only snapshots of a process that is rapidly evolving (7). We hypothesized that dynamic observations of early changes in clinical variables can predict clinical deterioration requiring intensive care. This study therefore investigated the ability of rapid changes on a panel of clinical variables, measured in COVID-19 patients in the emergency department, to discriminate between those who require admission to an intensive care unit (ICU) and those who can be treated in a nonintensive medical ward.

METHODS

This retrospective case-control study was conducted at the Bari Policlinic, the largest academic hospital in Puglia Region. The study protocol was approved by the institutional ethics board, which waived the need for informed consent, and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

The study considered all adults (aged ≥18 years) who presented to the Emergency Department between March 13 and April 1, 2020 (during the peak of the outbreak in Puglia Region) with suspected COVID-19, and were subsequently admitted to either the ICU (cases) or a medical ward (non-ICU, controls) for laboratory-confirmed SARS-CoV-2 infection.

Patients were identified from Edotto, the regional health information system. Clinical data, collected from Galileo electronic health records, included age, sex, smoking habit, triage vital signs and presenting symptoms, comorbidities, current medications, laboratory test results (pre-defined disease-specific panel), and duration and outcome of follow-up. Laboratory confirmation of SARS-CoV-2 was defined by a positive result on a real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay performed on nasopharyngeal swabs or lower respiratory tract aspirates.

Statistical Analyses

Qualitative variables were described in terms of absolute numbers and percentages. Associations between qualitative variables and group assignment were tested for significance using Pearson's chi square or Fisher's exact test. Quantitative variables were described using median and interquartile range (IQR). The Shapiro-Wilk test indicated that quantitative data were not normally distributed, so the non-parametric Wilcoxon rank-sum test was used to compare these variables (and their changes over time) between case and control groups.

Survival analysis was performed by applying the Kaplan-Meier estimator and log-rank test for equality of survivor functions. The association between clinical variables and overall survival was analyzed with the Cox model of proportional hazards, and the assumption was verified by the Schoenfeld test.

Correlations among selected variables at baseline (t^0) were tested using Spearman's rho, for cases and controls separately. These analyses were done only for variables with well-established pathophysiological connections and documented alterations in patients with MERS-CoV and SARS-CoV infection (12, 13), and they served to identify any variables that were associated with higher probability than the expected by chance.

Unadjusted odds ratios (crude ORs) and corresponding 95% CIs were calculated in univariate analyses using the Wald test to assess relationships between study group assignment (ICU vs. non-ICU) and changes in laboratory variables (Δ, t^1-t^0). Multivariable logistic regression was done to identify the mutually adjusted effect on group assignment of laboratory variables included on the basis of statistical significance in the univariate analyses, clinical judgment, and contribution to the model (likelihood-ratio test). Age and sex were used as adjusting variables. The goodness of fit of the regression model was assessed using the Hosmer-Lemeshow test. For all analyses, a *P*-value

$\leq$ 0.05 was considered significant (two-sided). All analyses were performed using Stata software v15.1 (StataCorp, College Station, USA).

RESULTS

Of the 95 patients who presented to the emergency department for COVID-19 during the 20-day study period, 25 were admitted to the ICU (cases) and 70 were admitted to a non-ICU medical ward (controls). The patients underwent a medical examination and blood testing at presentation to the emergency department (t^0) and had another blood panel done just prior to being transferred to an inpatient unit (t^1). The median length of stay in the emergency department was 6 h (IQR, 3–19 h), during which time patients were observed and received initial treatments. Cases and controls were similar in terms of age and sex, with both groups having a predominance of men (**Table 1**). At presentation (t^0), cases required the administration of higher fractions of oxygen ($P = 0.01$). Fever was the prevailing symptom in both groups, but cases more frequently were dyspneic ($P = 0.01$) and needed noninvasive ventilation ($P < 0.001$). Hypertension was the most common comorbidity in both groups, while obesity was seen only in cases ($P < 0.001$). Systemic corticosteroids were administered to one case (4.0%) and two controls (2.9%; $P > 0.99$), and intravenous fluids were used liberally in all patients.

The patients were followed for a median of 20 days (IQR, 12.5–30 days) after transfer to an inpatient unit. During this time, 17 cases (68%) and 7 controls (10%) died (**Supplementary Figure 1**), confirming the greater severity of disease among those in the ICU. Notably, overall survival was significantly shorter in patients admitted to ICU (median, 21 days) than to a medical ward [median not reached; hazard ratio (HR) = 6.32, 95% CI, 2.61–15.26, $X^2_{LR} = 22.31$; $P < 0.0001$)]. Strikingly, these results maintained significance in the multivariable analysis (HR = 7.07; 95% CI, 2.04–24.54; $P = 0.002$; **Supplementary Table 1**).

Laboratory tests at presentation (t^0) showed that cases had lower lymphocyte counts ($P = 0.003$) and higher neutrophil-to-lymphocyte ratios (NLR, $P = 0.004$) than controls (**Table 2**). Cases also had lower serum sodium ($P = 0.004$), calcium ($P < 0.001$) and albumin ($P = 0.015$), and higher C-reactive protein (P= 0.002), presepsin ($P = 0.04$), D-dimer ($P = 0.007$), lactate dehydrogenase (LDH, $P < 0.001$), hypersensitive troponin I ($P = 0.003$), and NT-proBNP ($P = 0.04$). These differences were confirmed by repeat testing at t^1, which also showed higher neutrophil counts ($P < 0.001$) and urea-to-creatinine ratios (UCR, $P < 0.001$) in cases (**Table 2**). In addition, at t^1 cases had higher serum levels of interleukin-6 (not tested at t^0; $P = 0.03$).

We next examined the changes in laboratory test results between presentation (t^0) and admission (t^1) (**Table 3**). During this short interval, neutrophil counts increased in cases but decreased in controls ($P = 0.006$), lymphocyte counts decreased in cases but increased in controls ($P < 0.001$), and eosinophil counts increased only in controls. NLR and UCR values increased in cases but did not change in controls ($P < 0.001$). Serum albumin dropped in both cases and controls, but the change was more severe in cases ($P = 0.004$), and D-dimer increased in cases but did not change in controls ($P = 0.004$).

To determine if the examined variables had more interaction among themselves than what would be expected from a random set, we examined correlations among selected laboratory

TABLE 1 | Clinical characteristics of cases and controls at presentation (t^0).

Variable	ICU ($n = 25$)	Non-ICU ($n = 70$)	P
Age, median (IQR), y	71.0 (60.0–75.0)	60.0 (52.0–74.8)	0.19[a]
Sex, no. (%)			0.65[b]
Male	18 (72.0)	45 (64.3)	
Female	7 (28.0)	25 (35.7)	
Current smokers	0 (0)	2 (3.2)	>0.99[c]
Systolic arterial pressure, median (IQR), mmHg	127.0 (120.0–135.0)	125.0 (116.5, 140.0)	0.63[a]
Diastolic arterial pressure, median (IQR), mmHg	70.0 (67.5–78.5)	74.0 (70.0–80.0)	0.55[a]
Heart rate, median (IQR), bpm	93.5 (76.0–100.0)	90.0 (76.0–101.0)	0.71[a]
Body temperature, median (IQR), °C	36.7 (36.4–37.8)	37.0 (36.2–38.0)	0.81[a]
Peripheral capillary oxygen saturation, median (IQR), %	94.0 (92.5–98.0)	97.0 (94.3–98.0)	0.23[a]
Fraction of inspired oxygen, median (IQR), %	22.5 (21.0–75.0)	21.0 (21.0–21.0)	0.01[a]
COVID-19 SYMPTOMS, NO. (%)			
Fever history	23 (100.0)	59 (88.1)	0.11[c]
Dyspnea	19 (79.2)	31 (47.0)	0.01[b]
Noninvasive ventilation in ED	9 (45.0)	3 (4.9)	<0.001[b]
COMORBIDITIES, NO. (%)			
Hypertension	14 (60.9)	29 (51.8)	0.63[b]
Obesity	9 (37.5)	0 (0)	<0.001[c]
Chronic heart failure	4 (16.7)	9 (14.5)	0.75[c]
COPD	4 (16.7)	6 (9.7)	0.46[c]
Type 2 diabetes mellitus	3 (12.5)	12 (19.4)	0.54[c]
Allergy	3 (12.5)	5 (7.9)	0.68[c]
CNS disease	1 (4.2)	9 (14.5)	0.27[c]
Atrial fibrillation	1 (4.2)	5 (8.1)	>0.99[c]
Cancer	1 (4.2)	4 (6.5)	>0.99[c]
Chronic kidney disease (≥III KDOQI)	1 (4.2)	5 (8.1)	>0.99[c]
Autoimmune disease	1 (4.2)	1 (1.6)	0.48[c]
CURRENT MEDICATIONS, NO. (%)			
Antiplatelet drugs	6 (35.3)	9 (17.3)	0.17[c]
ACE inhibitors or ARB	4 (33.3)	14 (28.6)	0.74[c]
Other antihypertensive drugs	4 (33.3)	18 (36.7)	>0.99[c]
Inhalants	2 (11.8)	0 (0)	0.06[c]
Warfarin or DOAC	1 (5.9)	5 (9.4)	>0.99[c]
Systemic corticosteroids	0 (0)	2 (3.8)	>0.99[c]
Immunosuppressants	0 (0)	2 (3.8)	>0.99[c]
Low-molecular-weight heparin	0 (0)	0 (0.0)	>0.99[c]
Chemotherapy	0 (0)	2 (3.8)	>0.99[c]

[a]*Wilcoxon's rank sum test;* [b]*Pearson's chi-square test;* [c]*Fisher's exact test.*
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulants; ED, emergency department; ICU, intensive care unit; KDOQI, Kidney Disease Outcomes Quality Initiative.

TABLE 2 | Laboratory test results for cases (ICU) and controls (non-ICU), at presentation (t^0) and admission (t^1).

	t^0			t^1			
Variable	**ICU ($n = 25$)**	**Non-ICU ($n = 70$)**	***P*[a]**	**ICU ($n = 25$)**	**Non-ICU (n=70)**	***P*[a]**	**Reference values**
Red blood cell count, $\times 10^{12}$/L	4.68 (4.27–5.07)	4.71 (4.26–5.08)	0.98	4.1 (3.9–4.5)	4.3 (4.0–4.6)	0.15	3.85–5.16
Hemoglobin, g/dL	13.0 (11.4–14.2)	13.8 (12.3–14.7)	0.35	11.5 (9.9–12.7)	12.7 (11.7–13.7)	0.04	12.0–15.0
White blood cell count, $\times 10^6$/L	6,220 (4,870–7,610)	5,570 (4,520–7,942)	0.57	7,150 (5,710–10,560)	5,965 (4,500–7,490)	0.01	3,900–11,700
Neutrophil count, $\times 10^6$/L	5,103 (3,940–6,716)	3,942 (3,204–6,269)	0.17	6,328 (4,900–9,409)	3,751 (2,901–5,628)	<0.001	1,550–8,740
Lymphocyte count, $\times 10^6$/L	654.0 (595.0–936.1)	994.5 (691.7–1,255.7)	0.003	484.8 (416.5–582.1)	1,058.1 (778.8–1,430.2)	<0.001	820–6,200
Eosinophil count, $\times 10^6$/L	12.4 (7.1–19.5)	10.5 (6.6–20.2)	0.77	12.8 (6.9–27.5)	53.5 (12.0–107.2)	0.001	20–850
Basophil count, $\times 10^6$/L	23.7 (11.1–43.1)	27.6 (12.1–159.3)	0.24	21.3 (12.7–48.0)	29.2 (13.4–51.0)	0.68	8–120
Monocyte count, $\times 10^6$/L	304.8 (266.7–499.4)	359.8 (271.3–508.1)	0.42	314.1 (194.0–390.5)	443.5 (316.3–553.1)	0.009	100–770
Platelet count, $\times 10^9$/L	155.0 (121.0–226.0)	184.5 (149.2–219.8)	0.46	228.0 (158.0–337.0)	247.0 (183.0–308.0)	0.54	172–440
Neutrophil-to-lymphocyte ratio	7.0 (4.9–11.8)	4.6 (3.0–6.6)	0.004	13.7 (8.1–18.2)	3.5 (2.4–6.0)	<0.001	–
Platelet-to-lymphocyte ratio	0.26 (0.17–0.33)	0.2 (0.15–0.27)	0.08	0.39 (0.27–0.69)	0.23 (0.16–0.31)	<0.001	–
Plasma glucose, mg/dL	97.0 (95.0–122.0)	105.0 (90.0–126.0)	0.94	124.0 (94.0–167.0)	90.5 (75.5–105.8)	<0.001	<100.0
Prothrombin time INR	1.08 (1.04–1.12)	1.06 (1.02–1.10)	0.08	1.10 (1.06–1.17)	1.07 (1.03–1.12)	0.12	<1.2
Activated partial thromboplastin time ratio	1.13 (1.08–1.22)	1.11 (1.04–1.19)	0.51	1.13 (1.04–1.28)	1.11 (1.07–1.19)	0.48	<1.2
Fibrinogen, mg/dL	461.0 (372.8–501.2)	422.0 (378.2–479.2)	0.49	462.0 (435.0–566.0)	441.0 (364.0–518.0)	0.07	200.0–400.0
Creatinine, mg/dL	0.96 (0.79–1.47)	0.91 (0.74–1.12)	0.51	0.78 (0.64–1.00)	0.88 (0.71–1.09)	0.22	0.51–0.95
Estimated glomerular filtration rate, mL/min	73.0 (54.0–87.0)	85.0 (66.8–98.8)	0.20	93.0 (64.0–99.0)	84.5 (72.0–99.8)	0.71	>90.0
Urea, mg/dL	45.0 (30.0–56.0)	34.0 (29.0–41.8)	0.11	40.0 (35.0–67.0)	31.5 (23.0–41.5)	0.004	15.0–38.0
Urea-to-creatinine ratio	43.0 (34.0–51.8)	37.9 (30.3–46.7)	0.14	56.3 (45.2–83.4)	33.8 (25.0–42.3)	<0.001	–
Serum sodium, mmol/L	135.0 (132.0–137.0)	137.0 (135.0–140.0)	0.004	139.0 (138.0–142.0)	139.0 (136.2–141.0)	0.87	136–145
Serum potassium, mmol/L	4.0 (3.7–4.2)	3.9 (3.7–4.3)	0.92	3.9 (3.6–4.2)	4.0 (3.7–4.2)	0.72	3.5–5.0
Serum total calcium, mg/dL	7.9 (7.7–8.2)	8.3 (8.0–8.7)	<0.001	7.6 (7.2–7.8)	8.2 (8.0–8.5)	<0.001	8.5–10.1
Serum albumin-corrected calcium, mg/dL	8.7 (8.6–8.8)	8.9 (8.7–9.1)	0.04	8.8 (8.7–9.2)	9.1 (8.8–9.5)	0.04	8.5–10.1
Albumin, g/dL	3.05 (2.68–3.23)	3.20 (2.92–3.50)	0.015	2.2 (2.0–2.5)	2.8 (2.6–3.2)	<0.001	3.4–5.0
Total plasma protein, g/dL	6.4 (6.33–6.9)	6.6 (6.4–7.2)	0.36	6.0 (5.6–6.3)	6.5 (6.2–6.7)	<0.001	6.4–8.2
Total bilirubin, mg/dL	0.6 (0.5–0.7)	0.5 (0.4–0.6)	0.20	0.6 (0.4–0.9)	0.7 (0.4–0.9)	0.80	0.2–1.0
Direct bilirubin, mg/dL	0.24 (0.18–0.33)	0.19 (0.15–0.24)	0.02	0.28 (0.23–0.47)	0.23 (0.18–0.42)	0.09	0.0–0.2
Indirect bilirubin, mg/dL	0.33 (0.27–0.43)	0.32 (0.25–0.42)	0.58	0.28 (0.17–0.46)	0.36 (0.22–0.62)	0.05	0.0–0.75
Aspartate aminotransferase, U/L	48.5 (42.7–62.8)	36.0 (30.0–60.0)	0.04	50.0 (32.0–65.8)	33.0 (26.3–52.3)	0.02	15.0–37.0
Alanine aminotransferase, U/L	33.0 (27.0–39.0)	33.0 (25.0–44.8)	0.79	29.0 (23.8–40.8)	33.0 (21.3–51.0)	0.52	12.0–78.0
Gamma-glutamyltransferase, U/L	39.0 (28.0–70.0)	46.0 (28.0–69.0)	0.94	39.5 (26.5–83.5)	40.0 (27.0–65.0)	0.88	5.0–55.0
C-reactive protein, mg/L	118.0 (75.8–148.0)	47.8 (26.4–96.0)	0.002	145.0 (107.0–171.2)	49.8 (22.7–108.8)	<0.001	<2.9
Presepsin, pg/mL	531.0 (433.5–914.8)	424.0 (313.0–706.0)	0.04	666.0 (418.5–779.0)	299.0 (209.0–520.0)	0.002	20.0–200.0
D-dimer, μg/L	1,276.0 (718.5–2,816.5)	641.0 (463.5–1,124.5)	0.007	1,936.0 (1,545.0–4,342.0)	635.0 (417.5–1,195.0)	<0.001	<500.0
Lactate dehydrogenase, U/L	410.0 (338.3, 467.0)	281.0 (213.8, 349.8)	<0.001	409.0 (336.0–454.0)	246.5 (204.5–309.8)	<0.001	84.0–246.0
Hypersensitive troponin I, pg/mL	23.9 (15.7–48.6)	10.7 (6.1–26.2)	0.003	38.6 (19.5–56.2)	16.9 (8.8–45.1)	0.16	<74.9
NT-proBNP, pg/mL	342.0 (82.0–1,109.0)	85.0 (44.0–308.0)	0.04	603.0 (368.0–1,770.0)	203.0 (86.8–985.5)	<0.001	0.0–166.0
Interleukin-6, pg/mL	–	–	–	114.0 (36.1–294.5)	33.6 (18.1–105.4)	0.03	0.0–7.0

[a]*Wilcoxon's rank-sum test.*

Data are expressed as median and interquartile range.

test results at t^0 in cases and controls separately (**Figure 1**). Specifically, we selected those variables with well-established pathophysiological connections and known alterations in other severe coronavirus-induced diseases. In both groups, NLR correlated negatively with albumin (cases, rho = −0.489, $P < 0.05$; controls, rho = −0.401, $P < 0.05$) and positively with C-reactive protein (cases, rho = 0.510, $P < 0.05$; controls, rho = 0.530, $P < 0.05$). UCR correlated negatively with serum albumin (cases, rho = −0.455, $P = 0.02$; controls: rho = −0.290, $P = 0.01$). A positive correlation also emerged between two critical cardiac parameters, NT-proBNP and hypersensitive troponin I (hsTnI, cases, rho = 0.576, $P < 0.05$; controls, rho = 0.597, $P < 0.05$) in both groups.

Finally, to identify clinical variables whose short-term change (Δ, t^1-t^0) is predictive of ICU admission, we first calculated crude ORs (**Figure 2**, **Supplementary Table 2**). This analysis

TABLE 3 | Changes in laboratory test results from t^0 to t^1.

Variable ($\Delta = t^1$-t^0)	ICU ($n = 25$)	Non-ICU ($n = 70$)	P^a
Red blood cell count, $\times 10^{12}$/L	−0.57 (−0.69, −0.25)	−0.36 (−0.65, −0.12)	0.19
Hemoglobin, g/dL	−1.40 (−2.10, −0.80)	−1.20 (−2.00, −0.30)	0.21
White blood cell count, $\times 10^6$/L	790.00 (−340.00, 2,120.00)	−55.00 (−1,407.50, 1,295.00)	0.10
Neutrophil count, $\times 10^6$/L	934.17 (136.98, 2,146.06)	−295.13 (−1,397.49, 876.87)	0.006
Lymphocyte count, $\times 10^6$/L	−184.36 (−321.84, −54.47)	108.56 (−121.70, 354.93)	<0.001
Eosinophil count, $\times 10^6$/L	0.91 (−12.22, 15.17)	20.87 (2.66, 76.78)	<0.001
Basophil count, $\times 10^6$/L	−2.51 (−19.80, 9.44)	0.02 (−110.68, 24.91)	0.94
Monocyte count, $\times 10^6$/L	−75.08 (−165.18, 101.81)	90.31 (−58.32, 166.59)	0.008
Platelet count, $\times 10^9$/L	51.00 (2.00, 127.00)	52.00 (12.00, 101.50)	0.71
Neutrophil-to-lymphocyte ratio	6.09 (2.53, 10.62)	−0.63 (−2.48, 0.44)	<0.001
Platelet-to-lymphocyte ratio	0.21 (0.04, 0.42)	0.03 (−0.03, 0.08)	<0.001
Plasma glucose, mg/dL	15.00 (−9.00, 32.00)	−15.00 (−37.00, 0.00)	0.001
Prothrombin time INR	0.02 (−0.03, 0.08)	0.00 (−0.03, 0.04)	0.57
Activated partial thromboplastin time ratio	0.04 (−0.08, 0.13)	−0.01 (−0.06, 0.08)	0.51
Fibrinogen, mg/dL	78.50 (−100.25, 121.50)	−0.50 (−70.50, 67.75)	0.23
Creatinine, mg/dL	−0.19 (−0.36, −0.04)	−0.03 (−0.11, 0.09)	<0.001
Estimated glomerular filtration rate, mL/min	13.00 (2.00, 24.00)	1.50 (−5.00, 7.75)	0.001
Urea, mg/dL	5.00 (−4.25, 10.50)	−3.00 (−8.00, 8.00)	0.18
Urea-to-creatinine ratio	20.43 (2.91, 29.41)	−1.89 (−9.92, 7.38)	<0.001
Serum sodium, mmol/L	5.00 (2.00, 7.00)	2.00 (−0.75, 5.00)	0.008
Serum potassium, mmol/L	−0.05 (−0.42, 0.30)	0.00 (−0.40, 0.40)	0.46
Serum total calcium, mg/dL	−0.35 (−0.70, −0.20)	−0.20 (−0.50, 0.20)	0.034
Serum albumin-corrected calcium, mg/dL	0.20 (−0.05, 0.40)	0.10 (−0.10, 0.50)	0.68
Albumin, g/dL	−0.70 (−0.90, −0.55)	−0.40 (−0.60, −0.30)	<0.001
Total plasma protein, g/dL	−0.40 (−0.60, −0.20)	−0.30 (−0.85, 0.10)	0.65
Total bilirubin, mg/dL	0.02 (−0.26, 0.33)	0.10 (−0.08, 0.48)	0.11
Direct bilirubin, mg/dL	0.04 (−0.03, 0.18)	0.04 (−0.02, 0.11)	0.88
Indirect bilirubin, mg/dL	−0.01 (−0.21, 0.08)	0.07 (−0.05, 0.34)	0.01
Aspartate aminotransferase, U/L	−2.00 (−21.75, 11.75)	−4.00 (−14.00, 5.00)	0.76
Alanine aminotransferase, U/L	−2.50 (−8.50, 2.50)	−3.00 (−11.00, 10.75)	0.98
Gamma-glutamyltransferase, U/L	0.00 (−6.50, 5.25)	−3.00 (−9.00, 2.00)	0.55
C-reactive protein, mg/L	30.50 (−33.83, 97.03)	1.10 (−24.70, 33.50)	0.12
Presepsin, pg/mL	84.00 (−160.75, 365.50)	−28.00 (−90.50, 20.50)	0.15
D-dimer, μg/L	733.00 (0.00, 3,267.00)	−46.50 (−198.50, 154.50)	0.004
Lactate dehydrogenase, U/L	35.00 (−76.25, 110.50)	−29.50 (−69.75, 18.00)	0.28
Hypersensitive troponin I, pg/mL	3.70 (−1.90, 22.30)	1.60 (−0.70, 7.10)	0.61
NT-proBNP, pg/mL	174.00 (−25.00, 548.50)	22.50 (−20.27, 117.50)	0.25

[a] *Wilcoxon's rank-sum test.*

Data are expressed as median and interquartile range.

identified six variables with OR > 1 (i.e., cases were more likely to have these variables increase than controls) and seven variables with OR < 1 (i.e., cases were less likely to have these variables increase). These variables were then tested in multivariable logistic regression, which showed that the probability of being admitted to ICU was higher in patients with large increases in UCR (ΔUCR for 10-unit change, OR = 1.72; 95% CI, 1.20–2.66; $P < 0.01$) and NLR (ΔNLR for 1-unit change, OR = 1.430; 95% CI, 1.160–1.763, $P < 0.001$) in the short term. The Hosmer-Lemeshow goodness-of-fit test indicated that the model appropriately described the data [$X^2(8) = 5.29$, $P = 0.73$].

DISCUSSION

This study identified two critical short-term changes in laboratory variables that are sufficient to sketch the identikit of a COVID-19 patient deserving close clinical monitoring and high-intensity care. These changes regard the neutrophil-to-lymphocyte ratio (NLR) and urea-to-creatinine ratio (UCR), which both increased in cases requiring ICU admission but did not change significantly in controls treated in a nonintensive medical ward. The changes in these two variables are statistically robust enough to explain, independently, patient assignment or not to the ICU.

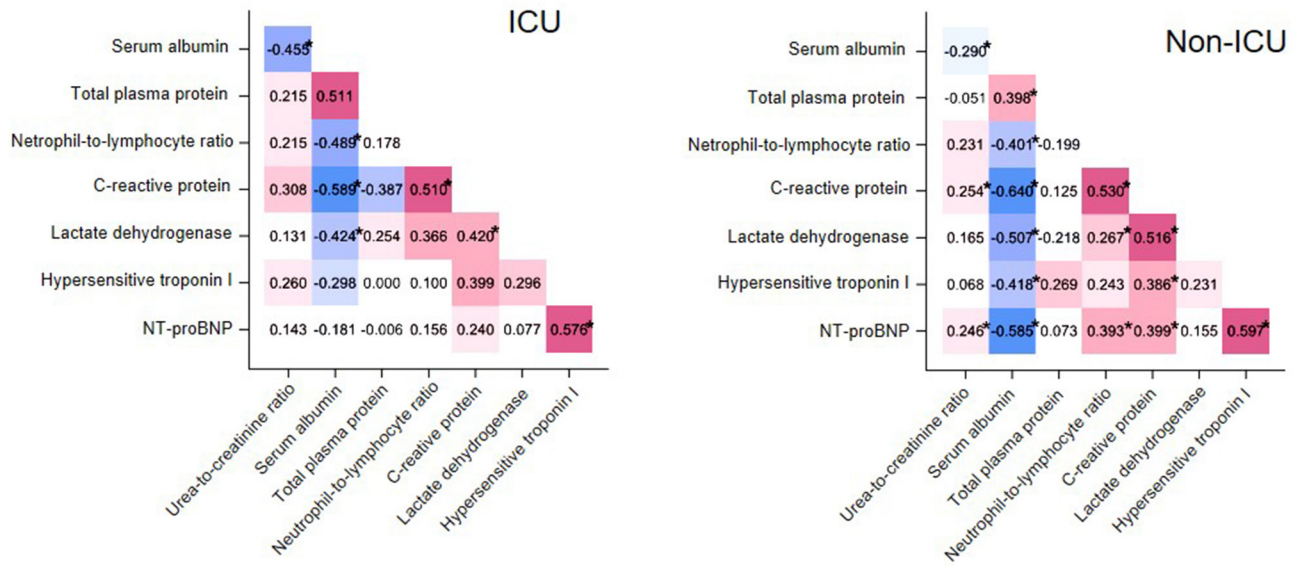
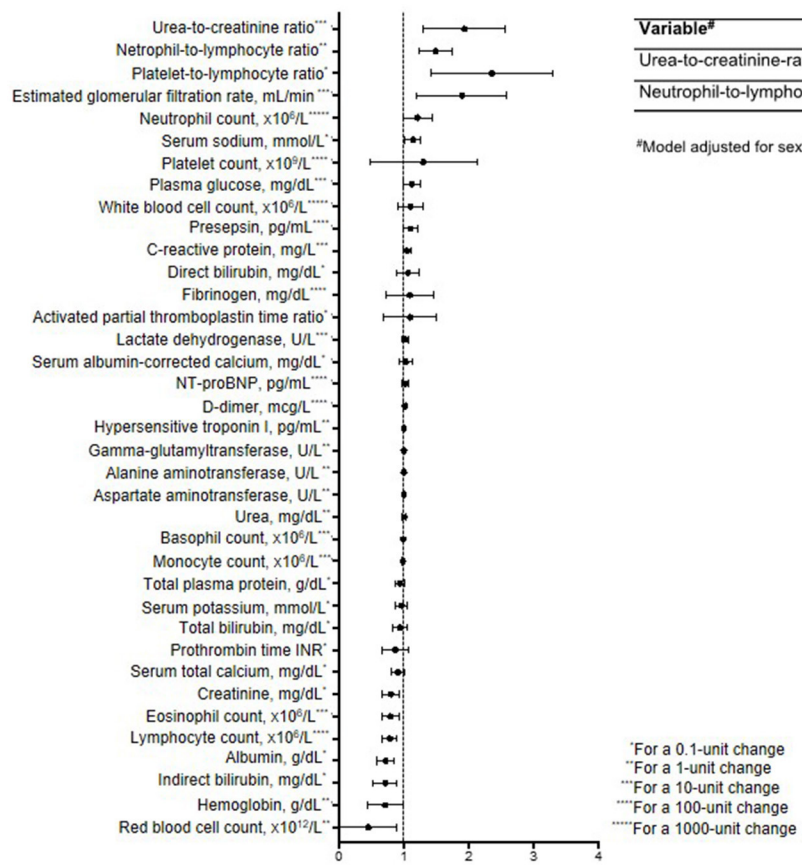


FIGURE 1 | Matrix heatmap representing correlations between laboratory test values in cases (ICU patients, **left**) and controls (non-ICU patients, **right**). Correlations with Spearman's rho < 0 and rho > 0 are colored blue and red, respectively, while the saturation of the color reflects the magnitude of r. $^*P < 0.05$.



Variable#	ICU vs. Non-ICU	95% CI	*P*
Urea-to-creatinine-ratio***	1.72	1.20-2.66	<.01
Neutrophil-to-lymphocyte-ratio**	1.43	1.160-1.763	<.001

#Model adjusted for sex and age

FIGURE 2 | Forest plot reporting odds ratios and 95% confidence intervals for the impact of a short-term change (Δ, t^1-t^0) in laboratory variables on the need for ICU admission. The table insert reports the multivariable logistic regression model for predicting ICU status, adjusted for sex and age.

An increase in NLR is likely to parallel the strength of the immune-inflammatory response and cytokine storm, two phenomena that have been widely described in COVID-19 (14, 15). This increase can depend on neutrophilia, lymphopenia or both. Neutrophilia might be due to a virus-related cytokine storm, coagulation activation, hypoxia or shock (12, 16). Interestingly, an accumulation of inflammatory neutrophils and monocyte-macrophages was promoted, in a mouse model of SARS, by the rapid kinetics of virus replication and the subsequent delay in interferon type I signaling (17). Lymphopenia is believed to be determined by tissue sequestration, cell destruction in peripheral blood, or bone marrow failure singly or together (18, 19), as already demonstrated in MERS-CoV and SARS-CoV infections (20, 21). Lymphocyte sequestration, in particular, seems to play the major role and has been shown to occur in the lungs, gastrointestinal tract, and lymphoid tissues of COVID-19 patients (22, 23).

An increase in UCR is likely to reflect the acute catabolic state (24) and renal injury (25) that characterize the critical phase of COVID-19. The dynamic UCR profiles (urea increase, and creatinine decrease or stability) of our patients seem to contradict recent evidence that high serum creatinine concentration correlates with catastrophic COVID-19 outcome (acute kidney injury or death) (26). Our findings can be explained by the simultaneous decrease in serum albumin; decreases in albumin are associated with muscle catabolism and persistent critical illness (27, 28) and are found in other chronic disease states (29, 30).

It should be noted that the use of corticosteroids during hospitalization may also account for a decrease in lymphocytes, as already observed in SARS patients (31), and that fluid restriction strategies in the management of COVID-19 patients may contribute to the UCR elevation. Although we cannot entirely rule out these confounding variables when interpreting our results, we also cannot overstate that the use of corticosteroids in our study population was negligible and that no restrictive fluid protocols were followed, given the absence of consensus recommendations.

Our study has some other limitations. First, the sample size might not have been adequate to assess risk factors for poor clinical outcome. Second, due to the retrospective study design, we might have underestimated some laboratory and clinical findings predicting in-hospital mortality. Statistically powered clinical trials are therefore needed to corroborate our findings. Finally, both NLR and UCR are not disease-specific and need to be supported by clinical judgment.

The predictive significance of NLR for COVID-19 severity and mortality was evaluated in several studies whose findings have been used in five meta-analyses (32–36), all finding that NLR was higher in patients with than without severe disease. So far, only one single-center study reported that UCR, alone or in combination with NLR, was an independent predictor of COVID-19 severity (37). In all studies, however, only single time points were considered. Our study extends these findings by showing that the magnitude of short-term variations in these two measures are also prognostic.

The construction and validation of new parameters to aid in severity assessment of COVID-19 patients are crucial. This, however, is complicated by the heterogeneous host response to infection, as well as the delayed onset of severe manifestations. Our study proposes short-time variations in NLR and UCR as novel indicators of disease severity that can contribute to the construction of a standardized set of criteria supporting the early identification of severe COVID-19 cases that require intensive care admission. These fast, affordable markers of disease severity should be evaluated before the onset of severe manifestations. If confirmed prospectively, they should facilitate the proper allocation of patients and the better use of resources for a disease that is putting enormous pressure on health systems all around the world.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Indipendente Azienda Ospedaliero-Universitaria Consorziale Policlinico - Bari (n. 6357). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AGS, NSu, PB, and VR contributed to study conception and design. GL, FP, RB, GI, BF, DB, MC, VC, SC, and PL contributed to data collection. PB, MP, NSu, AS, RR, VP, GM, AV, AGS, NSi, and VR contributed to data analysis. AGS, NSu, AV, and VR contributed to drafting and editing the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2020.625176/full#supplementary-material

Supplementary Figure 1 | Kaplan-Meier estimates of overall survival (OS) stratified for ICU admission status. X^2_{LR}, chi-squared log-rank test. NR, not reached.

Supplementary Table 1 | Cox proportional hazards model for overall survival.

Supplementary Table 2 | Odds ratios (ORs) and 95% confidence intervals for ICU admission, according to changes (t^1-t^0) in laboratory variables.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Medicine

SYSTEMATIC REVIEW
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Mortality Benefit of Remdesivir in COVID-19: A Systematic Review and Meta-Analysis

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Importance/Background: During current public health emergency of COVID-19 pandemic, repurposing of existing antiviral drugs may be an efficient strategy since there is no proven effective treatment. Published literature shows Remdesivir has broad-spectrum antiviral activity against numerous RNA viruses and has been recently recognized as a promising therapy against SARS-CoV-2.

Methods: A systematic search was conducted for full length manuscripts published between inception and July 19th, 2020 focussing on efficacy and safety of Remdesivir in COVID-19. The primary outcomes were defined as mortality rate and median days to recovery based on the available pooled data. The secondary outcome was adverse events rate and drug discontinuation rate.

Statistical Analysis: All outcomes were performed using Comprehensive Meta-Analysis software package (Bio stat, Englewood, NJ, USA).

Results: A total of 1,895 patients from 9 studies were included in this qualitative synthesis. In patients treated with Remdesivir, the mean recovery time was 15.84 days (95% CI 11.68–20, SE 2.12; $I^2 = 97.24$) and the pooled mortality rate was 11.3% (95% CI 7.9–16%; $I^2 = 74.85$). However, treatment with Remdesivir was associated with adverse effects (55.3%, 95% CI 31.5–76.9%; $I^2 = 97.66$) eventually warranting the discontinuation of the drug (17.8%, 95% CI 8.6–33.1%; $I^2 = 95.64$). The meta-analysis of three clinical trials indicated that administration of Remdesivir significantly reduces the mortality compared to the placebo (OR 0.70, 95% CI 0.58–0.84, $p \leq 0.001$; $I^2 = 16.6$).

Conclusions and Relevance: The result of contemporary meta-analysis suggests mortality benefit with Remdesivir in COVID-19 and median recovery time was over 2 weeks. The pooled mortality with Remdesivir was found to be very low, and this analysis can shed light on this potential treatment for COVID-19 patients.

Keywords: Remdesivir (GS-5734), COVID-19, SARS-CoV-2, mortality, systematic review, meta-analysis

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HIGHLIGHTS

What We Already Know About This Topic

- COVID-19 is global pandemic and Remdesivir is emerging as a promising therapeutic drug.
- Preliminary clinical trial results propose that there may be a satisfactory safety profile and better clinical outcome for Remdesivir group compared with placebo or standard of care; however, data is limited at the current time.

What This Article Tells Us That Is New

- Our systematic review and meta-analysis provides a detailed overview of existing literature on Remdesivir in COVID-19 to evaluate the mortality benefits and adverse events.

INTRODUCTION

The city of Wuhan in China initially noted and reported the first case of coronavirus, termed as SARS-CoV-2, in December 2019 (1). The World Health Organization (WHO) confirmed the coronavirus outbreak as a worldwide public health emergency on January 30th, 2020, and a pandemic on March 11th, 2020 (2). The WHO estimated that significant illness could happen in as high as 13.8%, and as high as 6.1% could be serious (3). The 2019–2020 pandemic has infected more than 12 million people (4). This has resulted in more than 550,000 fatalities and correspond to a crude case mortality rate of ∼4.57% (4, 5).

In current medical and public health emergency, the rapid detection of effective treatment option against SARS-CoV-2 remains challenge. The utilization of existing antiviral drugs and screening of available databases could be considered as an efficient strategy. Remdesivir, an antiviral drug, has been recently recognized as a potential therapy against SARS-CoV-2 (6, 7). On April 21st, 2020, "Solidarity," an international clinical trial, was launched by the World Health Organization (8). The aim of the study is to compare four treatment options, including Remdesivir, to find effective therapies. On May 1st, 2020, the U.S. Food and Drug Administration allowed the emergency use of Remdesivir for the management of COVID-19 in critically ill hospitalized patients (9).

Given the limited information known about Remdesivir in COVID-19, our systemic review and meta-analysis provide a detailed overview of existing literature on Remdesivir in COVID-19 to evaluate the benefits and adverse events. This may help plan future randomized controlled trials with an appropriate size to establish the efficacy and safety of Remdesivir.

Abbreviations: ACTT, the Adaptive COVID-19 Treatment Trial; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence Interval; COVID 19, Coronavirus Disease 2019; DNA, deoxyribonucleic acid; FDA, Food and Drug Administration; HIV, Human Immunodeficiency Virus; HR, Hazard Ratio; IV, intravenous; MERS, Middle Eastern Respiratory Syndrome; MERS-CoV 1, Middle Eastern Respiratory Syndrome Coronavirus 1; NJ, New Jersey; NIH, National Institute of Health; NAID, National Institute of Allergy and Infectious Diseases; OR, Odds Ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; PREVAIL study, Partnership for Research on Ebola Virus in Liberia study; PALM study, PAmoja TuLinde Maisha study; RNA, ribonucleic acid; RCT, Randomized Clinical Trial; RSV, Respiratory Syncytial Virus; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SARS-CoV-1, Severe Acute Respiratory Syndrome Coronavirus 1; USA, United States of America; VHF, Viral Hemorrhagic Fever; WHO, World Health Organization.

METHODS

Search Method and Strategy

A systematic search was conducted from COVID19 inception through July 19th, 2020, for full-length articles focusing on the efficacy and safety of Remdesivir in COVID-19. The search strategy consisted of keywords "Remdesivir," "SARS-CoV-2," and "COVID-19" across the COVID 19 database provided by WHO Global Research Database, CDC COVID-19 Research Articles Downloadable Database, and LitCovid database. All available databases were automatically searched from inception through July 2020 for articles describing the outcomes of COVID-19 which include Medline (Ovid and PubMed), Embase, Academic Search Complete, CAB Abstracts, Africa Wide Information, Global Health, ProQuest Central, PsycInfo, Cochrane Library, Scopus, the Virtual Health Library, CINAHL, SciFinder, and LitCovid. Other literature sources such as the Euro surveillance, China CDC Weekly, Homeland Security Digital Library, ClinicalTrials.gov, bioRxiv (preprints), medRxiv (preprints), chemRxiv (preprints), and SSRN (preprints) were searched as well. After a thorough search was performed, full-length articles meeting the inclusion criteria were evaluated. Subsequently, a manual search of the references of the included articles was accomplished. Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were used [(10); **Figure 1**].

The inclusion criteria for the systematic review are as follows:

1. Studies reporting outcomes such as mortality and adverse events of Remdesivir in hospitalized patients with COVID-19.
2. Full text, peer-reviewed articles (Meta-analysis, case-studies and case series, systematic reviews, randomized controlled trials).

Once the studies met the inclusion criteria, each study was reviewed by two reviewers (KM and IG) independently, and disagreements were discussed amongst all author-reviewers and resolved via a consensus. Subsequently, the data was collected and tabulated using Microsoft Excel. The included data was checked for accuracy by all authors. Studies focussing on patients <18 years of age, pregnant females, and studies limited to particular co-morbidities and organ dysfunctions were excluded to avoid selection bias. Also, *in-vitro* studies not pertaining to the efficacy of Remdesivir in COVID-19 were excluded from quantitative synthesis (**Supplementary Table 1**). The data was extracted from publicly available studies; thus, IRB approval was not necessary.

Outcomes

Primary outcomes were defined as Mortality benefit for the patients on Remdesivir in COVID-19. The mortality rate was evaluated in comparison to the control group (placebo or no

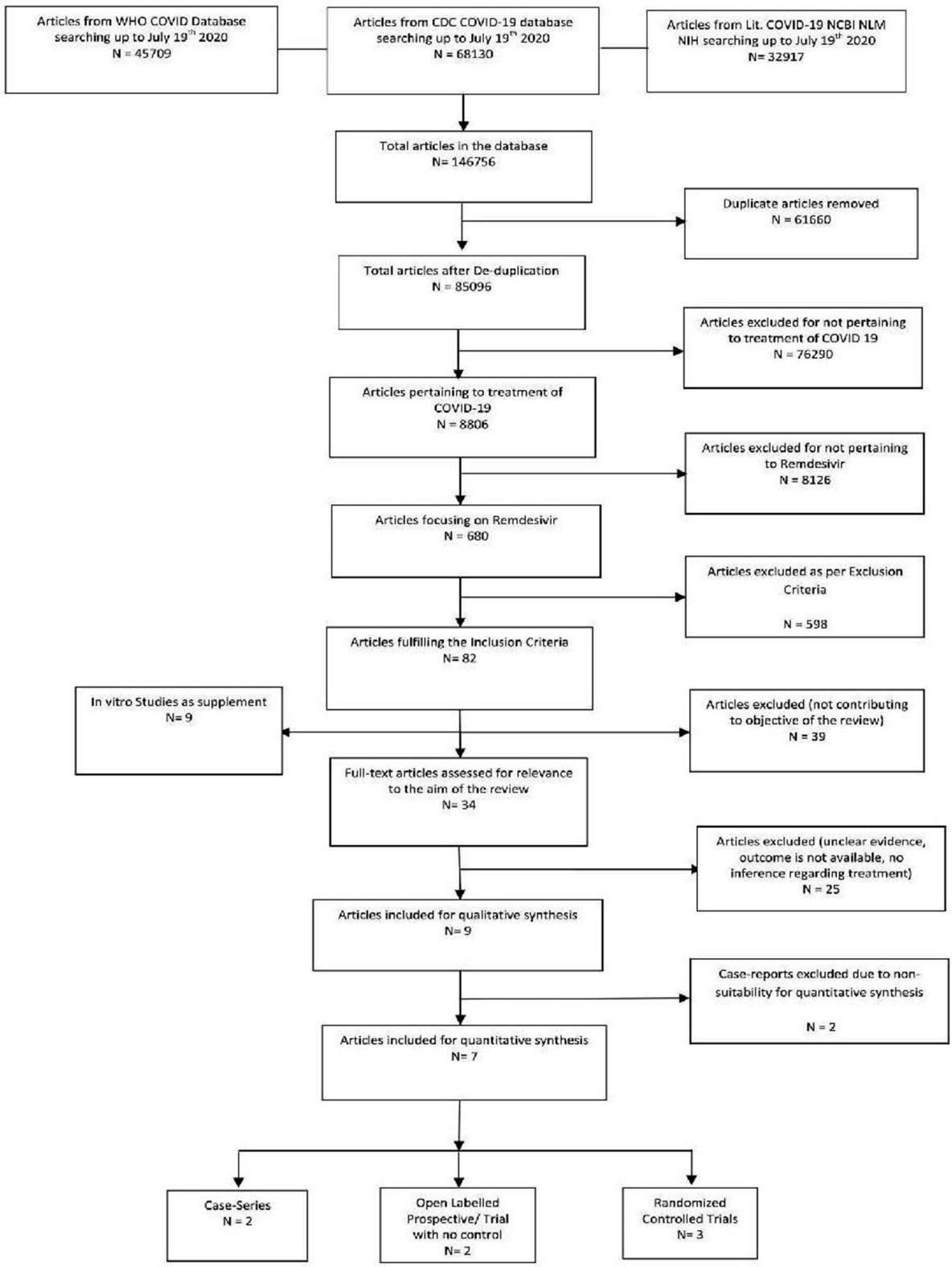

FIGURE 1 | PRISMA study flow diagram.

Remdesivir). The defined secondary outcome was pooled adverse events rate, pooled mortality rate, the median time to recovery, and pooled drug discontinuation rate.

Statistical Analysis

All outcomes were analyzed utilizing the Comprehensive Meta-Analysis software package (Biostat, Englewood, NJ, USA) (11). The final pooled risk estimates were obtained using random effects models (12). Raw data for events and non-events from each study were used to calculate crude odd's ratio (OR) for each study with respective 95% confidence intervals (CI) by using a random-effects model (12). To evaluate continuous outcomes, the median was converted to mean by a previously validated method (13). Subsequently, the estimates for mean recovery time were obtained using the random effects model. The Cochrane Q and the I^2 statistics were evaluated to estimate heterogeneity between studies (14). $P < 0.10$ for the chi-square test and $I^2 < 20\%$ were interpreted as low-level heterogeneity (14). The possibility of publication bias was estimated using funnel plots and with Egger's test (15).

Risk of Bias

Two authors (KM and IG) independently assessed the risk of bias of each study included. All disagreements were discussed with all the authors, and the decision was made via a consensus. Cochrane tool for Risk of Bias (16) was used for Randomized controlled trials, and Correlation of Quality measures with estimates of treatment effects in meta-analyses of randomized controlled trials tool (17) was used for quality assessment of the same (**Table 1A**: Quality assessment and Risk of Bias assessment for RCT).

Non-randomized studies were evaluated using the NIH Quality Assessment Tool for Case Series Studies (18). Quality assessments were conducted independently, and discrepancies were resolved by consensus (**Table 1B**: Quality Assessment of Case series).

RESULTS

Search Results

The initial library search identified potentially relevant citations from PubMed, Medline, CENTRAL, EMBASE, Scopus, Web of Sciences, and clinical trial registries, comprised of 1,46,756 articles. Subsequently, 61,660 duplicates were removed. Out of the remaining 85,096 articles, 8,806 were focusing on the treatment of COVID-19, out of which 680 articles described Remdesivir. A total of 82 articles fulfilled the inclusion criteria, while 598 did not. The remaining manuscripts were scrutinized further, and 48 were further excluded: 39 due to non-relevance to the objective of the manuscript while 9 being *in-vitro* studies. Out of the remaining 34 articles, 26 were additionally excluded due to unclear evidence, unavailable outcome, and no reference regarding Remdesivir treatment. Thus, 9 studies were included in their entirety as shown in the qualitative synthesis, and 7 in the quantitative synthesis (2 Case series, 3 Randomized controlled trials, and 2 open-labeled prospective studies) as 2 case reports were excluded due to non-suitability for qualitative synthesis (**Figure 1**).

Study Characteristics

A total of 1,895 patients from 9 articles (6, 19–26) were included in qualitative synthesis, and 7 studies were included for quantitative synthesis. Out of these, 1,237 patients were treated with Remdesivir, and 656 were not treated with Remdesivir. Among these articles, a total of three studies compared outcomes of Remdesivir in COVID-19 with placebo treatment; two were double-blinded randomized controlled trials (19, 24) while one was a simulated two-arm controlled study (22). A randomized open-label study by Goldman et al. (20) compared outcomes of 5 days course vs. 10 days course of Remdesivir. Similarly, another, open-label study also reported clinical outcomes on the 10th and 28th day of Remdesivir treatment (26). The other included studies were 2 case series (6, 23), including the study describing the compassionate use of Remdesivir in COVID-19. The study characteristics and outcomes are mentioned in **Table 2**.

Dose and Treatment Regimen of Remdesivir

According to the INMI COVID-19 Treatment Group (ICOTRE Guidelines), the standard dose of Remdesivir is a loading dose of 200 mg given as an intravenous (IV) infusion over 30 min and a maintenance dose of 100 mg per day for 10 days (27). This dosing regimen was consistent with all the articles included in the analysis except one. Goldman et al. (20) compared the outcomes of a 5 vs. 10-day IV Remdesivir course in a randomized trial and found that clinical improvement on an ordinal scale was similar in both groups ($P = 0.14$).

Primary Outcomes

Mortality Benefits in Remdesivir Treated Patients

Three studies described mortality in patients treated with Remdesivir compare to No-Remdesivir. Wang et al. (24) reported 28-day mortality; Beigel et al. (19) described 14-day mortality; and Hsu et al. (22) observed a statistically significant reduction of death using Remdesivir.

The meta-analysis on the available 3 RCTs indicated that the administration of Remdesivir significantly reduces the mortality in comparison to placebo (OR 0.70, 95% CI 0.58–0.84, $p < 0.0001$; $I^2 = 16.59$) (**Figure 2**).

Secondary Outcomes

Pooled Mortality Rate in Remdesivir Treated Patients

The pooled mortality from all studies in patients treated with Remdesivir was 11.3% (95% CI 7.9–16%; $I^2 = 74.85$) (**Supplementary Figure 1A**). Wang et al. (24) reported the highest mortality rate (14%), while Beigel et al. (19) described the lowest mortality rate (7.1%).

Recovery Time in Remdesivir Treated Patients

In patients treated with Remdesivir, the pooled mean recovery time from five studies was 15.84 days (95% CI 11.68–20.00, SE = 2.125) (**Supplementary Figure 1B**). As per the studies included in the analysis, average days of hospitalization in

TABLE 1A | Quality assessment for RCT studies.

Study ID	Biegel et al.	Wang et al.	Hsu et al.	Goldman et al.	Antinori et al.
DOI	10.1056/NEJMoa2007764	10.1016/S0140 6736(20)31022-9	10.1101/ 2020.05.02. 20088559	10.1056/NEJMoa2015301	10.1016/ j.phrs.2020.104899
Correlation of quality measures with estimates of treatment effects in meta-analyses of randomized controlled trials					
Study question well-defined in introduction and methods	Adequate	Adequate	Adequate	Adequate	Adequate
Study question well defined anywhere in the article	Adequate	Adequate	Adequate	Adequate	Adequate
Placebo control	Adequate	Adequate	Not Defined	Not described	Not Defined
Appropriate outcome studied	Adequate	Adequate	Adequate	Adequate	Adequate
Multicenter Study	Multicenter	Multicenter	Single-center	Multicenter	Single-center
Study country	United States (45 sites), Denmark (8), the United Kingdom (5), Greece (4), Germany (3), Korea (2), Mexico (2), Spain (2), Japan (1), and Singapore (1).	China	Taiwan	United States, China, France, Germany, Hong Kong, Italy, Japan, Korea, the Netherlands, Singapore, Spain, Sweden, Switzerland, Taiwan, and the United Kingdom.	Italy
Adequate selection criteria	Adequate	Adequate	Adequate	Adequate	Adequate
Randomization methods described	Not described	The permuted block (30 patients per block) randomization sequence, including stratification, was prepared by a statistician not involved in the trial using SAS software, version 9.4	Not described	Randomized	Not described
Central randomization site	Not described	Not described	Not described	Not described	Not described
Allocation concealment	Adequate	Adequate	Inadequate	Not described	Inadequate
Patients blinded	Yes	Yes	Not described	Not described	Not described
Caregivers blinded	Yes	Yes	Not described	Not described	Not described
Outcome assessors blinded	Not described	Not described	Not described	Not described	Not described
Data analysts blinded	Yes	Not described	Not described	Not described	Not described
Double blinded	Yes	Yes	Not described	Not described	Not described
Vital statistical measures	Adequate	Adequate	Not described	Not described	Adequate
Statistician author or acknowledged	Yes	Yes	Not described	Not described	Not described
Intention-to-treat analysis	Yes	Yes	Not described	Not described	Not described
Power calculation reported	Yes	Not described	Not described	Not described	Not described
Stopping rules described	Yes	Yes	Not described	Not described	Not described
Baseline characteristics reported	Yes	Yes	Not described	Not described	Yes
Groups similar at baseline	Yes	Yes	Yes	Yes	Yes
Confounders accounted for	Not described	Not described	Not described	Not described	Not described
Percentage dropouts	Not described	10%	Not described	Not described	27%
Reasons for dropout given	Yes	Not described	Not described	Not described	Yes
Findings support conclusion	Yes	Yes	Yes	Not described	Yes
Risk of bias as per "cochrane modified cochrane risk of bias tool" 2019					
Random sequence generation (selection bias)	Medium risk	Low risk	Low risk	Low risk	Medium risk
Allocation concealment (selection bias)	Low risk	Low risk	Low risk	Unclear risk	Medium risk
Selective reporting (reporting bias)	Medium risk	Low risk	Low risk	Medium risk	Low risk

(Continued)

TABLE 1A | Continued

Study ID	Biegel et al.	Wang et al.	Hsu et al.	Goldman et al.	Antinori et al.
Other sources of bias (other bias)	Low risk	Low risk	Low risk	Low risk	Low risk
Blinding (participants and personnel) (performance bias)	Low risk	Low risk	Low risk	High risk	Low risk
Blinding (outcome assessment) (performance bias)	Low risk	Low risk	Medium risk	High risk	Low risk
Incomplete outcome data (attrition bias)	Low risk	Low risk	Low risk	Low risk	Low risk
Overall	The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.	The study is judged to be at low risk of bias for all domains for this result.	The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.	The study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.	The study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

TABLE 1B | NIH quality assessment tool for case series studies.

Study ID	Grein et al.	Kajawski et al.
1. Was the study question or objective clearly stated?	Yes	Yes
2. Was the study population clearly and fully described, including a case definition?	Yes	Yes
3. Were the cases consecutive?	Yes	Yes
4. Were the subjects comparable?	Yes	Yes
5. Was the intervention clearly described?	Yes	Yes
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes
7. Was the length of follow-up adequate?	Yes	Yes
8. Were the statistical methods well described?	N/A	N/A
9. Were the results well described?	Yes	Yes
Quality rating (Good, Fair, and Poor)	Good	Good

patients treated with Remdesivir ranged between 14 and 37 days. A 4-day reduction in hospital length of stay was noted by Beigel et al. (19) with a 31% shorter recovery time in the treatment arm compared to placebo (**Table 2**). According to Hsu et al. (22), Remdesivir treated patients had a 33% (95% CI 28–38%) increased odds of discharge than the control group and had a shorter hospital stay (**Table 2**). Hsu et al. (22) also found that the severity of COVID-19 was directly associated with a longer recovery time (**Table 2**). The shortest recovery time was noted in the case-report by Holshue et al. (21), were within 48 h of administration of Remdesivir, the clinical condition of the patients improved remarkably. This result was also reflected by the resolution of these patient's pulmonary lesions within 48–72 h [(21); **Table 2**].

Adverse Effects of Remdesivir

The pooled adverse event rate from six studies with Remdesivir was 55.3% (95% CI 31.5–76.9%; $I^2 = 97.66$) (**Supplementary Figure 1C**). Common adverse effects reported are constipation, increased total bilirubin, increased aminotransferase levels (reversible), infusion site reactions, hypoalbuminemia, hypokalaemia, anemia, thrombocytopenia, hypoglycaemia, and pyrexia. Serious adverse effects reported are multiple-organ-dysfunction syndrome, septic shock, and acute kidney injury (**Table 2**).

Discontinuation Rate

The pooled Remdesivir discontinuation rate from five studies with Remdesivir was 17.8% (95% CI 8.6–33.1%; $I^2 = 95.64$) (**Supplementary Figure 1D**). The reasons for discontinuation of Remdesivir were the serious adverse effects in all the cases, and no drop cases reported in any studies (**Table 2**).

Publication Bias

The funnel plot along with Egger's test (as shown in **Supplementary Figure 2**) revealed no publication bias. However, as there were <10 studies included in the analysis; thus publication bias cannot be completely excluded.

Quality Assessment of Included Studies

The quality of the studies was assessed using the Cochrane Risk of Bias Tool for RCTs [(16); **Table 1A**]. All RCTs had adequate selection criteria. Hsu et al. (22) did not report adequate concealment, whereas Goldman et al. (20) also did not describe concealment measures. Wang et al. (24) reported adequate measures of randomization. Overall, the modified risk of bias tool showed that the included studies had low to medium risk bias.

The NIH Quality Assessment Tool (18) for Case Series was used for case series (**Table 1B**). Both included studies reported

TABLE 2 | Study characteristics and outcomes.

Study	Type of study	Total patients	Treatment arm	Control arm	Defined outcome	Average recovery time	Clinical improvement		Days of hospitalization	Mortality	Adverse events
Grein et al. (6)	Case series	53	53	0	Decrease of 2 points or more on 6 point ordinal scale or discharge at day 28	18 days	Discontinued for 36/53 (68%) and 8/53 (15%) worsened	20/34 [17/30–57% OF IMV, 3/4 (75%) OF ECMO]	28 days	7/53 (13%)	32/53 (60%), 12/53 (23%) serious side effects and 4/32 (8%) needed discontinuation due to organ failure
Kujawski et al./ COVID-Investigation Team (23)	Case series	12 (7 hospitalized)	3	4	Recovery in clinical symptoms and maintaining SpO2 above 94	Mean 14 days (6–37 days)	Not applicable	Not applicable	Mean 14 days (6–37 days)	Not mentioned	All patients had transient gastrointestinal symptoms, including nausea, vomiting, gastroparesis or rectal bleeding
Holshue et al. (21)	Case report	1	1	0	Clinical improvement and radiological findings resolution	2 days	Discontinued (for 1/1 100%) maintained spO2-96%	NA	<28 days	0	0
Hillaker et al. (25)	Case report	1	1	0	Clinical improvement and radiological findings resolution	2–4 days	Discontinued (for 1/1 100%)	1/1 (100%) extubated	<28 days	0	0
Wang et al. (24)	RCT	236	158	78	Clinical improvement up to day 28, defined as decline of two levels on a six-point ordinal scale of clinical status or discharged alive from hospital, whichever came first	Mean 19 days in treatment group vs. 21 days in control group	Discontinued for 88% in treatment group and 83% in control group	4/6 (67%) in treatment group and 1/4 (25%) in control group extubated	Mean 25 days in treatment group and 24 days in control group	22 (14%) in treatment arm vs. 10 (13%) in control group	102 (66%) in treatment arm vs. 50 (64%) in the control group, 18(12%) of Remdesivir group, and 4(5%) of control group needed discontinuation due to organ failure
Hsu et al. (22)	RCT	106	53	53	Reduction in mortality and increase in probability of discharge	5.5, 16.5, and 29.5 days for low-, medium-, and high-risk state	Not mentioned	Not mentioned	5.5, 16.5, and 29.5 days for low-, medium-, and high-risk state	7/53 (13.2%)	Not mentioned

(Continued)

TABLE 2 | Continued

Study	Type of study	Total patients	Treatment arm	Control arm	Defined outcome	Average recovery time	Clinical improvement	Days of hospitalization	Mortality	Adverse events
Beigel et al. (19)	RCT	1,059	538	521	Time to recovery, defined by either discharge from the hospital or hospitalization for infection control purposes	Mean 11 days for cases vs. 15 days for the placebo group ($P < 0.001$)	Not mentioned	Not mentioned	31% shorter in treatment arm than in those who received placebo, with a 4-day reduction in hospitalization time	7.1% in treatment arm vs. 11.9% with placebo	114/541 (21.1%) in the treatment arm vs. 141/522 (27.0%) in the placebo group
NCT04292899/ Goldman et al. (20)	RCT	397	397	0	Two or more points improvement in ordinal scale	14 days	Not mentioned	Not mentioned	14 days	37/397 (9.31%)	286/396 (72.04%), 29 needed discontinuation
Antinori et al. (26)	Prospective compassionate open-label study	35	35	0	Change in clinical status based on a 7-category ordinal scale	28 days follow up. Not provided mean or median recovery time	20/35discharged, nine died, three mechanically ventilated, and three improved	Not applicable	28 days	9/35	8/35 discontinued due to any adverse effects

and fully described the population with adequate follow up. Therefore, both the studies were rated as useful on the scale.

Narrative Synthesis *in-vitro* Studies

Remdesivir is a broad-spectrum antiviral agent that demonstrated *in vitro* and *in vivo* activity against RNA viruses (**Supplementary Table 1**). Remdesivir has also established broad-spectrum antiviral activity against an array of RNA virus families including Coronaviridae [SARS, MERS, and other CoV (alpha-FIP, beta-MHV, SARS1, MERS, SARS-2, and delta)], Filoviridae (Flaviviridae-Marburg and Ebola, VHF), Paramyxoviridae [Paramyxovirus (Mumps and Para-influenza), Pneumovirus (RSV), Morbillivirus (Measles), and Henipavirus (Nipah, Hendra)] (28–36); **Supplementary Table 2**.

DISCUSSION

To combat the urgent medical and public health emergency due to COVID-19, the use of existing antiviral drugs based on systematic review and meta-analysis provides the most trustworthy data regarding the outcomes of Remdesivir in COVID-19. As the information about this promising drug is limited to small sample size trials and studies, we conducted a meta-analysis and systematic review to provide high-quality evidence on the outcomes of Remdesivir in COVID-19. This provides an overview of Remdesivir's *in-vitro* studies and analyses published clinical data regarding Remdesivir's use in COVID-19.This is the first systematic review and meta-analysis to provide evidence on the efficacy and safety of Remdesivir in COVID-19.

Recently, the results from the first randomized, double-blind, placebo-controlled clinical trial using Remdesivir in COVID-19 was published (24). The study suggested a non-significant reduction in the median time to clinical improvement. However, the study may have been underpowered to detect significant differences. The Adaptive COVID-19 Treatment Trial (ACTT) (19) reported a significant reduction in recovery time in the Remdesivir group as compared to the placebo group. Additionally, the study reported a decrease in mortality amongst Remdesivir cohort as compared to placebo (19). A decision was then made by the National Institute of Allergy and Infectious Diseases (NIAID) to end this trial earlier than expected due to significant benefit of Remdesivir determined in the interim analysis (37). Similar to these findings, our result also supports the published data and confirms that Remdesivir may even reduce mortality compared with placebo or standard of care and improves time to recovery.

Our analysis also suggests a lower pooled mortality rate of 11.3% (95% CI 7.9–16%, $I^2 = 74.85$) in COVID-19 patients. One of the reasons for lower pooled mortality could be that at the beginning of the pandemic, due to potential side effects of Remdesivir, many of the most serious patients may not have been considered to treatment and later, the inclusion of the drug in treatment protocols in less severely ill, may have introduced a confounding factor as Remdesivir treated patients are less severe.

The study which contributed significantly to the mortality benefit in our meta-analysis was the study by Hsu et al. (22).

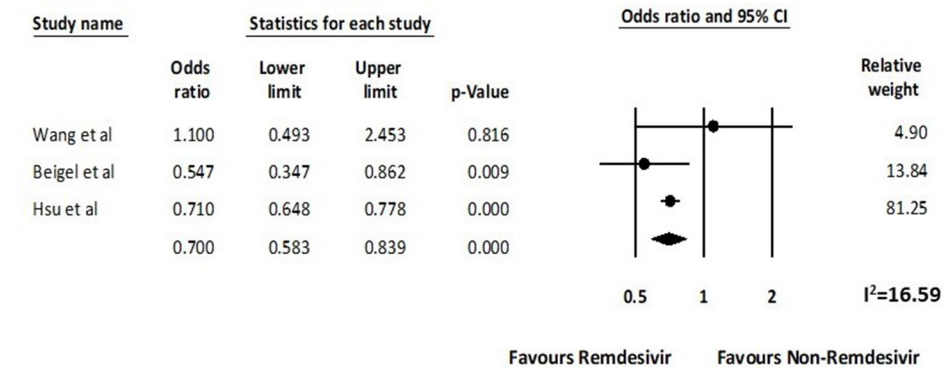

FIGURE 2 | Remdesivir and mortality outcome.

They reported 29% (95% CI 22–35%) reduction in odds of mortality with Remdesivir and a 39% decrease in the risk for the combined endpoint of severe status and death compared to the control group (22). This suggests that Remdesivir might be more effective as compared to the use in Ebola (34). A possible explanation of the improved clinical outcomes with Remdesivir could be the multiple mechanisms of action such as mutagenesis, chain termination, and perturbation of natural nucleotide triphosphate pools (33, 38). This has been shown in multiple prior *in vitro* studies (**Supplementary Table 2**). Remdesivir has revealed antiviral and clinical effects against SARS-CoV-1 and MERS-CoV infections in various animal models (28, 29, 31, 32, 35).

Even though some studies suggested that Remdesivir could be effective at a relatively low micro molar concentration compared with its cytotoxic concentration (29, 31), the safety of the drug in humans is still uncertain. The pooled adverse event rate from all studies with Remdesivir was 55.3% (95% CI 31.5–76.9%; $I^2 = 97.66$). Even though some patients reported severe adverse events in the Remdesivir group compared with the placebo cohort, a higher number of patients discontinued Remdesivir (24). However, it is unknown if the liver enzyme abnormalities are a consequence of the COVID-19 itself or related to the drug. However, these abnormalities were also noticed in healthy volunteers, which may indicate that Remdesivir could be the culprit. Similar to Remdesivir, other nucleoside analogs are known to lead to liver enzyme elevations (39, 40). The most frequent mechanism postulated for increase the liver enzyme elevation is the inhibition of mitochondrial DNA synthesis. The subsequent mitochondrial dysfunction leads to multiple manifestations such as liver enzyme elevation, myopathy, pancreatitis or bone marrow suppression (39, 40). Another mechanism could be via hypersensitivity reaction or the production of toxic metabolites (39). However, these elevations tend to be idiosyncratic and uncommon, whereas liver enzyme elevations are frequently described in Remdesivir cohort. We observed that the Remdesivir discontinuation rate is relatively high 17.8% (95% CI 8.6–33.1%; $I^2 = 95.64$). The most common reason for discontinuation of the drug was worsening respiratory failure or acute respiratory distress syndrome (24). Other reasons being elevated liver enzymes (24). The adverse events rate and drug discontinuation rate should be interpreted with caution, as causality cannot be inferred.

The strengths of our study lie in the modest number of patients across the included studies. The meta-analysis relies on shared subjectivity rather than objectivity and deals with the main effects so that results can be generalized to the target population.

Despite a large number of patients in the analysis, the meta-analysis has some limitations. A limitation of our meta-analysis based on mortality rate is inherent to the methodology. Summarizing large amounts of varying information that are useful for clinical outcomes in terms of a single number may ignore essential differences between studies. However, this limitation is a controversial aspect of meta-analysis (41). However, a meta-analysis generalizes results despite differences in primary research and does not merely report a summary effect. We observed a significant amount of heterogeneity in our studies primarily related to recovery time, pooled adverse event rate, and drug discontinuation rate. This observed heterogeneity might be due to the geographical location of the studies along with the clinical practice differences in the COVID-19 care. Another reason for heterogeneity could be the dissimilar time periods in the background of the evolving clinical evidence. The timing of Remdesivir therapy in COVID-19 may also influence outcomes, as seen in ACTT-1 trial (19). However, we were unable to pool data according to the severity of COVID-19 subgroups due to lack of available information. We would like to mention that our study predominantly describes the clinical data and incidence rates in hospitalized patients. Also the number of included studies is very few, and the analysis

relied on data from case-series and clinical trials in the early phase, with a low level of evidence. Lastly, case series could also have publication bias. However, the case series were not utilized for evaluation of primary outcome and therefore less likely to influence the results overall. Even though no publication was found on visual examination of the funnel plot, further studies are needed to confirm the same. Larger scale studies (42) estimating the various systemic involvements are needed to confirm the findings.

CONCLUSION

Our systemic review and meta-analysis suggest that there may be a favorable risk-benefit profile for Remdesivir compared with placebo in severe COVID-19 infection. Presently, there are no pharmacologic therapies that have shown significant benefit in COVID-19. The present COVID-19 management strategy is focused on providing supportive care and preventing complications (43, 44). Effective agents are, therefore, urgently required to relieve the burden on healthcare systems. The larger observational studies (42) and clinical trials are warranted to confirm these findings (**Supplementary Table 3**).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

KM and VB contributed equally in the defining the study outline and manuscript writing. Data review and collection done by KM, IG, SH, JM, and NM. Statistical analysis was done by VB and AB. Study design and critical review done by IM and RK. VB, KM, and AB were guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2020.606429/full#supplementary-material

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CASE REPORT
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Case Report: Sublingual Microcirculatory Alterations in a Covid-19 Patient With Subcutaneous Emphysema, Venous Thrombosis, and Pneumomediastinum

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The Corona virus disease 2019 (Covid-19) has brought a wide range of challenges in intensive care medicine. Understanding of the pathophysiology of Covid-19 relies on interpreting of its impact on the vascular, particularly microcirculatory system. Herein we report on the first use of the latest generation hand-held vital microscope to evaluate the sublingual microcirculation in a Covid-19 patient with subcutaneous emphysema, venous thrombosis and pneumomediastinum. Remarkably, microcirculatory parameters of the patient were increased during the exacerbation period, which is not a usual finding in critically ill patients mostly presenting with a loss of hemodynamic coherence. In contrast, recovery from the disease led to a subsequent amelioration of these parameters. This report clearly shows the importance of microcirculatory monitoring for evaluating the course and the adequacy of therapy in Covid-19 patients.

Keywords: COVID-19, pneumomediastinum, venous thrombosis, subcutaneous emphysema, sublingual microcirculation, IDF imaging

INTRODUCTION

The Corona virus disease 2019 (Covid-19) has brought a wide range of challenges in intensive care medicine. Understanding of the pathophysiology of Covid-19 primarily relies on interpreting of its effects on the vascular, particularly microcirculatory system (1).

In critically ill, microcirculatory alterations can be directly visualized at the bedside via handheld vital microscopy (HVM) (2). HVM devices, equipped with imaging techniques such as orthogonal polarization spectral (OPS) imaging and side-stream dark field (SDF) or incident dark field (IDF) imaging, have enabled real time microvascular monitoring in this cohort. Accordingly, microcirculatory alterations have been identified in advance of changes in systemic hemodynamic parameters in many clinical settings that are associated with cardiovascular compromise such as cardiac surgery and sepsis (3). Among HVM devices, Cytocam represents the newest generation IDF microscope which provides better image quality than the initially used devices (4).

Herein, we applied this technology to directly observe the sublingual microcirculation in a Covid-19 patient with subcutaneous emphysema, venous thrombosis and pneumomediastinum.

CASE REPORT

A 56-year-old man was admitted to our institution with an 11-day history of persistent dry cough, fever, and progressive shortness of breath. On arrival at the hospital, he was hypoxemic, with a SpO_2 of 91% and a respiratory rate of 35 breaths per minute requiring ambient oxygen therapy with a flow of 15 L/min via a non-rebreather mask. Hemodynamically, he showed a stable profile with a blood pressure of 120/80 mmHg and a heart rate of 84 bpm. His body temperature was 38.1°C. Laboratory tests revealed an elevated C-reactive protein concentration of 37 mg/L (reference: <5 mg/L), a leukocyte count of 7.7×10^9/L (reference: 4–10 $\times 10^9$/L) and D-dimer of 0.41 mg/L (reference: <0.50 mg/L). The chest radiograph demonstrated bilateral basal consolidations. The suspicion of Covid-19 was confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) analysis of nasopharyngeal swab samples.

The patient was primarily admitted to a designated Covid-19 ward for further observation and oxygen therapy. Due to severe hypoxemic respiratory failure within 24 h after admission, he was immediately transferred to the intensive care unit (ICU) where he was intubated. On the 5th day of ICU admission (T_0), the patient developed a high fever accompanied with an increase in inflammatory parameters (**Table 1**). Hemodynamic parameters did not indicate an unstable course (**Table 1**). Microcirculatory monitoring was carried out sublingually using Cytocam-IDF imaging (CytoCam, Braedius Medical, Huizen, The Netherlands). Image analysis which was performed offline using MicroTools, showed an increase in microcirculatory density (total vessel density and perfused vessel density) and perfusion parameters (proportion of perfused vessels and microvascular mean flow index) as well as in red blood cell (RBC) velocity (**Table 2**). Subsequent CT-scan demonstrated extensive subcutaneous emphysema and pneumomediastinum as well as a thrombus in the right jugular vein extending to the superior vena cava and into the right brachial vein (**Figure 1**). A tracheal defect was ruled out by bronchoscopy. There was no pneumothorax or evidence of esophageal rupture.

The patient was ventilated for 19 days and a temporary tracheostomy was performed for a gradual wean from the ventilator. Unfractionated heparin was given in therapeutic doses for his venous thrombus. Chest CT obtained at 19th (T_1) and 25th day of ICU admission (T_2) showed complete resorption of mediastinal air and venous thrombus (**Figure 1**). Concurrent microcirculatory images revealed a recovery of microcirculatory alterations (**Table 2** and **Figure 1**). Thereupon on the 30th day of ICU admission, the tracheostomy was removed and the patient was discharged to the ward after 32 days of ICU stay in stable hemodynamic and respiratory condition.

TABLE 1 | Case timeline.

Variable	T_0	T_1	T_2
Day of onset of Covid-19 symptoms	16	30	36
Day of intensive care unit admission	5	19	25
Heart rate, beats/min	81	129	106
Mean arterial pressure, mmHg	105/56	126/61	136/79
PaO_2/FiO_2, mmHg	115.5	112.5	174.3
Mode of ventilation	PCV	PCV	PSV
Tidal volume, ml	450	348	446
Positive end-expiratory pressure, cmH_2O	16	6	5
Fraction of inspired oxygen, %	50	50	40
Driving pressure, cmH_2O	14	24	9
Compliance respiratory system, ml/cmH_2O	18.8	14.5	27
Temperature, °C	37.5	37.2	38.3
Fluid balance, ml	270	−2,000	−2,600
Creatinine, μmol/L	75	96	48
C-reactive protein, mg/L	213	226	382
Hematocrit, %	41	30	34
Thrombocyte count, $\times 10^9$/L	473	483	144
Leukocyte count, $\times 10^9$/L	14.2	17.8	16.3
pH	7.46	7.32	7.36
$PaCO_2$, kPa	5.8	7.7	8.4
PaO_2, kPa	7.7	7.5	9.3
Bicarbonate, mmol/L	30	27	31
Base excess, mmol/L	6.7	3.7	8.8
Oxygen saturation, %	90	90	94
Lactate, mmol/L	1.9	0.6	0.8

T, time point; COVID-19, Coronavirus Disease 2019; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; PCV, pressure-controlled ventilation; PSV, pressure-supported ventilation.

TABLE 2 | Microcirculatory parameters.

Variable	T_0	T_1	T_2
FCD, mm/mm^2	29.61 ± 0.92	28.02 ± 3.0	21.74 ± 3.84
PPV, %	95 ± 2	96 ± 2	98 ± 1
RBCv, μm/s	298.13 ± 19.61	327.10 ±18.89	354.81 ± 23.89
TVD, mm/mm^2	31.24 ± 1.24	29.23 ± 2.67	22.15 ± 3.82

Values are presented as mean ± standard deviation.
T, time point; FCD, functional capillary density; PPV, proportion of perfused vessels; RBCv, red blood cell velocity; TVD, total vessel density.

DISCUSSION

To our knowledge this is the first case report demonstrating microcirculatory alterations in a Covid-19 patient with subcutaneous emphysema and pneumomediastinum. Remarkably, microcirculatory parameters and RBC velocity of the patient showed an increase during the exacerbation period, which is not a usual finding in critically ill patients mostly presenting with a loss of hemodynamic coherence (3). In contrast, recovery from the disease led to a subsequent amelioration of these parameters.

The increase in microcirculatory parameters and RBC velocity in this patient may be explained by an intact compensatory mechanism of the microcirculation capable of responding to hypoxia (5). This compensatory mechanism is aimed at increasing the oxygen extraction capacity of the microcirculation by decreasing diffusion distances between capillaries (increased TVD) and by increasing convection of RBCs (increased RBC flow). Similar microcirculatory response to hypoxia has been reported in recent microcirculation studies which demonstrated increased sublingual microcirculatory vessel density as a response to hypoxic conditions at high altitude (6, 7). Notably, this intact

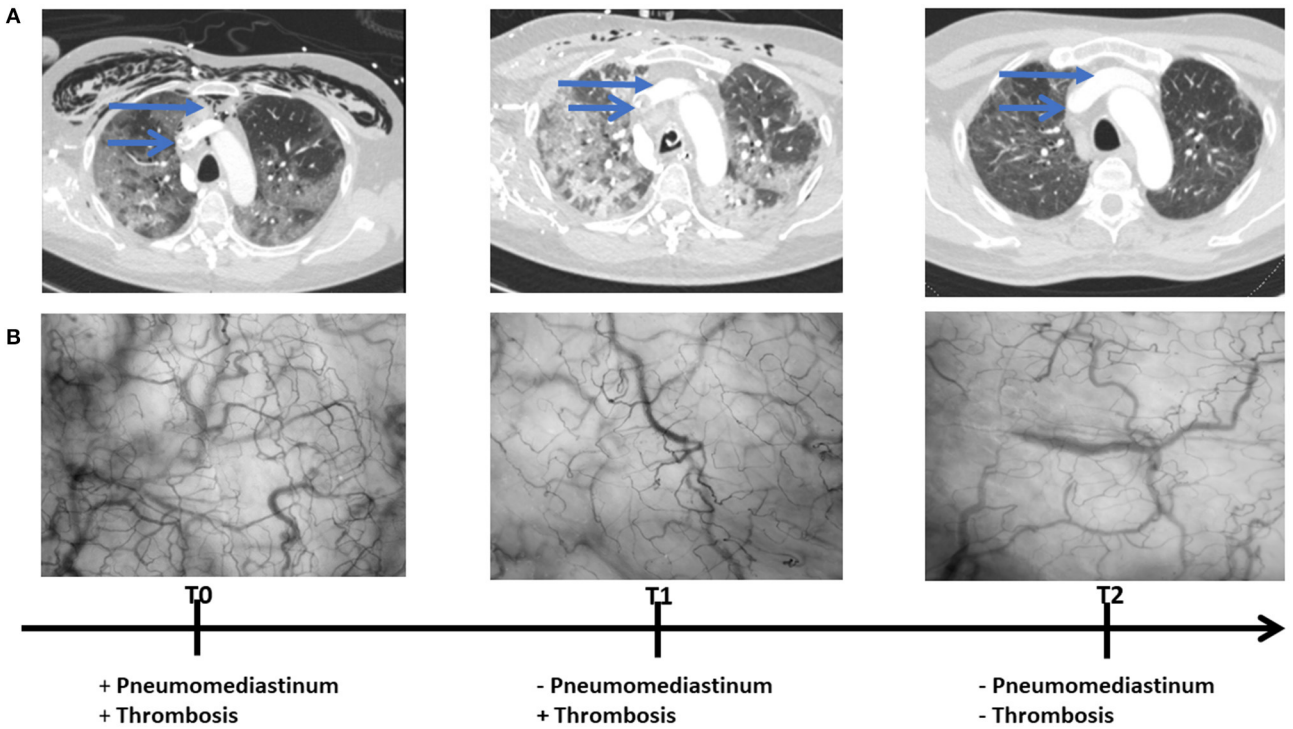

FIGURE 1 | Chest CT **(A)** and microcirculatory images **(B)** obtained at 5th (T_0), 19th (T_1), and 25th (T_2) day of intensive care admission.

compensatory mechanism may also explain the ability of Covid-19 patients to cope with low levels of oxygen which has been described as "happy hypoxia" (8).

Indeed, contrary to our results, Edul et al. (9) showed a decline in RBC velocity accompanied by an increase in vessel density in patients suffering from Covid-19 pneumonia. Furthermore, Rovas et al. (10) noted reductions in RBC velocity with decreases in vessel density in this cohort. Since hypoxemia induces both capillary recruitment and angiogenesis (9), differences might be related to the higher compromise of pulmonary oxygenation in our patient [PaO_2/FiO_2 ratio, 112.5 mmHg vs. 122 ± 43 mmHg (9) vs. 194.88 (145.76–234.0) mmHg (10)]. Spontaneous pneumomediastinum associated with Covid-19 has occasionally been reported (11). The presumed etiology involves a virus induced diffuse alveolar damage during an increase in intra-alveolar pressure, leading to alveolar rupture, a mechanism known as the Macklin effect (12). Ultimately, this pathology together with venous thrombus might have also influenced microcirculatory parameters in our patient, amplifying the microcirculatory response to hypoxia. Furthermore, the increase in microcirculatory parameters might have only been caused by these pathologies.

The main limitation of our study concerns the small sample size, thus making it difficult to generalize conclusions. Although in our patient a spontaneous pneumomediastinum was associated with a severe course of COVID-19 pneumonia, it is yet unclear to what extend the increase in microcirculatory parameters might predict the severity of disease in Covid-19 patients who don't present with pneumomediastinum. Notwithstanding the limitations of our study, we obtained a valuable patient perspective. Overall, our patient felt well and did not have any complications. Remarkably, he appreciated the care he received in our hospital.

In conclusion, this report clearly shows the importance of microcirculatory monitoring for evaluating the course and the adequacy of therapy in Covid-19 patients. Future studies are warranted to assess whether microcirculatory parameters could find potential clinical use as a predictor of the severity of disease in this cohort.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical approval was not required according to the local legislation and institutional guidelines. Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SG, BH and RN performed the IDF imaging and contributed to the manuscript revision. GA participated in the interpretation of the data, and drafted and revised the manuscript. BE was

involved in the image analysis and the manuscript revision. CI and SA participated in the design of the study and contributed to the manuscript revision. All authors read and approved the final version of the manuscript.

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Conflict of Interest: CI has developed SDF imaging and is listed as an inventor on related patents that were commercialized by Micro Vision Medical (MVM) under a license from the Academic Medical Center (AMC). He receives no royalties or benefits from this license. He has been a consultant for MVM in the past but has not been involved with this company for more than five years and holds no shares or stock. Braedius Medical, which is a company that is owned by a relative of CI, has developed and designed a handheld microscope, namely, the CytoCam-IDF imaging microscope. The images used in the present study were obtained using this technology. CI has no financial relationship with Braedius Medical of any sort. He has never owned shares or received consultancy or speaker fees from this company. MicroTools software that was used for analysis of the images is being developed by CI and Dr. Mathias Hilty and owned by Active Medical BV Leiden, The Netherlands. Active Medical also runs an internet site called microcirculationacademy.org which offers educational courses and services that are related to clinical microcirculation. CI discloses that he is a shareholder of this company.

The remaining authors declare that they do not have any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Prognostic Accuracy of Early Warning Scores for Clinical Deterioration in Patients With COVID-19

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Background: Early Warning Scores (EWS), including the National Early Warning Score 2 (NEWS2) and Modified NEWS (NEWS-C), have been recommended for triage decision in patients with COVID-19. However, the effectiveness of these EWS in COVID-19 has not been fully validated. The study aimed to investigate the predictive value of EWS to detect clinical deterioration in patients with COVID-19.

Methods: Between February 7, 2020 and February 17, 2020, patients confirmed with COVID-19 were screened for this study. The outcomes were early deterioration of respiratory function (EDRF) and need for intensive respiratory support (IRS) during the treatment process. The EDRF was defined as changes in the respiratory component of the sequential organ failure assessment (SOFA) score at day 3 ($\Delta SOFA_{resp}$ = SOFA $_{resp}$ at day 3–$SOFA_{resp}$ on admission), in which the positive value reflects clinical deterioration. The IRS was defined as the use of high flow nasal cannula oxygen therapy, noninvasive or invasive mechanical ventilation. The performances of EWS including NEWS, NEWS 2, NEWS-C, Modified Early Warning Scores (MEWS), Hamilton Early Warning Scores (HEWS), and quick sepsis-related organ failure assessment (qSOFA) for predicting EDRF and IRS were compared using the area under the receiver operating characteristic curve (AUROC).

Results: A total of 116 patients were included in this study. Of them, 27 patients (23.3%) developed EDRF and 24 patients (20.7%) required IRS. Among these EWS, NEWS-C was the most accurate scoring system for predicting EDRF [AUROC 0.79 (95% CI, 0.69–0.89)] and IRS [AUROC 0.89 (95% CI, 0.82–0.96)], while NEWS 2 had the lowest accuracy in predicting EDRF [AUROC 0.59 (95% CI, 0.46–0.720)] and IRS [AUROC 0.69 (95% CI, 0.57–0.81)]. A NEWS-C $\geq$ 9 had a sensitivity of 59.3% and a specificity of 85.4% for predicting EDRF. For predicting IRS, a NEWS-C $\geq$ 9 had a sensitivity of 75% and a specificity of 88%.

Conclusions: The NEWS-C was the most accurate scoring system among common EWS to identify patients with COVID-19 at risk for EDRF and need for IRS. The NEWS-C could be recommended as an early triage tool for patients with COVID-19.

Keywords: COVID-19, community-acquired pneumonia, early warning score, NEWS, NEWS 2, NEWS-C, quick sequential organ failure assessment

INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19) has recently become a public health emergency of international concern (1). A novel coronavirus, termed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was isolated as the pathogen of COVID-19 (2). As of October 18, 2020, there have been more than 40 million confirmed COVID-19 cases and 1.1 million deaths globally from World Health Organization reports.

With a sharp increase in the number of cases and limited medical resources, healthcare systems worldwide are facing unprecedented challenges (3). Although the majority of patients with COVID-19 have mild symptoms, patients with advanced age and chronic comorbidities such as hypertension tend to have poor outcomes (4, 5). Patients infected with SARS-CoV-2 tend to get worse from illness onset with a median duration of 7 days, in which severe type may deteriorate to acute respiratory distress syndrome (ARDS) or multiple organ failure (6, 7). During the outbreak of the COVID-19 crisis, early and quick recognition of patients who are at high risk of clinical deterioration would therefore be significantly important (8). A severity-based approach is urgently needed for triaging high risk patients with COVID-19 (9).

The Early Warning Scores (EWS) are a variety of physiologic scoring systems widely used in the world. These systems are based on bedside indices that can be obtained easily and rapidly such as heart rate, respiratory rate, systolic blood pressure, and peripheral oxygen saturation (SpO_2), allowing quick and accurate identify patients at high risk of clinical deterioration. Now, various EWS were developed for early recognition of clinical deterioration. The National Early Warning Score (NEWS), the most common EWS, was initially recommended by the Royal College of Physicians (RCP) (10). It has been proved that NEWS was associated with ICU admission and death outside ICU (11, 12). Its updated version, the National Early Warning Score 2 (NEWS2), with a new SpO_2 scoring scale, was published by the RCP in 2017 to improve prediction for clinical deterioration in patients with a hypercapnic respiratory failure (13). Other versions of EWS such as the Modified Early Warning Score (MEWS) (14, 15) and Hamilton Early Warning Score (HEWS) (16) have also been recently developed to improve the early recognition of hospitalized patients at risk for deterioration, with a significant degree of variation in the clinical variables and the weightings assigned.

Currently, guidelines from the RCP recommends the use of the NEWS2 for initial assessment in patients with COVID-19 (17). Moreover, NEWS-C, a new version of modified NEWS, has also been recommended for triage decisions in patients with COVID-19 (18, 19). However, the recommendations were only based on expert opinions and have not been fully validated in COVID-19 patients.

In this study, we aimed to compare the performance of EWS including NEWS, NEWS2, NEWS-C, HEWS, MEWS, and quick sepsis-related organ failure assessment (qSOFA) to predict early deterioration of respiratory function (EDRF) and the need for intensive respiratory support (IRS) in patients with COVID-19.

MATERIALS AND METHODS

Study Design and Participants

The study was approved by the Ethics Commission of Renmin Hospital of Wuhan University (WDRY2020-K048) and was conducted in accordance with the amended Declaration of Helsinki. Written informed consent was waived by the Ethics Commission in the setting of COVID-19 crisis in Wuhan.

Patients with age $\geq$18 years and confirmed COVID-19 admitted between February 7, 2020 and February 17, 2020 were screened in our study. We excluded patients for pregnancy, death within 48 h of admission, or having a Do Not Resuscitate order. COVID-19 was diagnosed by the real-time RT-PCR method on nasal or pharyngeal swab specimens.

Date Collection

Baseline demographics, clinical characteristics on hospital arrival including symptoms, vital signs, and oxygen therapy, laboratory findings, treatments, and outcomes were prospectively collected by two trained reviewers. The NEWS, NEWS-C, NEWS2, HEWS, MEWS, and qSOFA were calculated based on the demographic and clinical characteristics of each patient (**Supplementary Table 1**).

Outcome Assessment

Respiratory function was assessed according to the respiratory component of the sequential organ failure assessment score ($SOFA_{resp}$). The EDRF was defined as a positive change in respiratory function at day 3 ($\Delta SOFA_{resp}$ = $SOFA_{resp}$ at day 3–$SOFA_{resp}$ on admission). The positive value of $\Delta SOFA_{resp}$ reflects clinical deterioration. The IRS was defined as the use of high flow nasal cannula oxygen therapy, noninvasive or invasive mechanical ventilation. IRS was considered if the patients met the following criteria: a respiratory rate of $\geq$30 breaths per minute and arterial oxygen saturation (SaO_2) $\leq$ 93% or a ratio of the partial pressure of arterial oxygen (PaO_2) to inspired oxygen (FiO_2) of 300 mmHg or less while the patient was receiving oxygen therapy of $\geq$10 L/min for at least 15 min. The choices

TABLE 1 | Clinical characteristics of COVID-19 patients.

	Entire cohort	No EDRF	EDRF	*P* value	No need for IRS	Need for IRS	*P* value
Number of patients	116	89	27		92	24	
Age (years)	63 [51, 72]	61 [49, 69]	71 [64, 80]	<0.001	61 [48, 69]	73 [65, 81]	<0.001
Gender (male), *n* (%)	55 (47.4)	42 (47.2)	13 (48.1)	1.00	42 (45.7)	13 (54.2)	0.50
Smoking history, *n* (%)	10 (8.6)	8 (9.0)	2 (7.4)	1.00	9 (9.8)	1 (4.2)	0.69
Comorbidities							
Hypertension, *n* (%)	38 (32.8)	22 (24.7)	16 (59.3)	0.002	25 (27.2)	13 (54.2)	0.02
Diabetes mellitus, *n* (%)	20 (17.2)	16 (18.0)	4 (14.8)	1.00	15 (16.3)	5 (20.8)	0.56
CAD, *n* (%)	12 (10.3)	9 (10.1)	3 (11.1)	1.00	9 (9.8)	3 (12.5)	0.71
COPD, *n* (%)	2 (1.7)	2 (2.2)	0 (0)	1.00	0 (0)	2 (8.3)	0.04
Cerebrovascular disease, *n* (%)	2 (1.7)	0 (0)	2 (7.4)	0.05	1 (1.1)	1 (4.2)	0.37
Chronic renal disease, *n* (%)	4 (3.4)	3 (3.4)	1 (3.7)	1.00	3 (3.3)	1 (4.2)	1.00
Signs and symptoms							
Fever, *n* (%)	100 (86.2)	75 (84.3)	25 (92.6)	0.35	77 (83.7)	23 (95.8)	0.19
Cough, *n* (%)	80 (69.0)	58 (65.2)	22 (81.5)	0.15	62 (67.4)	18 (75)	0.62
Sputum production, *n* (%)	15 (12.9)	9 (10.1)	6 (22.2)	0.11	11 (12)	4 (16.7)	0.51
Fatigue, *n* (%)	99 (85.3)	73 (82.0)	26 (96.3)	0.12	77 (83.7)	22 (91.7)	0.52
Headache, *n* (%)	6 (5.2)	6 (6.7)	0 (0)	0.33	6 (6.65)	0 (0)	0.34
Dyspnea, *n* (%)	66 (56.9)	42 (47.2)	24 (88.9)	<0.001	44 (47.8)	22 (91.7)	<0.001
Nausea or vomiting, *n* (%)	25 (21.6)	17 (19.1)	8 (29.6)	0.29	19 (20.7)	6 (25)	0.78
Diarrhea, *n* (%)	23 (19.8)	18 (20.2)	5 (18.5)	1.00	19 (20.7)	4 (16.7)	0.78
Anorexia, *n* (%)	8 (6.9)	3 (3.4)	5 (18.5)	0.02	2 (2.2)	6 (25)	<0.001
Myalgia or arthralgia, *n* (%)	10 (8.6)	8 (9.0)	2 (7.4)	1.00	8 (8.7)	2 (8.3)	1.00
Onset of symptom to hospital admission, days	12 [9, 16]	12 [9, 18]	9 [6, 13]	0.02	12 [9, 17]	10 [7, 16]	0.16
Vital signs at hospital admission							
Altered mental status, *n* (%)	6 (5.2)	1 (1.1)	5 (18.5)	0.003	0 (0)	6 (25)	<0.001
Heart rate, beats/minute	90 [79, 102]	89 [79, 101]	96 [83, 106]	0.09	88 [78, 101]	95 [86, 107]	0.02
Respiratory rate, breaths/minute	23 [20, 29]	22 [20, 26]	28 [21, 34]	<0.01	22 [20, 25]	32 [22, 35]	<0.001
Systolic blood pressure, mm Hg	132 [122, 145]	131 [122, 144]	141 [127, 151]	0.19	131 [122, 144]	139 [122, 152]	0.25
Diastolic blood pressure, mm Hg	78 [68, 84]	78 [69, 83]	77 [66, 93]	0.52	79 [69, 84]	75 [66, 92]	0.96
Early warning scores at hospital admission							
NEWS	5 [3, 7]	5 [3, 6]	7 [5, 9]	<0.001	5 [3, 6]	8 [6, 10]	<0.001
NEWS-C	6 [5, 9]	6 [5, 8]	10 [6, 12]	<0.001	6 [4, 8]	10 [8, 13]	<0.001
NEWS 2	6 [5, 8]	6 [5, 8]	7 [4, 9]	0.16	6 [4, 8]	7 [6, 9]	0.004
HEWS	3 [2, 5]	3 [2, 4]	6 [3, 9]	0.001	3 [1, 4]	7 [5, 10]	<0.001
MEWS	2 [2, 3]	2 [1, 3]	3 [2, 5]	0.001	2 [1, 3]	4 [3, 5]	<0.001
qSOFA	1 [0, 1]	1 [0, 1]	1 [0, 1]	0.03	1 [0, 1]	1 [1, 2]	<0.001
Respiratory status assessment							
PaO_2 on admission, mmHg	90 [69, 95]	92 [78, 96]	69 [55, 88]	<0.001	92 [77, 96]	69 [55, 83]	<0.001
$PaCO_2$ on admission, mmHg	41 [38, 44]	42 [39, 45]	39 [37, 44]	0.11	41 [38, 45]	41 [38, 44]	0.62
PaO_2/FiO_2 on admission, mmHg	292 [245, 326]	305 [272, 328]	245 [167, 303]	0.001	305 [274, 329]	196 [150, 260]	<0.001
$SOFA_{resp}$ on admission	2 [1, 2]	1 [1, 2]	2 [1, 3]	0.004	1 [1, 2]	3 [2, 3]	<0.001
PaO_2 at day 3, mmHg	94 [85, 96]	95 [92, 97]	63 [52, 84]	<0.001	95 [92, 97]	63 [51, 80]	<0.001
$PaCO_2$ at day 3, mmHg	41 [37, 46]	42 [38, 46]	39 [36, 45]	0.10	41 [37, 46]	42 [38, 46]	0.85
PaO_2/FiO_2 at day 3, mmHg	314 [241, 330]	326 [277, 349]	156 [87, 197]	<0.001	326 [277, 334]	102 [74, 159]	<0.001
$SOFA_{resp}$ at day 3	1 [1, 2]	1 [1, 2]	3 [3, 4]	<0.001	1 [1, 2]	3 [3, 4]	<0.001
EDRF, *n* (%)	27 (23.3)	0 (0)	27 (100)	<0.001	7 (7.6)	20 (83.3)	<0.001
Need for IRS, *n* (%)	24 (20.7)	4 (4.5)	20 (74.1)	<0.001	0 (0)	24 (100)	<0.001
Respiratory support							
High flow nasal cannula, *n* (%)	24 (20.7)	4 (4.5)	20 (74.1)	<0.001	0 (0)	24 (100)	<0.001

(Continued)

TABLE 1 | Continued

	Entire cohort	No EDRF	EDRF	*P* value	No need for IRS	Need for IRS	*P* value
Non-invasive mechanical ventilation, *n* (%)	5 (4.3)	0 (0)	5 (18.5)	<0.001	0 (0)	5 (20.8)	<0.001
Invasive mechanical ventilation, *n* (%)	8 (6.9)	1 (1.1)	7 (25.9)	<0.001	0 (0)	8 (33.3)	<0.001
Need for vasopressor support, *n* (%)	9 (7.8)	2 (2.2)	7 (25.9)	<0.001	1 (1.1)	8 (33.3)	<0.001
Renal replacement therapy, *n* (%)	3 (2.6)	2 (2.2)	1 (3.7)	0.55	2 (2.2)	1 (4.2)	0.50
Extracorporeal membrane oxygenation, *n* (%)	1 (0.9)	0 (0)	1 (3.7)	0.23	0 (0)	1 (4.2)	0.21
Hospital mortality, *n* (%)	9 (7.8)	1 (1.1)	8 (29.6)	<0.001	0 (0)	9 (37.5)	<0.001
Hospital length of stay, days	29 [18, 36]	28 [18, 34]	38 [8, 49]	0.04	29 [18, 35]	37 [7, 49]	0.28

Continuous variables are shown as the mean ± SD or median [IQR], as appropriate. Categorical variables are shown as number (%).
COVID-19, coronavirus disease 2019; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen; HEWS, Hamilton Early Warning Score; MEWS, Modified Early Warning Score; NEWS, National Early Warning Score; NEWS-C, modified NEWS; NEWS 2, National Early Warning Score 2; qSOFA, quick Sepsis-related Organ Failure Assessment; EDRF, early deterioration of respiratory function; IRS, intensive respiratory support.

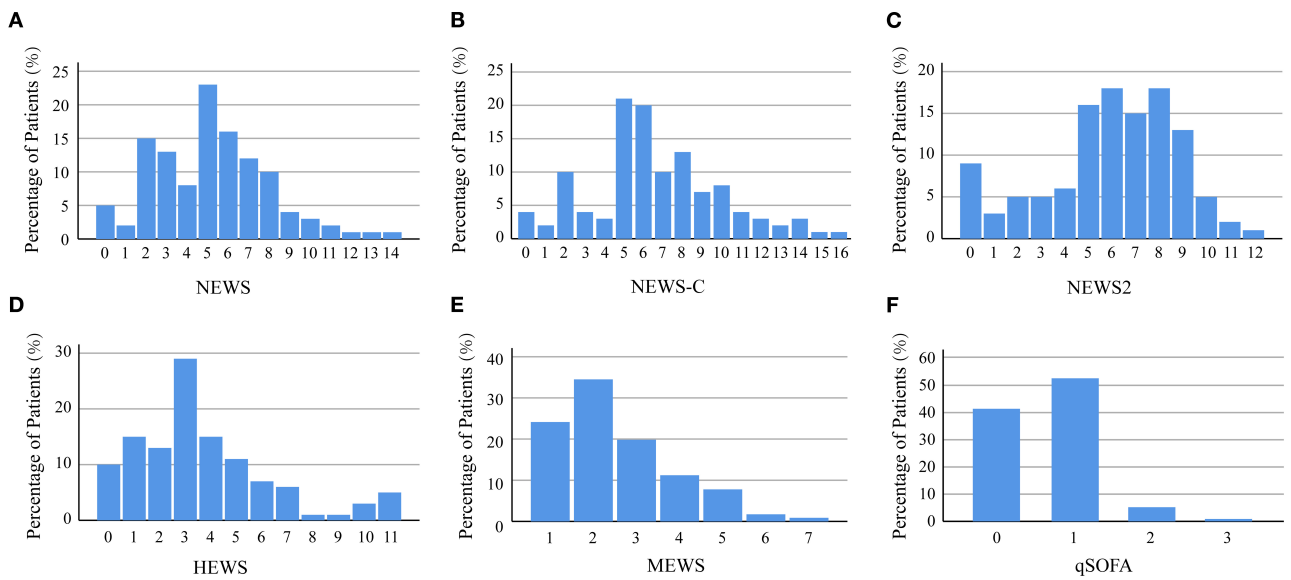

FIGURE 1 | Distribution of patients by NEWS **(A)**, NEWS-C **(B)**, NEWS2 **(C)**, HEWS **(D)**, MEWS **(E)**, and qSOFA **(F)**. HEWS, Hamilton Early Warning Score; MEWS, Modified Early Warning Score; NEWS, National Early Warning Score; NEWS-C, modified NEWS; NEWS 2, National Early Warning Score 2; qSOFA, quick Sepsis-related Organ Failure Assessment.

of respiratory support method (high flow nasal cannula oxygen therapy, noninvasive or invasive mechanical ventilation) were at the discretion of the attending clinicians.

Statistical Analysis

Data distribution was evaluated using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation or median interquartile range as appropriate. Categorical variables were expressed as frequencies and percentages. Baseline data were compared using the Student's *t*-test or the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Receiver operating characteristic (ROC) curves were constructed to assess the performance of EWS, and the optimal cut-off values were calculated by the Youden index. The area under the receiver operating characteristic curve (AUROC) were compared by the method described by Hanley and McNeil (20). All statistical analyses were performed using the SPSS software package, version 13.0 (SPSS, Inc., Chicago, IL, USA) and MedCalc software 15.0 (MedCalc Software Ltd, Ostend, Belgium). A two-tailed *P* value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Between February 7, 2020 and February 17, 2020, a total of 123 patients with COVID-19 were screened for inclusion. Of these patients, seven patients were excluded, including one patient with pregnancy, three patients who died within 48 h after admission, and three patients with DNR order. Finally, 116 patients were included for this study.

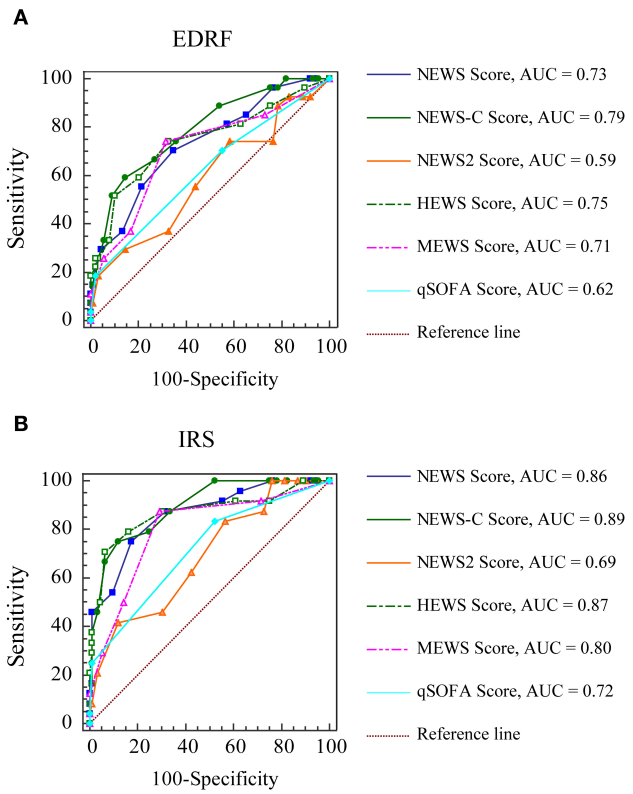

FIGURE 2 | The receiver operating characteristic curves of early warning scores for clinical deterioration. **(A)** EDRF; **(B)** IRS. AUC, area under the curve; HEWS, Hamilton Early Warning Score; MEWS, Modified Early Warning Score; NEWS, National Early Warning Score; NEWS-C, modified NEWS; NEWS 2, National Early Warning Score 2; qSOFA, quick Sepsis-related Organ Failure Assessment; EDRF, early deterioration of respiratory function; IRS, intensive respiratory support.

The baseline characteristics were shown in **Table 1**. Of 116 patients, the median age was 63 [IQR 51, 72] years and 47.4% were men. Fever was the most common symptom (86.2%), followed by fatigue (85.3%), cough (69.0%), and dyspnea (56.9%). The baseline NEWS, NEWS-C, NEWS2, HEWS, MEWS, and qSOFA at admission were 5 [3, 7], 6 [5, 9], 6 [5, 8], 3 [2, 5], 2 [2, 3], and 1 [0, 1], respectively. The distributions of all patients by NEWS, NEWS-C, NEWS2, HEWS, MEWS, and qSOFA at admission were presented in **Figure 1**.

The baseline PaO_2/FiO_2 on admission was 292 [245, 326] mmHg. At day 3, the median PaO_2/FiO_2 was 314 [241, 330] mmHg. A total of 27 (23.3%) patients developed EDRF according to the $\Delta SOFA_{resp}$ ($SOFA_{resp}$ at day 3–baseline $SOFA_{resp}$), in which a positive value reflected clinical deterioration. Patients with EDRF tended to be older and had a higher rate of hypertension than those without EDRF (all $P < 0.01$). Compared with the patients without EDRF, the patients with EDRF have higher proportions of dyspnea (88.9 vs. 47.2%; $P < 0.001$) and higher respiratory rate [28 (21, 22) vs. 22 (20, 23) breaths/minute; $P < 0.01$] but lower baseline PaO_2/FiO_2 value [245 (167, 303) vs. 305 (272, 328) mmHg; $P < 0.001$]. On admission, patients with EDRF had higher NEWS, NEWS-C, HEWS, MEWS, and qSOFA than non-EDRF patients (all $P < 0.05$; **Table 1**). However, the NEWS2 between patients with EDRF and non-EDRF was comparable ($P = 0.16$; **Table 1**).

A total of 24 patients (20.7%) needed IRS during the period of hospital stay. Patients with IRS also tended to be older and had a higher rate of hypertension than those without IRS (all $P < 0.05$). Compared with the patients without IRS, the patients requiring IRS have higher proportions of dyspnea (91.7 vs. 47.8%; $P < 0.001$) and a higher respiratory rate [32 (24, 25) vs. 22 (20, 26); $P < 0.001$] but a lower baseline PaO_2/FiO_2 value [196 (150, 260) vs. 305 (274, 329); $P < 0.001$]. Patients with IRS had a higher NEWS, NEWS-C, NEWS2, HEWS, MEWS, and qSOFA than non-IRS patients (all $P < 0.001$; **Table 1**). A total of 20 patients (17.2%) developed both IRS and EDRF in this cohort. The hospital mortality rate was 7.8%. The mortality in patients with EDRF or IRS was higher than those without EDRF or IRS (all $P < 0.001$).

Performance of EWS for Clinical Deterioration

To assess the utility of EWS to predict EDRF and need for IRS, the ROC curves were constructed and the AUROCs were calculated (**Figure 2**). **Table 2** listed AUROC, optimal cutoff value, sensitivity, specificity, and positive and negative predictive values of EWS.

Among these EWS, NEWS-C was the most accurate scoring system for predicting EDRF {AUROC 0.79 [95% confidence interval (CI), 0.69–0.89]}. The AUROC of the NEWS-C for predicting EDRF was much higher than that for NEWS2 (0.59, 95% CI 0.46–0.72; $P < 0.001$) and qSOFA (0.62, 95% CI 0.51–0.74; $P < 0.001$). The AUROC of NEWS-C for predicting EDRF was also larger than NEWS (0.73, 95% CI 0.62–0.84), HEWS (0.75, 95% CI 0.63–0.86), and MEWS (0.71, 95% CI 0.59–0.83), although the difference is not statistically significant (**Table 3**). A NEWS-C ≥ 9 had a sensitivity of 59.3% and a specificity of 85.4% for predicting EDRF.

Among these EWS, NEWS-C was the most accurate scoring system for predicting IRS [AUROC 0.89 (95% CI, 0.82–0.96)]. The AUROC of the NEWS-C for predicting IRS was much higher than that for NEWS2 (0.69, 95% CI 0.57–0.81; $P < 0.001$), MEWS (0.80, 95% CI 0.70–0.90; $P = 0.03$), and qSOFA (0.72, 95% CI 0.61–0.82; $P < 0.001$). The AUROC of NEWS-C for predicting IRS was also higher than NEWS (0.86, 95% CI 0.78–0.95) and HEWS (0.87, 95% CI 0.77–0.97), although the difference is not statistically significant (**Table 4**). For predicting IRS, a NEWS-C ≥ 9 had a sensitivity of 75% and a specificity of 88%.

DISCUSSION

Until now, there are limited studies to evaluate the predictive value of EWS in patients with COVID-19. In the current study, we found that the NEWS-C was the most accurate scoring system among common EWS for predicting EDRF and IRS in patients with COVID-19. On the contrary, NEWS 2 had the lowest accuracy for predicting both outcomes.

TABLE 2 | Performance of early warning scores in predicting clinical deterioration.

Outcomes	Predictors	AUROC	95% CI	P	Cut-off	Sensitivity (%)	Specificity (%)	PPV	NPV	LR+	LR–
EDRF	NEWS	0.73 ± 0.06	0.62–0.84	<0.001	5	81.5	42.7	30.1	88.4	1.42	0.43
					6	**70.4**	**65.2**	**38**	**87.9**	**2.02**	**0.45**
					7	55.6	78.7	44.1	85.4	2.6	0.57
	NEWS-C	0.79 ± 0.05	0.69–0.89	<0.001	8	66.7	73.0	42.9	87.8	2.47	0.46
					9	**59.3**	**85.4**	**55.2**	**87.4**	**4.06**	**0.48**
					10	51.9	91.0	63.6	86.2	5.77	0.53
	NEWS2	0.59 ± 0.07	0.46–0.72	0.18	5	74.1	23.6	22.7	75	0.97	1.1
					6	**74.1**	**41.6**	**27.8**	**84.1**	**1.27**	**0.62**
					7	55.6	56.2	27.8	80.6	1.27	0.79
	HEWS	0.75 ± 0.06	0.63–0.86	<0.001	5	59.3	79.8	47.1	86.6	2.93	0.51
					6	**51.9**	**89.9**	**60.9**	**86.0**	**5.13**	**0.54**
					7	33.3	92.1	56.2	82	4.24	0.72
	MEWS	0.71 ± 0.06	0.59–0.83	<0.001	2	85.2	27.0	26.1	85.7	1.17	0.55
					3	**74.1**	**68.5**	**41.7**	**89.7**	**2.35**	**0.38**
					4	37.0	83.2	40	81.3	2.2	0.76
	qSOFA	0.62 ± 0.06	0.51–0.74	0.04	1	70.4	44.9	27.9	83.3	1.28	0.66
					2	**18.5**	**97.8**	**71.4**	**79.8**	**8.24**	**0.83**
Need for IRS	NEWS	0.86 ± 0.04	0.78–0.95	<0.001	6	87.5	68.5	42	95.5	2.78	0.18
					7	**75**	**82.6**	**52.9**	**92.7**	**4.31**	**0.3**
					8	54.2	90.2	59.1	88.3	5.54	0.51
	NEWS-C	0.89 ± 0.03	0.82–0.96	<0.001	8	79.2	75	45.2	93.2	3.17	0.28
					9	**75**	**88**	**62.1**	**93.1**	**6.27**	**0.28**
					10	66.7	93.5	72.7	91.5	10.22	0.36
	NEWS2	0.69 ± 0.06	0.57–0.81	0.002	8	45.8	69.6	28.2	83.1	1.51	0.78
					9	**41.7**	**88.0**	**47.6**	**85.3**	**3.48**	**0.66**
					10	20.8	96.7	62.5	82.4	6.39	0.82
	HEWS	0.87 ± 0.05	0.77–0.97	<0.001	5	79.2	83.7	55.9	93.9	4.86	0.25
					6	**70.8**	**93.5**	**73.9**	**92.5**	**10.86**	**0.31**
					7	50	95.7	75	88	11.5	0.52
	MEWS	0.80 ± 0.05	0.70–0.90	<0.001	2	91.7	28.3	25	92.9	1.28	0.29
					3	**87.5**	**70.7**	**43.7**	**95.6**	**2.98**	**0.18**
					4	50	85.9	48	86.8	3.54	0.58
	qSOFA	0.72 ± 0.05	0.61–0.82	<0.001	**1**	**83.3**	**47.8**	**29.4**	**91.7**	**1.6**	**0.35**
					2	25	98.9	85.7	83.5	23	0.76

AUROC, area under the receiver operating characteristic curve; CI, confidence interval; LR, likelihood ratio; PPV, positive predictive value; NPV, negative predictive value; HEWS, Hamilton Early Warning Score; MEWS, Modified Early Warning Score; NEWS, National Early Warning Score; NEWS-C, modified NEWS; NEWS 2, National Early Warning Score 2; qSOFA, quick Sepsis-related Organ Failure Assessment; EDRF, early deterioration of respiratory function; IRS, intensive respiratory support. Bold: the optimal cut-off values according to Youden index.

EWS have been developed and widely used around the world for early recognition of clinical deterioration (21). The NEWS, endorsed by RCP, is already used for predicting deterioration in many hospitals across the United Kingdom (10). It is reported that the NEWS has better performance than other EWS to identify patients at risk of ICU admission and mortality (12). Moreover, the NEWS was more accurate in predicting clinical deterioration than qSOFA in infected patients outside the ICU (24).

The NEWS 2, updated version of NEWS, was recommended by RCP in 2017. The new SpO_2 scoring scale in NEWS 2, with a lower SpO_2 threshold than NEWS, was implemented to avoid over-use of supplemental oxygen and facilitate management in hypercapnic patients (27). Recently, the NEWS 2 has been recommended for predicting clinical deterioration in patients with COVID-19 (17). In our study, NEWS 2 had a lower performance than NEWS in predicting EDRF and IRS. This is in accordance with previous study, which demonstrated that NEWS 2 did not predict clinical outcome in elderly patients with COVID-19 (28). The possible reasons were as follows: (1) the incidence of type II respiratory failure in patients with COVID-19 was low in this study; and (2) the NEWS2 modifications to NEWS may not improve discrimination of poor outcome in hospital patients including those with type II respiratory failure (26). Therefore, NEWS 2 may be inappropriate for triage decision in patients with COVID-19.

TABLE 3 | The cross-comparisons between AUROCs of early warning scores for predicting EDRF.

AUROC		NEWS	NEWS-C	NEWS2	HEMS	MEWS	qSOFA
		0.73 [0.62–0.84]	**0.79 [0.69–0.89]**	**0.59 [0.46–0.72]**	**0.75 [0.63–0.86]**	**0.71 [0.59–0.83]**	**0.62 [0.51–0.74]**
NEWS	0.73 [0.62–0.84]	/	0.07	0.006	0.66	0.49	0.004
NEWS-C	0.79 [0.69–0.89]	0.07	/	<0.001	0.31	0.08	<0.001
NEWS2	0.59 [0.46–0.72]	0.006	<0.001	/	0.003	0.02	0.57
HEMS	0.75 [0.63–0.86]	0.66	0.31	0.003	/	0.17	0.008
MEWS	0.71 [0.59–0.83]	0.49	0.08	0.02	0.17	/	0.10
qSOFA	0.62 [0.51–0.74]	0.004	<0.001	0.57	0.008	0.10	/

AUROC, area under the receiver operating characteristic curve; HEWS, Hamilton Early Warning Score; MEWS, Modified Early Warning Score; NEWS, National Early Warning Score; NEWS-C, modified NEWS; NEWS 2, National Early Warning Score 2; qSOFA, quick Sepsis-related Organ Failure Assessment; IRS, intensive respiratory support.

TABLE 4 | The cross-comparisons between AUROCs of Early Warning Scores for predicting IRS.

AUROC		NEWS	NEWS-C	NEWS2	HEMS	MEWS	qSOFA
		0.86 [0.78–0.95]	**0.89 [0.82–0.96]**	**0.69 [0.57–0.81]**	**0.87 [0.77–0.97]**	**0.80 [0.70–0.90]**	**0.72 [0.61–0.82]**
NEWS	0.86 [0.78–0.95]	/	0.28	0.001	0.82	0.049	<0.001
NEWS-C	0.89 [0.82–0.96]	0.28	/	<0.001	0.54	0.03	<0.001
NEWS2	0.69 [0.57–0.81]	0.001	<0.001	/		0.04	0.60
HEMS	0.87 [0.77–0.97]	0.82	0.54	0.003	/	0.01	0.001
MEWS	0.80 [0.70–0.90]	0.049	0.03	0.04		/	0.10
qSOFA	0.72 [0.61–0.82]	<0.001	<0.001	0.60	0.001	0.10	/

AUROC, area under the receiver operating characteristic curve; HEWS, Hamilton Early Warning Score; MEWS, Modified Early Warning Score; NEWS, National Early Warning Score; NEWS-C, modified NEWS; NEWS 2, National Early Warning Score 2; qSOFA, quick Sepsis-related Organ Failure Assessment; IRS, intensive respiratory support.

A modified NEWS, termed NEWS-C, has also been recommended for triage decision in patients with COVID-19 (18, 19). The MEWS (14) and HEWS (16) have been developed to early identify clinical deterioration in generally hospitalized patients, with a significant degree of variation in the clinical variables and the weightings assigned. In this study, the NEWS-C had largest AUROC for predicting EDRF and IRS in these EWS. NEWS-C modifications to EWS added an age ≥65 years as an independent component. Several studies have showed that old aging was independently associated with mortality in patients with COVID-19 (4, 23). Therefore, it may offer better predictive performance than other EWS.

qSOFA, consisting of three clinical variables (mental status, respiratory rate, and blood pressure), has been proposed as a rapid screening tool for infected patients (29). The effectiveness of the qSOFA has been validated in various heterogeneous sepsis patients (30, 31). Recently, several reports have demonstrated that the qSOFA can accurately assess the severity of community-acquired pneumonia (32–34). However, qSOFA had a lower performance in predicting clinical deterioration compared with other EWS in our study. This may be partially explained by the low percentage of hypotension and alter mental status in this cohort. The finding was also consistent with previous studies, in which qSOFA may not be appropriate to identify critically ill patients with COVID-19 (22, 35).

This study had several limitations. First, this was a retrospective study with relatively small sample size. A larger cohort validation is still required. Second, the changes in EWS during the treatment process was not recorded in this study. Third, as the intubation rate and mortality in this

population were lower than that in critically ill patients (25, 35, 36), caution must be taken in extrapolating the results of the study for critically ill patients. Additional assessments of organ dysfunction should be required in critically ill patients with COVID-19.

CONCLUSION

The NEWS-C was the most accurate scoring system among common EWS to identify patients with COVID-19 at risk for EDRF and need for IRS. The NEWS-C could be recommended as an early triage tool for COVID-19.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Commission of Renmin Hospital of Wuhan University. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

YS, G-wT, and ZL: conception and design. M-jJ, R-cX, and ZL: administrative support. YS, M-jJ, S-jY, J-lZ, and G-gM: provision of study materials or patients. YS, S-jY, J-lZ, KL, R-cX, and G-gM: collection and assembly of data. YS, G-wT, R-cX, M-jJ, and ZL: data analysis and interpretation. All authors: manuscript writing and final approval of manuscript.

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SUPPLEMENTARY MATERIAL

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Neutrophil Extracellular Traps in SARS-CoV2 Related Pneumonia in ICU Patients: The NETCOV2 Study

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Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a poorly understood disease involving a high inflammatory status. Neutrophil extracellular traps (NETs) have been described as a new pathway to contain infectious diseases but can also participate in the imbalance of the inflammatory and the coagulation systems. NETs could be a therapeutic target in COVID-19 patients.

Methods: Consecutive patients with SARS-CoV2 related pneumonia admitted to the intensive care unit were included in a prospective bicentric study. Neutrophil extracellular trap concentrations were quantified in whole blood samples at day-1 and day-3 by flow cytometry. The primary outcome was the association between the blood NET quantification at ICU admission and the number of days with refractory hypoxemia defined by a PaO_2/FIO_2 ratio $\leq$100 mmHg.

Results: Among 181 patients admitted to the ICUs for acute respiratory failure related to SARS-CoV2 pneumonia, 58 were included in the analysis. Patients were 62 [54, 69] years old in median, mostly male (75.9%). The median number of days with severe hypoxemia was 4 [2, 6] days and day-28 mortality was 27.6% ($n = 16$). The blood level of NETs significantly decreased between day-1 and day-3 in patients who survived (59.5 [30.5, 116.6] to 47 [33.2, 62.4] $p = 0.006$; 8.6 [3.4, 18.0] to 4 [1.4, 10.7] $p = 0.001$ and 7.4 [4.0, 16.7] to 2.6 [1.0, 8.3] $p = 0.001$ for MPO+, Cit-H3+, and MPO+ Cit-H3+ NETs, respectively) while it remained stable in patients who died (38.4 [26.0, 54.8] to 44.5 [36.4, 77.7] $p = 0.542$; 4.9 [1.3, 13.0] to 5.5 [2.8, 6.9] $p = 0.839$ and 4 [1.3, 13.6] to 2.7 [1.4, 4.5] $p = 0.421$ for MPO+, Cit-H3+, and MPO+ Cit-H3+ NETs, respectively). In multivariable negative binomial regression, the blood level of MPO+ NETs was negatively associated with the number of days with severe hypoxemia within 7 days (0.84 [0.73, 0.97]), while neither Cit-H3+ NETs nor double-positive NETs were significantly associated with the primary outcome.

Conclusion: The whole blood level of NETs at day-1 was negatively associated with the number of days with severe hypoxemia in patients admitted to the intensive care unit for SARS-CoV2 related pneumonia. The lack of decrease of the blood level of NETs between day-1 and day-3 discriminated patients who died within day-28.

Keywords: COVID19, SARS-CoV2, neutrophils extracellular traps neutrophils extracellular traps, coronavirus, pneumonia

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INTRODUCTION

Neutrophils extracellular traps (NETs) are the result of neutrophil extrusion of extracellular fibers composed of DNA, histones, and granule-derived proteins released by neutrophils, which trap and kill extracellular pathogens (1). NETosis is triggered by several metabolic pathways including NADPH oxidase (2) and peptidylarginine deaminase 4 (PAD4)-induced citrullination of histones (3) which converge to mediate the cellular process of chromatin decondensation necessary for NET release from neutrophils. The relative importance of NADPH oxidase and PAD4 for completion of NETosis may be dictated by the cellular stimulus. NETs are important players in the genesis, growth and resolution of the coagulation cascade (4, 5) and may participate in the imbalance of inflammation and coagulation in sepsis (6). This is particularly well-described in the context of acute respiratory distress syndrome (ARDS) related to bacterial (7–10) or influenza pneumonia (11–13), linked to the massive invasion of alveoli by an inflammatory infiltrate containing neutrophils, monocytes, macrophages, altered epithelial cells and numerous pro-inflammatory markers (14) Blood and alveoli levels of NETs in ARDS patients strongly correlate with the severity of respiratory disease (7, 15).

Respiratory failure is the leading cause of death in the coronavirus disease 19 (COVID-19) involving simultaneously and at different degrees lung injury related to viral invasion, pulmonary thrombosis and cytokine storm (16–18). Neutrophils may play a cornerstone role in the pathogenesis of the most severe cases (19). Increased counts of blood neutrophils and a high neutrophil-to-lymphocyte ratio are associated with severe respiratory disease and worse outcomes in this setting (20, 21). Interestingly, lung tissue microscopic examination evidenced neutrophilic infiltration in pulmonary capillaries, extravasation of neutrophils into the alveolar space, and neutrophilic mucositis as well as alveolar capillary microthrombi (22, 23).

Taken together, NETs may represent an interesting factor that could be associated with both viral pneumonia and thrombosis. Thus, we decided to investigate the association between the whole blood levels of NETs at ICU admission and the respiratory failure evolution toward refractory hypoxemia in ICU patients with SARS-COV2 related pneumonia.

MATERIALS AND METHODS

Patients and Data Collection

All consecutive patients admitted to the ICU meeting the following inclusion criteria were included: age $\geq$18 years, SARS-CoV2 related pneumonia documented at least on one of the following criteria: SARS-CoV2 positive PCR on a sample of the upper and/or lower airways and/or typical CT scan lung pattern, as previously described (24). Patients were not included in case of pregnancy, guardianship or curatorship or if they had signed an opposition form.

Demographics, clinical and laboratory variables were recorded during intensive care unit stay as well as the use of adjuvant therapies for ARDS, the need for hemodialysis or vasopressors, corticosteroid administration, the occurrence of thrombotic events (both venous thromboembolism and arterial thrombotic complications), the number of ventilator- and organ failure–free days at day 28, and the duration of mechanical ventilation. Vital status at day-28 was also recorded.

The electronic CRF (e-CRF) developed by Clinfile were used for data collection from each center.

Controls

Healthy volunteer blood donors were used as "controls."

Outcomes

The primary clinical endpoint was the association between the blood level of NETs at ICU admission and the number of days with refractory hypoxemia defined by a PaO_2/FIO_2 ratio lower than 100.

Secondary outcomes included the association between the blood NET measurements at ICU admission and (1) the need for orotracheal intubation, (2) criteria for ARDS in mechanically ventilated patients according to the Berlin classification (25), (3) admission severity scores, i.e., the simplified acute physiology score (SAPS II) and the sequential organ failure assessment (SOFA) (26–28), (4) the blood levels of inflammatory biomarkers [procalcitonin and C-reactive protein (CRP)], (5) day-28 all-cause mortality, (6) the number of mechanical ventilation free days (number of days without mechanical ventilation, patients who died on mechanical ventilation being rated zero), (7) the main markers of blood hemostasis [i.e., prothrombin ratio, activated partial thromboplastin time (aPTT) ratio, blood platelets level, D-dimers, antithrombin-III, C protein as well as fibrinogen] and anticoagulation regimens, and (8) the occurrence of thrombotic events (both venous thromboembolism and arterial thrombotic complications) and pulmonary circulatory failure. Pulmonary circulatory failure was assessed by critical care echocardiography; right ventricular dysfunction was retained if there was a right ventricular dilation defined as a ratio of end diastolic area of right ventricle on left ventricle >0.6 or an *acute cor pulmonale* (29, 30).

NET Quantification

NETs were quantified in whole blood samples at day-1 and day-3 and bronchoalveolar fluid (BAL) (in intubated patients performed at the time of intubation) by flow cytometry according to an in-house technique adapted from Gavillet and Masuda et al. (31, 32). As nothing was known regarding SARS-COV2-induced NETosis, we quantified several NET sub populations: single positive MPO+, single positive Cit-H3+ and double positive MPO+ Cit-H3+. Staining was performed with a "lysis-no wash" protocol to preserve NET integrity. 50 µL from whole blood sample or 1 mL from BAL were stained with the DNA-dye Hoechst 34580 (Life Technologies, Courtaboeuf, France) and Histone H3 (citrulline R2 + R8 + R17) rabbit polyclonal antibody (Abcam, Amsterdam, Netherlands) according to manufacturers' instructions and incubated 30 min at 37°C. Cells were then stained with SYTOX Green Dead Cell stain (Life Technologies, Courtaboeuf, France), Goat Anti-Rabbit IgG H&L-APC (Abcam), MPO-PE (Becton Dickinson, San Jose, CA, USA) according to manufacturers' instructions and

incubated 30 min at room temperature. Red blood cell lysing was then performed using BD Pharm Lyse (Becton Dickinson) according to manufacturer's instructions. Data were acquired using a Lyric cytometer (Becton Dickinson) and analyzed using the Kaluza software (Beckman Coulter, Roissy, France). Positivity thresholds for MPO and Cit-H3 were assessed using negative isotypic controls.

The analytical strategy of NETs quantification is depicted in **Figure 1**. Nucleated cells were isolated using a Hoechst 34580 labeling and SYTOX Green positive cells (SYTOX+ cells) were gated as previously described (32), Single-positive (MPO+ or Cit-H3+) and double-positive (MPO+ Cit-H3+). NETs were then quantified as a percentage of nucleated cells and absolute values were calculated using leukocyte count or BAL cell count.

Statistical Analysis

Data were described according to the primary outcome by the *n* (percentage) for the qualitative and median [interquartile] variables for the quantitative variables. Qualitative variables were compared using a Pearson chi-2 test or an exact Fisher test as appropriate. Quantitative variables were compared using a non-parametric Mann-Whitney.

The data were also described according to the blood NETs quantification on day-1 (divided into tertiles). The comparison between groups were performed using the Jonckheere-Terpstra test to take into account the order of categories (33, 34).

Pearson's correlation coefficients were calculated to assess the correlation between the day-1 blood level of NETs and hemostasis markers as listed above.

A negative binomial regression model was used to obtain an estimate of the effect of the blood level of NETs at day-1 on the number of days with severe hypoxemia within day-7. The exponential form of the estimate is called the incidence rate ratio. We included in the multivariable model all the relevant variables as well as the blood level of NETs. Relevant interactions were tested.

A p-value <0.05 was considered significant. The analysis was performed using R (35).

Ethics

The present study was approved by the Research Ethics Board of the Foch Hospital (Suresnes, France, n° 20-04-01) on April 6th, 2020.

RESULTS

Baseline Characteristics

Baseline characteristics of the 58 patients included in the analysis are shown in **Table 1**. Patients were 62 [iqr 54, 69] years old in median, mostly male (75.9%). COVID-19 diagnosis relied on a positive PCR in 55 (94.8%) cases and an abnormal lung CT-scan in all cases. ICU admission occurred after 9 [iqr 7, 11] days in median after symptom onset. Median Charlson score was 3 [1, 3]. Median SAPS2 score was 32 [iqr 26, 46] at ICU admission.

NETosis

We observed a strong correlation between day-1 whole blood level of NETs and blood leucocytes (**Supplementary Figures 1, 2**) at day-1 and day-2. Blood levels of NETs were similar in controls and in SARS-CoV2 patients except for MPO+ CIt-H3+ NETs which were significantly higher in COVID-19 patients (**Supplementary Figure 3**).

Primary Outcome

Overall we observed a median number of days with severe hypoxemia (PaO_2/FIO_2 < 100 mHg) of 4 [iqr 2, 6] days. No difference was observed in the three tertiles of number of days with severe hypoxemia (**Table 1**). The blood level of NETs did not differ either across these three tertiles (**Supplementary Table 1**). Conversely, we did not observe any significant association between quartiles of blood levels of NETs at day-1 and the number of days with severe hypoxemia (**Supplementary Table 2**).

In multivariable negative binomial regression, after adjustment for age, gender, SAPS II and Charlson scores, lung CT-scan lesions and time interval between onset of symptoms and ICU admission, MPO+ NETs were negatively associated with the number of days with severe hypoxemia within 7 days, while neither Cit-H3+ NETs nor MPO+ Cit-H3+ NETs were significantly associated with the primary outcome (**Table 2**).

Secondary Outcomes

Respiratory SOFA

The association between the blood level of NETs at day-1 and respiratory SOFA at day-1, day-2, and day-3 is shown on **Figure 2**. We observed a significant negative association between MPO+ NETs and SOFA at day-1, 2, and 3 (p-value 0.035, 0.044, and 0.015, respectively) while all other levels did not differ over time. Similar observations were made with PaO_2/FIO_2 ratio (**Supplementary Figure 4**).

Day-3 Blood Levels of NETs

Overall, MPO+ NETs did not vary between day-1 and day-3 (44.1 [iqr 22.7, 88.6] and 47 [33.9, 66.7], $p = 0.375$) while Cit-H3+ NETs increased and MPO+ Cit-H3+ NETs decreased over time (4.1 [1.5, 10.4] vs. 1 [0, 3.1] $p < 0.001$ and 2.6 [1.1, 7.7] $p < 0.001$, respectively).

Day-28 Mortality

Day-28 mortality was 27.6% ($n = 16$). The blood level of NETs significantly decreased between day-1 and day-3 in patients who survived (59.5 [30.5, 116.6] to 47 [33.2, 62.4] $p = 0.006$; 8.6 [3.4, 18.0] to 4 [1.4, 10.7] $p = 0.001$; and 7.4 [4.0, 16.7] to 2.6 [1.0, 8.3] $p = 0.001$ for MPO+, Cit-H3+, and MPO+ Cit-H3+ NETs, respectively). The blood levels of NETs remained stable in patients who died between day-1 and day-3 (38.4 [26.0, 54.8] to 44.5 [36.4, 77.7] $p = 0.542$; 4.9 [1.3, 13.0] to 5.5 [2.8, 6.9] $p = 0.839$; and 4 [1.3, 13.6] to 2.7 [1.4, 4.5] $p = 0.421$ for MPO+, Cit-H3+, and MPO+ Cit-H3+ NETs, respectively) (38.4 [26.0, 54.8] vs. 44.5 [36.4, 77.7]) (**Figure 3**).

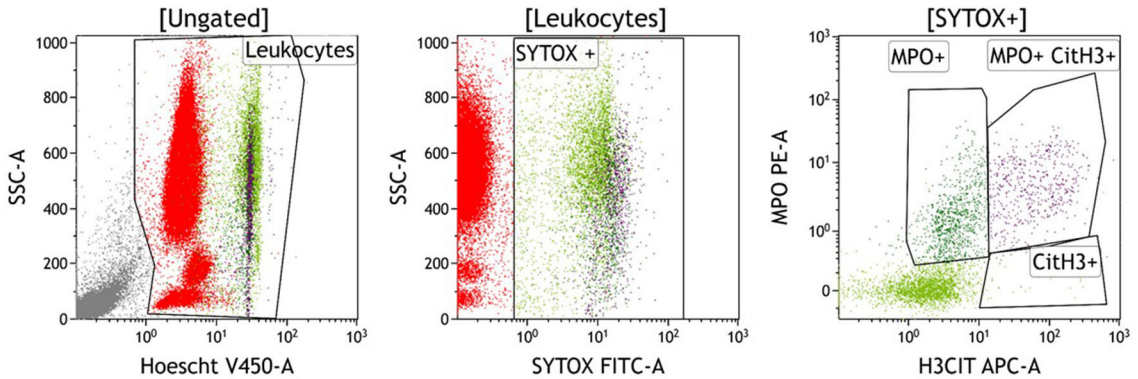

FIGURE 1 | Typical staining of NETs in blood sample of a patient with SARS-COV2. After gating of nucleated cells (Leukocytes) with the DNA marker Hoechst 34580 (Plot A), SYTOX positive cells (ie cells with compromised plasma membranes) were isolated within the Leukocytes gate (Plot B). Single-positive (MPO+ or Cit-H3+) and double-positive (MPO+ Cit-H3+) NETs were then quantified in the SYTOX+ population (Plot C), respectively at 0.90, 0.03, and 0.52% for this patient.

TABLE 1 | Baseline characteristics of the 58 included patients according to the number of days with severe hypoxemia within day-7.

	[0,3) days (*N* = 20)	[3,6) days (*N* = 18)	[6,8) days (*N* = 20)	All patients (*N* = 58)	*P*-value
Age, years	59.0 [45.0; 71.0]	63.0 [57.0; 69.0]	61.5 [56.0; 68.5]	62.0 [54.0; 69.0]	0.757
Male gender	12 (60.0)	15 (83.3)	17 (85.0)	44 (75.9)	0.122
Body mass index, kg/m²	25.5 [24.5; 30.5]	28.7 [24.7; 30.1]	27.5 [25.0; 37.2]	27.5 [24.6; 31.0]	0.496
Positive PCR SARS-CoV2	19 (95.0)	17 (94.4)	19 (95.0)	55 (94.8)	0.996
Lung-CT scan involvement					0.597
<25%	4 (20.0)	0 (0.0)	1 (5.6)	5 (9.1)	
25–50%	4 (20.0)	3 (17.6)	4 (22.2)	11 (20.0)	
50–75%	8 (40.0)	8 (47.1)	6 (33.3)	22 (40.0)	
>75%	4 (20.0)	6 (35.3)	7 (38.9)	17 (30.9)	
Time interval between symptoms onset and ICU admission, days	9.0 [6.5; 12.0]	10.0 [7.0; 11.0]	8.0 [7.0; 10.0]	9.0 [7.0; 11.0]	0.866
Pulmonary embolism	2 (11.8)	5 (27.8)	5 (26.3)	12 (22.2)	0.454
Deep-vein thrombosis	1 (5.6)	3 (17.6)	2 (11.1)	6 (11.3)	0.529
Anti-inflammatory drugs before admission	0 (0.0)	0 (0.0)	1 (5.0)	1 (1.7)	0.380
Corticosteroids before admission	2 (10.0)	1 (5.6)	4 (20.0)	7 (12.1)	0.371
Immunosuppressive drugs before admission	3 (15.0)	1 (5.6)	1 (5.0)	5 (8.6)	0.454
Charlson comorbidities score	2.5 [1.0; 4.0]	2.5 [2.0; 3.0]	3.0 [1.0; 3.0]	3.0 [1.0; 3.0]	0.943
SAPS2 score	34.0 [22.0; 50.5]	28.5 [25.0; 34.0]	35.5 [27.5; 51.0]	32.0 [26.0; 46.0]	0.426
SOFA score	3.5 [3.0; 5.5]	4.5 [4.0; 5.0]	5.0 [4.0; 5.0]	4.0 [3.0; 5.0]	0.245
Blood leucocytes, G/L	12.1 [8.1, 12.7]	10.2 [8.5, 12.4]	8.4 [4.5, 10.9]	9.8 [6.9, 12.6]	0.102
Blood polymorphonuclear cells, G/L	9.2 [5.7, 11.0]	8.7 [6.7, 11.5]	6.8 [3.2, 9.1]	8.2 [5.4, 10.8]	0.096
Blood lymphocytes, G/L	0.8 [0.7, 1.3]	0.7 [0.5, 1.0]	0.6 [0.4, 1.0]	0.7 [0.6, 1.1]	0.130
C-reactive protein, mg/L	183 [140, 305]	188 [125, 242]	183 [128, 250]	187 [127, 255]	0.731
Procalcitonin, mg/L	0.6 [0.2, 2.0]	0.4 [0.2, 1.7]	0.4 [0.2, 2.7]	0.4 [0.2, 2.0]	0.994
Fibrinogen, g/L	6.7 [6.5, 8.4]	6.3 [5.1, 6.6]	6.8 [5.4, 8.8]	6.7 [5.6, 8.4]	0.213

Hemostasis and Thrombosis

We observed significant correlations between day-1 blood level of NETs and platelets, prothrombin ratio and fibrinogen level (**Supplementary Figures 5–7**). Twelve patients (22.2%) received therapeutic-intensity anticoagulation with either low-molecular weight or unfractionated heparin, 11 (20.4%) received double-dose low-molecular weight heparin and 31 (57.4%) received single-dose low-molecular weight heparin. We observed at least one thrombotic event in 14/58 (24.1%) patients included in the analysis. No difference was observed between patients with

TABLE 2 | Association between blood levels of NETs at day-1 and number of days with severe hypoxemia within day-7.

	Incidence rate ratio [95% confidence interval]		
Age, per year	1.02 [1.00, 1.03]	1.02 [1.00, 1.04]	1.02 [1.00, 1.04]
Male gender	1.77 [1.18, 2.64]	1.91 [1.25, 2.91]	1.93 [1.27, 2.96]
SAPSII, per unit increase	1.01 [0.99, 1.02]	1.01 [0.99, 1.02]	1.01 [0.99, 1.02]
Charlson comorbidities score	0.84 [0.73, 0.97]	0.85 [0.74, 0.99]	0.85 [0.73, 0.98]
Lung CT-scan lesions*	1.18 [1.00, 1.39]	1.22 [1.02, 1.46]	1.22 [1.03, 1.46]
Time interval between onset of symptoms and ICU admission, days	0.98 [0.93, 1.02]	0.98 [0.93, 1.02]	0.97 [0.93, 1.02]
NETs MPO+, per 50/μmol increase	0.84 [0.73, 0.97]	–	–
Cit-H3+, per 5/μmol increase	–	0.99 [0.71, 1.37]	–
MPO+ Cit-H3+ per 5/μmol increase	–	–	0.99 [0.94, 1.04]

Multivariable negative binomial regression was performed adjusting for age, gender, SAPS II and Charlson score, lung CT-scan lesions and time interval between onset of symptoms and ICU admission. The interpretation of the incidence rate ratio is as follows: an increase of 50/μmol of the blood level of MPO+ NETs at day-1 increase the expected number of days with severe hypoxemia within day-7 by a factor 0.84, holding all other variables constant.

**The variable "Lung CT scan lesions" is an ordinal variable treated as follows: <25% (reference), 25–50%, 50–75%, >75%. The incidence rate ratio should be interpreted as the change between two increasing categories.*

and without thrombotic events regards to the anticoagulation regimen. Blood levels of NETs at day-1 were significantly lower in patients with compared to those without thrombotic events (39.7 [27.9, 74.4] vs. 47.9 [27.8, 88.6], 0.6 [0.0, 3.6] vs. 2.1 [0.2, 3.3], and 4.1 [0.8, 14.0] vs. 6.8 [2.6, 15.2] $p < 0.001$ for all, for MPO+, HCIT+, and MPO+ Cit-H3+ NETs) (**Supplementary Figure 8**).

Right Ventricular Dysfunction

Blood levels of NETs at day-1 was significantly lower in patients with vs. without a right ventricular dilation (40 [33.5, 105.6] vs. 63 [37.7, 88.6] $p < 0.001$, 0 [0, 0.3] vs. 3 [0.4, 4.9] $p = 0.622$, and 2.7 [0.8, 12.5] vs. 6.1 [2.6, 18.4] $p < 0.001$ for MPO+, Cit-H3+, and MPO+ Cit-H3+ NETs, respectively). Similar results were obtained in patients with vs. without *acute cor pulmonale* (36.3 [33.5, 55.1] vs. 60.3 [36.3, 101.2] $p < 0.001$, 0 [0, 0.1] vs. 2.3 [0.3, 4.6] $p < 0.001$, and 1.3 [0.7, 8.2] vs. 5.8 [1.9, 14.4] $p < 0.001$ for MPO+, Cit-H3+, and MPO+ Cit-H3+ NETs, respectively).

DISCUSSION

In this prospective observational study including 58 patients admitted to the intensive care unit for acute respiratory failure related to SARS-CoV2 pneumonia, we observed a negative association between the blood level of NETs at day-1 and (1) the severity of the respiratory status, (2) the occurrence of thrombotic events, and (3) the occurrence of right ventricular failure assessed by echocardiography. We also found that a stable level of NETs between day-1 and day-3 discriminated patients who died and those who were still alive at day-28.

NETs and Severity of Hypoxemia

In the present cohort, whole blood levels of NETs at day-1 strongly correlated with severity of hypoxemia. In multivariable analysis, it was independently associated with the number of days with severe hypoxemia (defined as PaO2/FIO_2 ratio < 100 mmHg). Moreover, the blood level of MPO+ Cit-H3+ NETs in healthy controls was lower than in patients admitted to the ICU for SARS-CoV2 related pneumonia.

Interestingly, these results were not expected. In animal models of influenza pneumonia, the presence of NETs was associated with acute lung injury (12). In human being admitted to the hospital for acute respiratory failure related to influenza, the plasma level of NETs was correlated with the severity of the respiratory status (36). However, in the latter, the plasma cell-free DNA levels did not correlate with PaO_2/FIO_2 values but with systemic inflammation (36). Plasma NETs levels were also associated with ARDS severity and mortality in a cohort of 104 ARDS patients (7). Interestingly, Bendib et al. found similar results in a prospective cohort of 35 ARDS patients. Alveolar NETosis in these ARDS patients was inversely associated with hypoxemia and there was no significant association with either day-28 mortality or the number of mechanical ventilation free days (6). Moreover, reduced NETosis under hypoxia has also been evidenced in previous publications (37, 38). In the COVID-19 setting, Middleton et al. reported similar findings in a small sample of COVID-19 patients with a negative relationship between NETosis evaluated using ELISA and severity of hypoxemia (39). Two hypotheses should be discussed to explain this observation. First, this decreased production of NETs could result from a functional defect of polymorphonuclear neutrophils cells, i.e., the number of neutrophils may be normal despite inability to release NETs. Furthermore, such a defect could be explained by the singular inflammatory phenotype of SARS-CoV2 infection in which an impaired type I interferon activity has been shown in a severity-dependent fashion (40). As interferon is a primer of NET production and release (41), the immunological specificities of COVID-19 may at least partly explain the observations we made. Second, we could hypothesize that the blood levels did not accurately reflect what happened in the lung. We were not able to provide sufficient data on alveolar liquid to answer this question. However, in two patients, one with a mild lung injury and the other with a severe one, we observed significantly different amounts of NETs (**Supplementary Figure 9**) but of course these results are too parcellar to draw robust conclusions. A sequestration in the

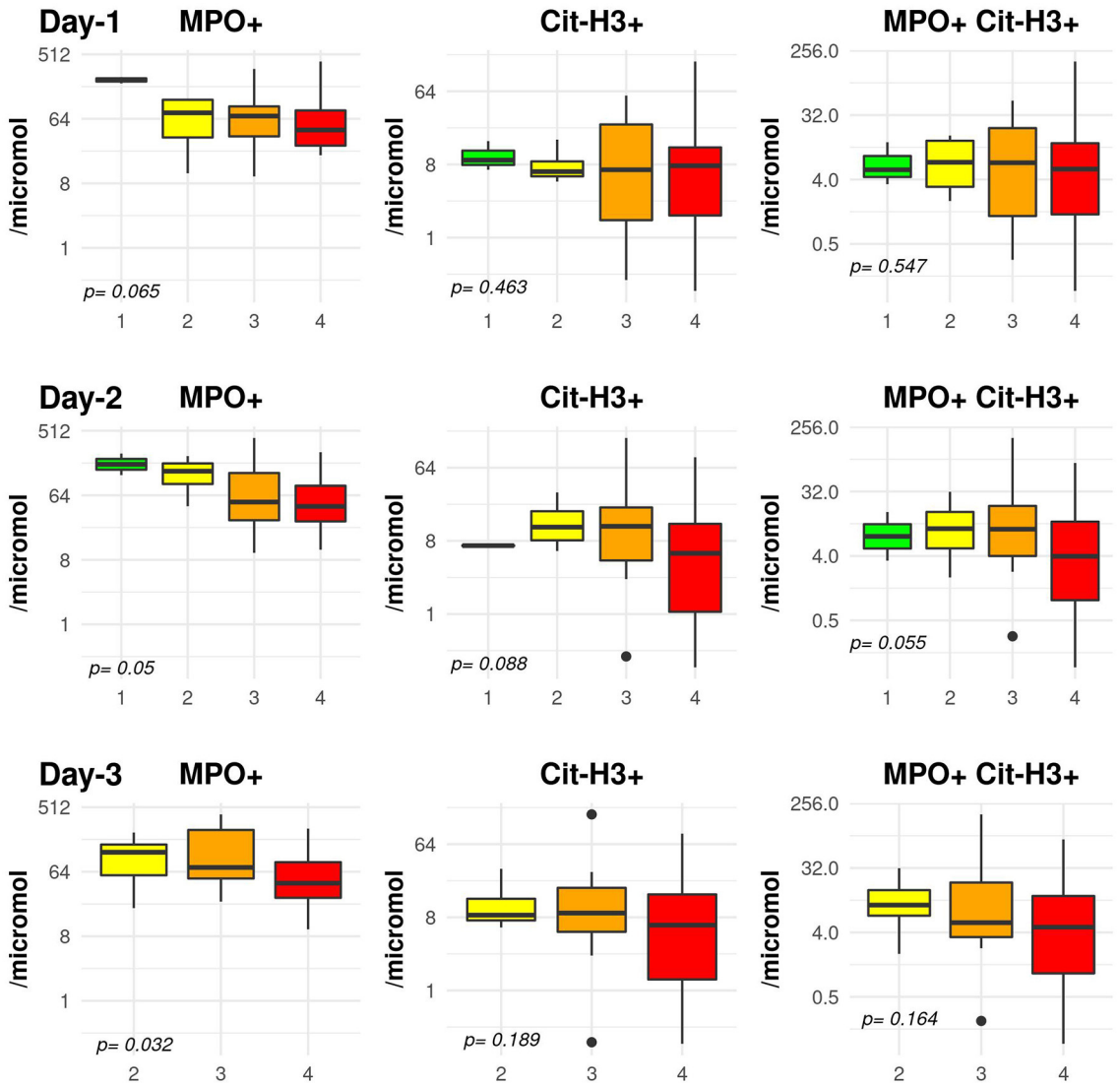

FIGURE 2 | Association between day-1 blood level of NETs and respiratory sequential organ failure assessment (SOFA) score at day-1, day-2, and day-3. The y-axis is shown using a logarithmic scale. The comparison is performed using a Jonckheere test to take into consideration the ordered respiratory SOFA score.

targeted organ of the virus could be part of the explanation of what we observed.

NETs and Day-28 Mortality

While the blood levels of NETs at day-1 did not differ between patients dead and alive at day-28, we found that the decrease of blood level of NETs between day-1 and day-3 was strongly correlated with survival to day 28. To the best of our knowledge, this is the first time such a finding is provided. Bendib et al. have already described that blood level of NETs decreased over time in critically ill patients while it remained constant in the bronchoalveolar fluid (8). This was suggestive of a "logical" targeted action of NETs in the lung of patients with pneumonia. However, no description was made in that study of the outcome according to the variations of blood levels of NETs over time. Such a finding could suggest that this lack of decrease in patients with an unfavorable outcome at day-28 reflects either the lack of control of the infection leading to the recruitment of more polymorphonuclear neutrophils and/or the detrimental effect of these NETs in response to the viral aggression. These detrimental effects have already been described in numerous publications. NETs may function as double-edged swords, as they may be a source of immune and pro-inflammatory effectors that may promote tissue damage and autoimmunity (42). In the context of COVID-19, such a mechanism could have amplified the cytokine release syndrome that has been observed in the most severe patients. We are not able to provide further explanation to this finding. However, this seems of interest as this could help to identify patients who could benefit for targeted therapies.

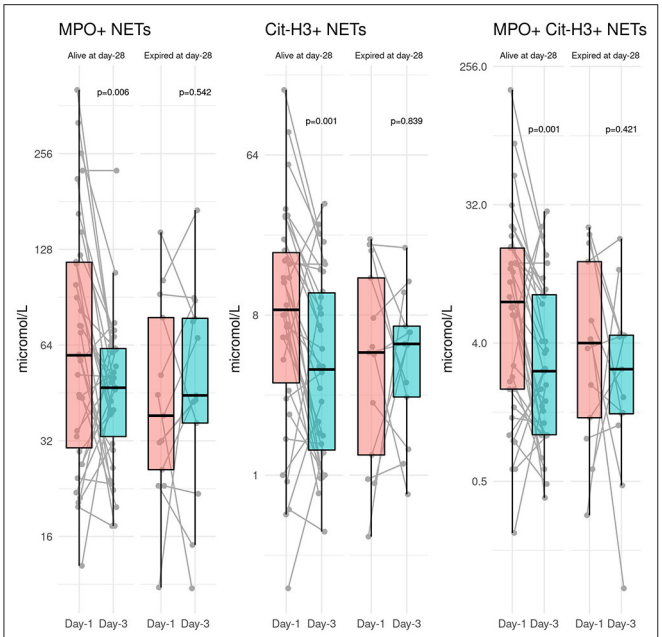

FIGURE 3 | Evolution of blood levels of NETs between day-1 and day-3 according to the vital status at day-28.

NETs, Thrombotic Events, and Right Ventricular Failure

In the present study, we also observed a negative association between blood levels of NETs and thrombotic events as well as the occurrence of right ventricular failure. While numerous publications have been reported so far about the high incidence of thrombotic events and right ventricular dysfunction in COVID-19 patients (43, 44), we could have expected a positive association of the blood level of NETs with the occurrence of thrombotic events. Indeed, the level of NETs has been strongly associated with both venous and arterial thrombosis (45, 46). These results could be interpreted in line with a recent publication that provides insights in the role of NETs in thrombosis (47). Nouboussie et al. have shown that NETs had no procoagulant effect *in vitro* while degradation products (such as single histones, purified DNA) activated the intrinsic pathway of coagulation (48). The mechanism explaining this observation remains unclear but this could be related to the neutralization of the negative charge of DNA on the NET surface. Our results add some contribution to these experimental findings, reinforcing the hypothesis that instead of targeting NETs, therapeutic strategies might be focused on components of NETs, leading to a better neutralization of their detrimental effects.

Limitations

We acknowledge some limitations. First, the present study is observational and what we observed does not imply causality but association. Second, we were not able to provide sufficient data about the level of NETs in the bronchoalveolar fluid. This could be of importance as such results could have been a better reflection of what happened in the lung of patients with mainly a respiratory involvement of COVID-19. However, we believe our results provide significant insights as COVID-19 has been shown a multi-systemic disease with autoimmune and thrombotic symptoms. Third, we did not provide functional assessment of neutrophil functions that could support the hypothesis that the negative association we observed was related to a decreased potential of neutrophils. Last, the evaluation of the occurrence of thrombotic events was made within the first days after ICU admission. This could preclude an accurate evaluation of the relationship between the blood level of NETs at day-1 and such an event that might have occurred a few days later.

CONCLUSION

The whole blood level of NETs at day-1 was negatively associated with the number of days with severe hypoxemia in patients admitted to the intensive care unit for SARS-CoV2 related pneumonia. The lack of decrease of the blood level of NETs between day-1 and day-3 discriminated the patients who died within day-28. Whether the NETs could be a therapeutic target in COVID-19 patients should be further investigated.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Board of the Foch Hospital (Suresnes, France, n° 20-04-01) on April 06, 2020. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MG, JZ, VB, and GG: study design. GG: statistical analysis. All authors: acquisition, analysis, or interpretation of the data, and critical revision of the manuscript for important intellectual content.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.615984/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glucocorticoids Should Be Used With Caution in Patients With SARS-CoV-2

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global pandemic, and the use of glucocorticoids in clinical practice is controversial. Our clinical experiences with glucocorticoid treatment suggested that, while use was effective in some cases, in other cases, glucocorticoid were ineffective and even resulted in immunosuppression that could lead to deterioration. Therefore, glucocorticoids should be used with caution in patients with SARS-CoV-2.

Keywords: glucocorticoid, COVID-19, SARS-CoV-2, pneumonia, inflammation

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INTRODUCTION

On December 31, 2019, a new type of coronavirus disease (SARS-CoV-2) was first reported in Wuhan, Hubei Province, and subsequently, a rapid epidemic was reported in China. However, while SARS-CoV-2 is a new type of infectious pneumonia that threatens patients' lives, medical staff, and scientific researchers lack a clear understanding of the pathophysiological process of severe new coronavirus pneumonia; however, diagnosis, and treatment experience is also accumulating. Therefore, clinical treatments have been based on previous experiences. Previous conventional treatments used for severe acute respiratory syndrome (SARS), influenza virus pneumonia, acute respiratory distress syndrome (ARDS), and other severe diseases include oxygen therapy, respiratory assistance therapy, extracorporeal membrane oxygenation (ECMO) life support, infection control, and nutritional support, but there is a lack of drugs with precise therapeutic effects (including antiviral drugs). The use of glucocorticoids in clinical practice is also controversial (1, 2).

CLINICAL CONTROVERSY IN THE USE OF GLUCOCORTICOIDS IN SEVERE VIRAL PNEUMONIA

During the acute phase of ARDS, alveolar injury is accompanied by a large number of inflammatory cell infiltrations, macrophage activation, and the release of a large number of inflammatory mediators. Early emergence of alveolar epithelial-mesenchyme transition and initiation of fibrosis are the pathophysiological basis of hormone-assisted therapy. Corticosteroids have potential advantages in the treatment of patients with ARDS because they can regulate the inflammatory response and slow the fibrosis process. However, the results of previous clinical studies based on SARS or severe influenza pneumonia are inconsistent about whether glucocorticoids improve patient outcomes. A clinical observational study on severe H7N9 influenza virus pneumonia showed that treatment with glucocorticoids (equivalent to methylprednisolone 80 mg/day; quartile range, 40–120 mg/day) for 7 days significantly increased the 60-day mortality of patients. In addition, high-dose glucocorticoids (equivalent to methylprednisolone > 150 mg/day) significantly

increased the 30- and 60-day mortality and delayed virus clearance (3). Among 309 patients with severe Middle East respiratory distress syndrome (MERS), ICU mortality and hospital mortality increased significantly in patients treated with glucocorticoids, and 90-day mortality in patients treated with glucocorticoids was not significantly different from that in patients without hormone treatments, but virus clearance was delayed (4). The results of a propensity score matching study involving 1,846 patients with severe influenza pneumonia showed that combined hormone therapy (equivalent to methylprednisolone 80 mg/day; quartile range, 60–120 mg/day) was associated with increased ICU mortality (5). A retrospective analysis of a small sample of 78 severely ill patients with SARS showed that hormone therapy could increase the chances of ICU admission or mortality by 20.7 times (6). Studies have also shown that early application of hormone therapy could increase plasma virus load and delay virus clearance (7). Therefore, scholars believe that the application of glucocorticoids for severe new coronavirus pneumonia will not benefit patients and may even be harmful; however, most of the above studies were observational or retrospective studies with selective bias and confounding factors, which might lead to the conclusion that hormone therapy was harmful and the evidence was insufficient. A retrospective analysis of a larger sample (401 cases) of patients with SARS showed that the combined use of hormone therapy did not benefit patients, but the application of hormones (methylprednisolone 133.5 $\pm$ 102.3 mg/day) in severe patients (152 cases) could shorten the length of hospital stay and reduce all-cause mortality (8). A prospective cohort study of 2,141 patients with H1N1 influenza virus pneumonia showed that low to moderate doses of glucocorticoids (equivalent to methylprednisolone 25–150 mg/day) could reduce mortality in patients with an oxygenation index below 300 mmHg (9). In addition, a systematic review showed that glucocorticoid therapy in severe community-acquired pneumonia can reduce patient mortality, shorten the duration of mechanical ventilation, and help to prevent ARDS (10).

CLINICAL STATUS OF GLUCOCORTICOID APPLICATION IN NEW CORONAVIRUS PNEUMONIA

The summary description of limited autopsy and puncture tissue pathology in the seventh edition of the "New Coronavirus Diagnosis and Treatment Program" shows that serous fluid, fibrin exudate, and transparent membrane formation are observed in the alveolar cavity, and the exudative cells are mainly monocytes and macrophages. The alveolar septum is hyperaemic and oedematous with infiltration of monocytes and lymphocytes. Degeneration and necrosis can be seen in cardiomyocytes, and infiltration of lymphocytes, monocytes, and neutrophils can be observed in the interstitium. Degeneration and focal necrosis with neutrophil infiltration were observed in hepatocytes. These pathological results indicate that severe inflammatory reactions or "inflammatory storms" may occur in patients with severe new coronavirus pneumonia. Therefore, the application of glucocorticoids may inhibit the inflammatory response and reduce organ damage. Academician Nanshan Zhong's team retrospectively analyzed the data of 1,099 patients with new coronavirus pneumonia and suggested that 5% of the severe patients were admitted to the ICU, and the overall mortality was 1.4%. However, the hospitalized mortality of severe patients was as high as 8.1%, and the proportion of severe patients using hormones was significantly higher than that of non-severe patients (44.5 vs. 13.7%) (11). Another observational study of patients with severe new coronavirus pneumonia showed that the 28-day mortality was as high as 61.5%, and patients who died were more likely to have ARDS than surviving patients (81 vs. 45%). Fifty-eight percent of patients were treated with combined hormone therapy and the survivors used hormones more often than the patients who died (70 vs. 50%) (12). In a retrospective analysis of 138 patients with new coronavirus pneumonia, 36 (26.1%) severe patients had a mortality rate of 16.6%, and the proportion of severe patients treated with glucocorticoids was significantly higher than that of non-severe patients (72.2 vs. 35.3%) (13). Clinicians are more inclined to use glucocorticoids for patients with severe new coronavirus pneumonia. The eighth editions of the "New Coronavirus Diagnosis and Treatment Program" (14) and "Shanghai Expert Consensus on Comprehensive Treatment of Coronavirus Diseases in 2019" (15) both recommend cautious limited use of glucocorticoids; they do not recommend routine use. For patients with acute exacerbation of dyspnoea, progressive deterioration of the oxygenation index and rapid progression on chest imaging, glucocorticoids (equivalent to methylprednisolone 1–2 mg/kg body weight/day, or 40–80 mg/day) can be used for a short period (3–5 days) as appropriate, and it should be noted that large doses of glucocorticoids will delay virus clearance due to immunosuppression.

EXPERIENCE IN THE APPLICATION OF GLUCOCORTICOIDS IN THE TREATMENT OF SEVERE NEW CORONAVIRUS PNEUMONIA

Our critical care team is involved in treating patients with severe new coronavirus pneumonia in the isolated ICU of the Shanghai public health clinical center, where critically ill patients require mechanical ventilation support, continuous blood purification, and even extracorporeal membrane oxygenation support. In the process of treating patients, we also face the following: (1) whether to use glucocorticoids in combination; (2) how much glucocorticoid should be used and for how long. In the following, we will provide a preliminary summary of the application of glucocorticoids in severe new coronavirus pneumonia based on the actual clinical diagnosis and treatment, previous ARDS drug treatment program, and literature evidence. Written informed consent was obtained from the [individual(s) AND/OR minor(s)' legal guardian/next of kin] for the publication of any potentially identifiable images or data included in this article. In addition, our retrospective observational case report was approved by the ethics committee of the relevant institution.

Patients with severe new coronavirus pneumonia often experience sudden exacerbation and a rapid progression of hypoxemia. Even if the patient is treated with non-invasive or invasive respiratory support in time, it is difficult for them to quickly improve their respiratory distress and hypoxia. At this time, the application of drugs must be considered for a comprehensive treatment. In addition to applying appropriate sedative and analgesic drugs to reduce oxygen consumption to adapt to the state of insufficient oxygen supply, it is also necessary to decide whether to use glucocorticoids and, if so, the dosage to use.

A 62-year-old female patient with a history of hypertension had been taking oral nifedipine tablets daily for a long time to control her blood pressure. She had no history of respiratory or immune system diseases. She was admitted to the hospital because of a "3-day fever." She returned to Shanghai from Wuhan 16 days before admission. Her fever started 3 days before admission, and her condition deteriorated sharply. On admission, chest CT showed multiple patches of increased density in the right lung, and the new coronavirus nucleic acid sample was positive. The patient was given high-flow oxygen therapy to improve oxygenation, but her hypoxemia rapidly deteriorated within 10 h. The oxygenation index continued to decrease from ∼200 to 60 mmHg. Under the condition of 60 L of oxygen flow and $FiO_2 = 0.9$, her SpO_2 was barely maintained at ∼90%. The patient's heart rate and blood pressure increased, and oxygen consumption also increased significantly. In this case, in addition to non-invasive face-mask mechanical ventilation support and appropriate analgesia and sedation, methylprednisolone was given intravenously 40 mg every 12 h, while antibiotics were used to cover possible pathogenic bacteria, especially fungi. The patient's symptoms were notably relieved after 24–48 h, and the oxygenation index also increased to 150–180 mmHg. Meanwhile, the lymphocyte counts, which had been reduced to $\sim 0.35 \times 10^9$/L, and CD4+ cell counts, which had been reduced to ∼100 cells/μL, were only slightly decreased. The methylprednisolone dose of 80 mg/day was changed to 40 mg/day after 5 days and then discontinued after 3 days. The patient was transferred out of the ICU 12 days after being admitted and is currently discharged. The lung CT in **Figure 1** shows that the lung inflammation in this patient was significantly reduced after glucocorticoid treatment.

Another patient was a 75-year-old male. He had a history of premature heart beats, no history of hypertension, and no history of respiratory or immune system diseases. There was also no clear history of travel to the epidemic area or exposure to the new coronavirus. Fever with shortness of breath and chest tightness appeared 10 days prior to admission. On admission, a CT scan of the chest showed extensive inflammation of both lungs, and SARS-CoV-2 infection was confirmed by a coronavirus nucleic acid test. Endotracheal intubation was given on the day of admission. The patients were given methylprednisolone at 40 mg every 12 h from admission. The dosage was reduced to 40 mg QD after 5 days and then stopped after 3 days. Tracheotomy was performed seven days after intubation. The patient's condition improved briefly after the first glucocorticoid treatment, but haemodynamic instability occurred suddenly, and lung compliance further decreased. The patient received ECMO support 7 days after tracheostomy ventilator support. At this point, the chest radiograph showed increased exudation of both lungs, and SpO_2 could only be maintained at 85–88% under ECMO with a 4.5 L flow rate. Due to the patient's persistent candidiasis and poor control with amphotericin B, it was necessary to consider whether the rapid deterioration of the disease was caused by the exacerbation of infection (including fungus, G-bacilli and G+ cocci mixed infection) leading to septic shock or aggravation of coronavirus pneumonia. We adjusted the analgesic and sedative drugs and added muscle relaxants to reduce oxygen consumption while giving enhanced anti-infective treatment (posaconazole and meropenem). In addition, methylprednisolone was still administered intravenously at 40 mg every 12 h for 3 days after ECMO support; the dosage was changed to 40 mg QD after 3 days and then stopped 2 days later. On the day of deterioration, the follow-up examination showed that IL-6 increased from 735 to 4,212 pg/ml, and the lymphocyte count decreased from 2.83 × 109/L to 0.94 × 109/L. After 24–48 h of treatment, the vital signs of the patient stabilized, and SpO_2 was maintained at ∼95%. Additionally, IL-6 decreased to 289 pg/ml, the lymphocyte count decreased to 0.45×10^9/L, and the CD4+ cell count decreased from 429 to 227 cells/μl. The above examination indicators showed a downward trend. However, at the same time, the blood culture continued to be positive for Candida, and retest with the fecal new coronavirus nucleic acid test was positive and continued to be strongly positive over the next few days. The chest radiograph of the patient showed that pulmonary inflammation did not improve significantly after glucocorticoid therapy (**Figure 2**). This patient died 5 weeks after ECMO support.

In the first case, we found that early use of small doses of glucocorticoid was helpful for the improvement of the disease. In the second case, the cause of death may be that the prolonged use of glucocorticoids resulted in immunosuppression and serious fungal infections. In our experience, there were also a few patients whose condition had deteriorated sharply, with severe pulmonary exudation and marked systemic oedema accompanied by increased abdominal pressure. On the 1st day of deterioration, a large dose of 0.5 g of methylprednisolone was used, followed by 240 mg on the 2nd day. The patients' critical condition was significantly relieved after 48 h, but severe lymphocyte reduction and secondary fungemia appeared, which made subsequent treatment difficult. A recent study (16) found that in hospitalized patients with SARS-CoV-2, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but did not result in lower 28-day mortality among those receiving no respiratory support. We believe that glucocorticosteroids can be used for the treatment of patients with SARS-CoV-2, but different therapeutic outcomes occur depending on the patient's underlying disease; comorbidities; severity of corona virus pneumonia; and type, timing, and dose of hormones used. Therefore, we are cautious about the use of glucocorticosteroids in the treatment of patients with SARS-CoV-2.

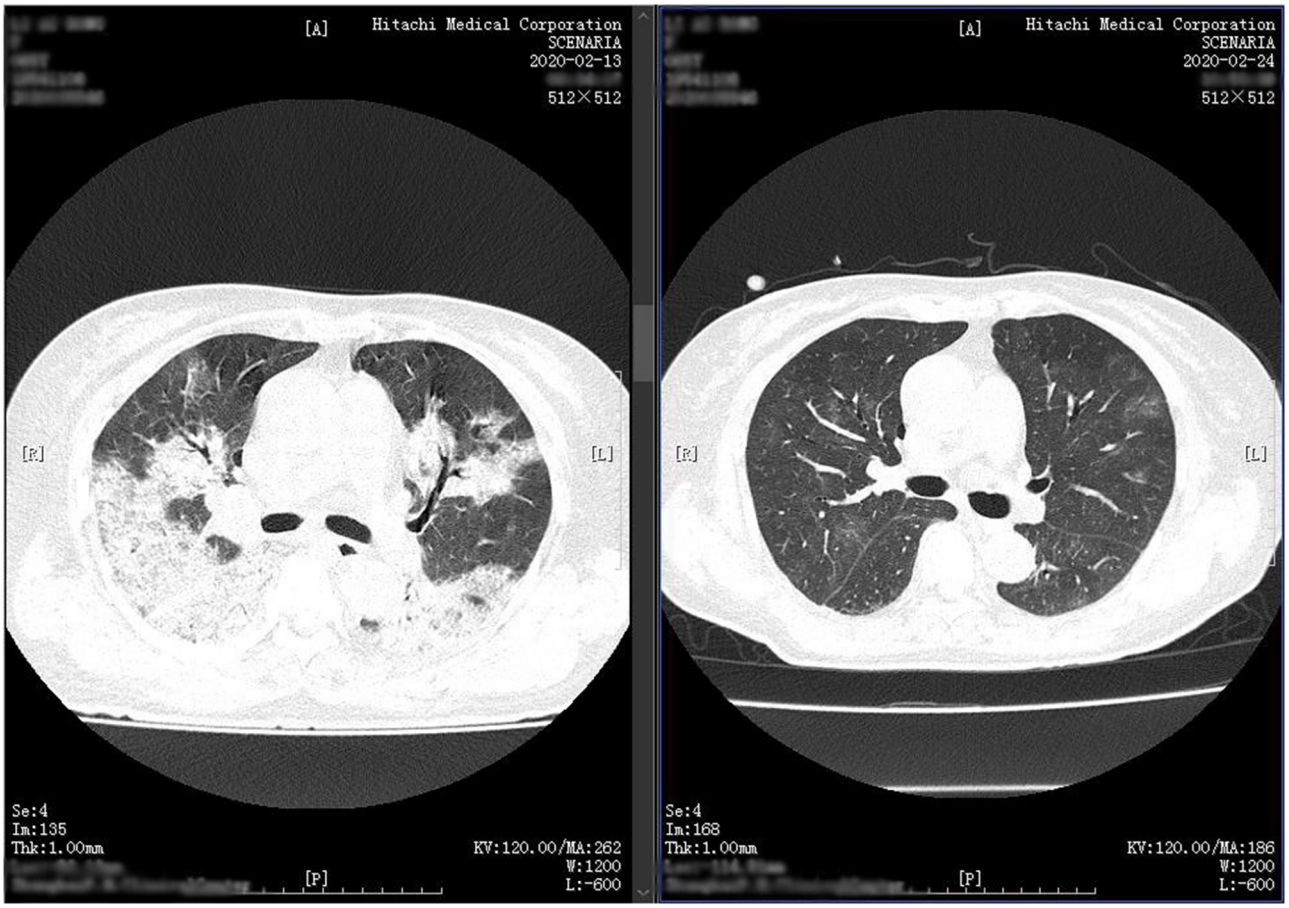

FIGURE 1 | After glucocorticoid therapy, chest CT showed a significant decrease in the exudation of both lungs, suggesting decreased pulmonary inflammation.

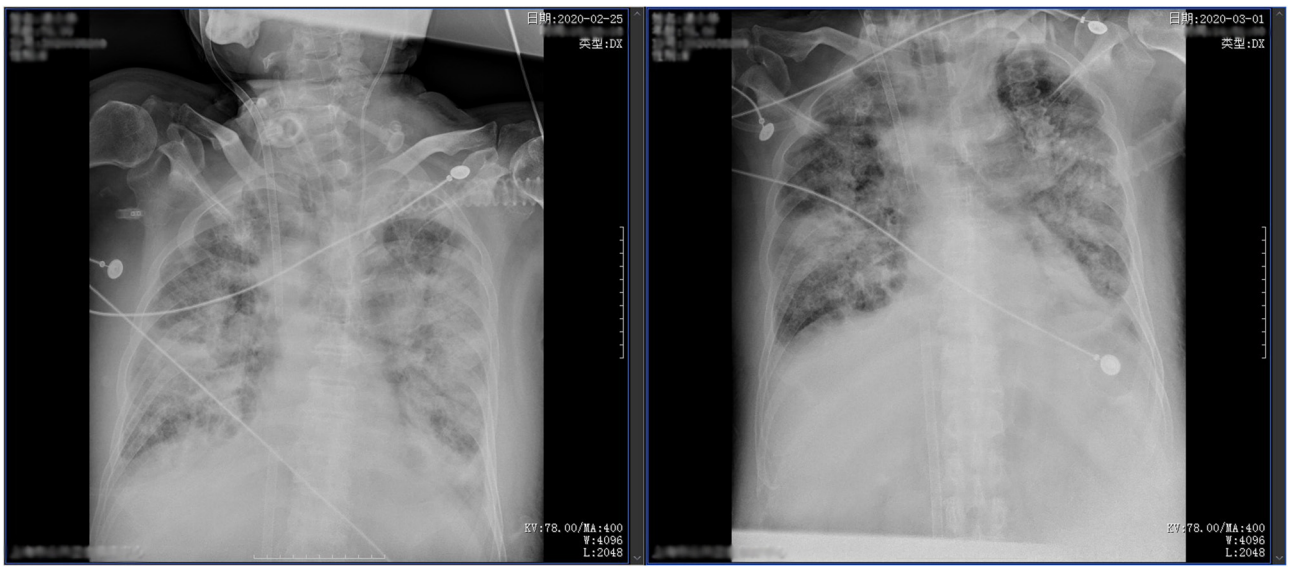

FIGURE 2 | After glucocorticoid therapy, chest radiographs showed no significant reduction in pulmonary exudation, suggesting no improvement in lung inflammation.

DISCUSSION

Our perspectives about glucocorticoid treatment is just based on the pharmacological characteristics of glucocorticoids and a small number of clinical cases, which is premature and need to be validated. Nevertheless, we are currently following the opinions, doses and timing of glucocorticoid application suggested in the Chinese Health Commission's recommendations (14, 15) during the process of diagnosis and treatment of severe new coronavirus pneumonia, and we have also observed some short-term effects in clinical practice. However, whether the long-term prognosis is improved requires further observation and research. The timing, dose, and type of glucocorticoid use, and even the patient's underlying conditions and comorbidities, also require stratified studies in multiple research centers with large sample sizes. In addition, it is noteworthy that although severe SARS-CoV-2 patients may experience excessive inflammation, they often suffer from severe cellular immune impairment (lymphocyte and CD4+ cell counts are significantly reduced). The application of glucocorticoids may further inhibit cellular immunity and delay virus clearance. Therefore, it is necessary to pay close attention to the possibility of fungal infections and perform a relevant culture. Prophylactic antifungal agents may be considered in critically ill patients to prevent the development of severe invasive fungal infections. Moreover, it is also well-known that the use of corticosteroids may also activate a previous underlying infection, such as hepatitis B virus or tuberculosis.

Glucocorticoids work by suppressing the abnormal immune response that destroys the body's organs rather than attacking the virus. In the case of new coronavirus pneumonia, the abnormal immune response seems to be more damaging than the replication of the virus in the body. The patient's age, underlying disease, comorbidities, severity of new coronavirus pneumonia, and timing and dosage of glucocorticoids used can all influence the effectiveness of treatment. Whether patients benefit from glucocorticoid therapy "depends on choosing the right dose at the right time, in the right patient."

DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Shanghai sixth people's hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Optimizing Management to Reduce the Mortality of COVID-19: Experience From a Designated Hospital for Severely and Critically Ill Patients in China

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Background: The coronavirus disease 2019 (COVID-19) has swept through the world at a tremendous speed, and there is still limited data available on the treatment for COVID-19. The mortality of severely and critically ill COVID-19 patients in the Optical Valley Branch of Tongji Hospital was low. We aimed to analyze the available treatment strategies to reduce mortality.

Methods: In this retrospective, single-center study, we included 1,106 COVID-19 patients admitted to the Optical Valley Branch of Tongji Hospital from February 9 to March 9, 2020. Cases were analyzed for demographic and clinical features, laboratory data, and treatment methods. Outcomes were followed up until March 29, 2020.

Results: Inflammation-related indices (hs-CRP, ESR, serum ferritin, and procalcitonin) were significantly higher in severe and critically ill patients than those in moderate patients. The levels of cytokines, including IL-6, IL2R, IL-8, and TNF-α, were also higher in the critical patients. Incidence of acute respiratory distress syndrome (ARDS) in the severely and critically ill group was 23.0% (99/431). Sixty-one patients underwent invasive mechanical ventilation. The correlation between SpO_2/FiO_2 and PaO_2/FiO_2 was confirmed, and the cut-off value of SpO_2/FiO_2 related to survival was 134.43. The mortality of patients with low SpO_2/FiO_2 (<134.43) at intubation was higher than that

of patients with high SpO_2/FiO_2 (>134.43) (72.7 vs. 33.3%). Among critical patients, the application rates of glucocorticoid therapy, continuous renal replacement therapy (CRRT), and anticoagulation treatment reached 55.2% (238/431), 7.2% (31/431), and 37.1% (160/431), respectively. Among the intubated patients, the application rates of glucocorticoid therapy, CRRT, and anticoagulation treatment were respectively 77.0% (47/61), 54.1% (33/61), and 98.4% (60/61).

Conclusion: No vaccines or specific antiviral drugs for COVID-19 have been shown to be sufficiently safe and effective to date. Comprehensive treatment including ventilatory support, multiple organ function preservation, glucocorticoid use, renal replacement therapy, anticoagulation, and restrictive fluid management was the main treatment strategy. Early recognition and intervention, multidisciplinary collaboration, multi-organ function support, and personalized treatment might be the key for reducing mortality.

Keywords: COVID-19, management, experience, mortality, severely and critically ill

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, has spread at a tremendous rate around the world (1). The World Health Organization (WHO) has declared it a public health emergency of international concern. As of September 16, 2020, the number of patients infected with SARS-CoV-2 has exceeded 7,266,074 globally, and more than 935 792 have died, with case fatality rates reaching more than 10% in some countries (2–9). This rapidly spreading pandemic has become a serious threat to worldwide health.

Relatively few studies have described the clinical characteristics of COVID-19 patients in countries such as United States and Italy (7–9). Although most COVID-19 patients have asymptomatic or mild disease with a good prognosis, a few cases may rapidly develop severe disease with high risk of mortality, and have to receive treatment in intensive care units (ICU) (5, 7). According to a report on 44 672 cases from the Chinese Center for Disease Control and Prevention (CDC), the mortality of the critical cases was 49.0% (6). Especially in those who developed acute respiratory distress syndrome (ARDS), the mortality can reach as high as 52.4∼64.7% (4–7). Therefore, reducing the mortality of severe COVID-19 patients is urgent and can save many lives.

During the outbreak of COVID-19 in China, the mild and moderate COVID-19 cases were transported and treated in Fangcang shelter hospitals, while the severe cases and critically ill patients were transferred to designated hospitals (10). Although the Optical Valley Branch of Tongji Hospital (Wuhan, China) was a designated hospital for severely and critically ill COVID-19 patient, the mortality of the severely and critically ill patients was 10.4%, and that of critically ill patients was 39.6%, which was lower than published data (4, 6, 11). To explore possible measures to reduce the mortality of severely and critically ill COVID-19 patients, in this study we retrospectively analyzed our therapeutic process, hoping to provide more evidence for better COVID-19 treatment.

METHODS

Study Design and Participants

This single-center, retrospective, observational study was conducted at the Optical Valley Branch of Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology. During the outbreak of COVID-19, the Optical Valley Branch of Tongji Hospital was reconstructed and designated as a hospital for treatment of severely and critically ill COVID-19 patients by the Chinese government from February 9, 2020 to March 30, 2020. The diagnosis and classification of the severity of COVID-19 was conducted according to the guidance for COVID-19 (the 7th version) established by the National Health Commission of China (12). Laboratory-confirmed cases with admission dates from February 9, 2020 to March 9, 2020 were included in our study. Patients younger than 18 years old, or lacking core sets of medical data like blood tests, or for whom the entire hospital stay lasted for <12 h were excluded from further analysis. This study was carried out under the authorization of the National Health Commission of China, and it was approved by the Ethics Commission of Tongji hospital (Approval No.: TJ-IRB20200334), and the written informed consent requirement was waived for anonymized data in view of the rapidly emerging infectious disease.

Data Collection and Definitions

We obtained epidemiological, demographic, clinical, laboratory, management, and outcome data from patients' medical records in the Tongji Cloud Hospital Information System (HIS) using standardized data collection forms. Clinical outcomes were followed up until March 29, 2020. The most intense level of oxygen support during hospitalization [nasal cannula, non-invasive mechanical ventilation (NMV), invasive mechanical ventilation (IMV), or IMV with extracorporeal membrane oxygenation (ECMO) were recorded]. Records of anticoagulant therapy, systemic glucocorticoid therapy, and continuous renal replacement therapy were also collected. All data were checked

by two clinicians (ZD and HF). If there was any difference in recording and interpreting the data by the two primary reviewers, the third researcher (GL) checked and adjudicated the difference.

ARDS and sepsis were defined according to the interim guidance of the WHO (13), while acute kidney injury (AKI), cardiac injury, acute heart failure, and acute liver injury were defined as described previously (14).

Laboratory and Radiological Measurements

The majority of the baseline clinical data was collected from the first day of admission. To diagnose COVID-19, respiratory specimens including pharyngeal swabs or sputum samples of patients were collected, and tested by real-time RT-PCR for SARS-CoV-2 as described previously, and/or blood tests for SARS-CoV-2-specific IgM and IgG antibodies. In addition, respiratory specimens were also tested to exclude the presence of other respiratory virus infections, including influenza virus A and B, respiratory syncytial virus, parainfluenza virus, and adenovirus. Initial laboratory tests included a complete blood count, coagulation profile, and serum biochemical tests [including liver and renal function, electrolytes, creatinine kinase, lactate dehydrogenase (LDH), and cytokines]. All patients had at least a chest X-ray or computed tomography (CT) scan on admission and/or during their hospital stay. The association of SpO_2/FiO_2 with mortality of intubated patients was analyzed, and in these patients, values of SpO_2/FiO_2 were measured 0.5h before intubation. PaO_2/FiO_2 were measured within 1 h before intubation. If repeated measurements of SpO_2/FiO_2 values were performed in this time period, mean levels were calculated and used for further analysis. Frequency of examinations was determined by clinicians treating COVID-19 patients.

Statistical Analysis

All statistical analyses were performed using R software, version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria), or SPSS 21.0 (IBM Corp, Armonk, NY, USA). Categorical variables were expressed using frequencies and percentages. Continuous variables were shown using the median (IQR) or mean (SD) values. Means for continuous variables were compared using the independent-samples *t*-test when the data were normally distributed; if not, the Mann–Whitney test was used. Proportions for categorical variables were compared using chi-squared and Fisher's exact tests. Descriptive analyses was performed for demographic, clinical, and laboratory data. Cumulative rates of in-hospital mortality were determined using the Kaplan–Meier method. The cut-off value of SpO_2/FiO_2 was confirmed using a maximally selected log-rank statistic. The ability of SpO_2/FiO_2 to distinguish non-survivors from survivors was also assessed by estimating the area under the ROC curve (AUC) using the method developed by DeLong et al. (15). Based on the oxygen dissociation curve, a linear fitting model was constructed to evaluate the relationship between SpO_2/FiO_2 and the oxygenation index of patients. Differences with $P < 0.05$ were considered statistically significant.

Role of the Funding Source

The corresponding authors had full access to all the data of the study and had final responsibility for the decision to submit for publication.

RESULTS

From February 9 to March 9, 2020, a total of 675 patients with moderate disease and 431 severely or critically ill COVID-19 patients were admitted to the Optical Valley Branch of Tongji Hospital (designated hospital for severely and critically ill COVID-19 patients). The overall mortality was 5.2% (58/1106), the mortality of severe and critically ill patients was 10.4% (45/431), and the mortality for critically ill patients was 39.6% (42/106) (**Supplementary Table 6**).

Demographics and Baseline Characteristics of COVID-19 Patients

As shown in **Table 1**, the severely ill patients (median age 65 years, range 23–92) were older than the patients with moderate disease (61 years, range 18–95). Of the 675 patients with moderate disease, 304 were male (45.0%), and 371 were female (55.0%). Of the 431 severely and critically ill patients, 220 were male (51.0%) and 211 were female (49.0%). The percentage of patients with preexisting conditions, including hypertension, diabetes, and chronic pulmonary disease among the severely and critically ill patients was higher than in patients with moderate disease [145 (33.6%) vs. 191 (28.3%), 80 (18.6%) vs. 90 (13.3%), 39 (9.0%) vs. 40 (5.9%)].

Compared to the patients with moderate disease, the severely and critically ill patients were more likely to have fever. Symptoms including shortness of breath, myalgia, rhinorrhea, anorexia, nausea or vomiting, headache and dizziness were more common in severely and critically ill patients. Vital signs including respiratory rate and pulse were higher in severely and critically ill patients than in those with moderate disease [22 (IQR20.0-30.0) vs. 20 (IQR18.0-20.0), 84 (IQR77.0-95.0) vs. 82 (IQR76.0-92.0)], and percutaneous oxygen saturation (SpO_2) in severely and critically ill patients was lower than in patients with moderate disease [96% (92.0–98.0) vs. 98% (96.0–99.0)]. The severely and critically ill patients were more likely to have comorbidities such as ARDS (23.0 vs. 3.4%), sepsis (17.6 vs. 4.3%), acute heart failure (21.9 vs. 7.2%), AKI (7.7 vs. 3.4%), acute liver injury (1.2 vs. 0.0%), and secondary bacterial infections (3.7 vs. 1.0%). The proportion of severely and critically ill patients requiring a high-flow nasal cannula (HFNC), NMV, IMV, CRRT, antibacterial agents, glucocorticoids, or immunoglobulins was higher than that of patients with moderate disease (**Table 1**).

Leukocyte and neutrophil counts in severely and critically ill patients were higher than in patients with moderate disease [6.05×10^9/L (IQR4.79–8.14) vs. 5.66×10^9/L (IQR4.62–7.00), 4.20×10^9/L (IQR2.83–6.15) vs. 3.46×10^9/L (IQR2.62–4.62)], while the lymphocyte count was lower in severely and critically ill patients than in those with moderate disease [1.07×10^9/L (IQR 0.71–1.47) vs. 1.41×10^9 (IQR1.04–1.83)]. D-dimer and fibrinogen levels were higher in severely

TABLE 1 | Baseline characteristics of COVID-2019 patients enrolled in this study.

	All (*N* = 1,106)	Moderate (*n* = 675)	Severe + Critically ill (*n* = 431)	*P* value
Demographic characteristics				
Age- yr	63 [18–95]	61 [18–95]	65 [23–92]	<0.001
Age≥ 65	482 (43.6)	264 (39.1)	218 (50.6)	<0.001
Gender-Female	582 (52.6)	371 (55.0)	211 (49.0)	0.056
Duration from illness onset to admission	15 [10, 22]	16 [10, 23]	15 [10, 21]	0.114
Personal history				
Smoking history	15 (1.4)	8 (1.2)	7 (1.6)	0.598
Current smoker	9 (0.8)	6 (0.9)	3 (0.7)	1
Former smoker	6 (0.5)	2 (0.3)	4 (0.9)	0.216
Coexisting disorder				
Cardiovascular disease	87 (7.9)	48 (7.1)	39 (9.0)	0.253
Hypertension	336 (30.4)	191 (28.3)	145 (33.6)	0.061
Diabetes	170 (15.4)	90 (13.3)	80 (18.6)	0.021
Cerebrovascular disease	34 (3.1)	17 (2.5)	17 (3.9)	0.212
Chronic pulmonary disease	79 (7.1)	40 (5.9)	39 (9.0)	0.055
Chronic kidney disease	40 (3.6)	27 (4.0)	13 (3.0)	0.415
Chronic liver disease	95 (8.6)	59 (8.7)	36 (8.4)	0.912
Malignancy	46 (4.2)	28 (4.1)	18 (4.2)	1
Other respiratory pathogen infection- no. /total no. (%)				
Other viruses	104 (9.4)	56 (8.3)	48 (11.1)	0.139
Symptoms				
Fever	784 (70.9)	460 (68.1)	324 (75.2)	0.012
Cough	862 (77.9)	516 (76.4)	346 (80.3)	0.138
Expectoration	641 (58.0)	380 (56.3)	261 (60.6)	0.17
Shortness of breath	472 (42.7)	266 (39.4)	206 (47.8)	0.006
Pharyngalgia	90 (8.1)	46 (6.8)	44 (10.2)	0.055
Rhinorrhoea	42 (3.8)	15 (2.2)	27 (6.3)	0.001
Fatigue	244 (22.1)	138 (20.4)	106 (24.6)	0.118
Chest pain	79 (7.1)	43 (6.4)	36 (8.4)	0.232
Diarrhea	227 (20.5)	133 (19.7)	94 (21.8)	0.402
Abdominal pain	28 (2.5)	14 (2.1)	14 (3.2)	0.243
Anorexia	198 (17.9)	105 (15.6)	93 (21.6)	0.013
Nausea or Vomiting	95 (8.6)	47 (7.0)	48 (11.1)	0.02
Myalgia	120 (10.8)	63 (9.3)	57 (13.2)	0.047
Headache	84 (7.6)	39 (5.8)	45 (10.4)	0.005
Dizziness	27 (2.4)	11 (1.6)	16 (3.7)	0.044
Vital signs				
Respiratory rate, breaths per minute	20.00 [19.00, 22.00]	20.00 [18.00, 20.00]	22.00 [20.00, 30.00]	<0.001
Pulse, beat per minute	82.00 [76.00, 94.00]	82.00 [76.00, 92.00]	84.00 [77.00, 95.00]	0.025
Median arterial pressure, mmHg	96.67 [88.67, 105.67]	96.67 [88.67, 105.67]	97.00 [89.33, 105.67]	0.679
percutaneous oxygen saturation, %	97.00 [95.00, 98.00]	98.00 [96.00, 99.00]	96.00 [92.00, 98.00]	<0.001
Comorbidities				
In-hospital death, %	58 (5.2)	13 (1.9)	45 (10.4)	<0.001
Acute respiratory distress syndrome	122 (11.0)	23 (3.4)	99 (23.0)	<0.001
Acute kidney injury	56 (5.1)	23 (3.4)	33 (7.7)	0.003

(Continued)

TABLE 1 | Continued

	All ($N = 1,106$)	Moderate ($n = 675$)	Severe + Critically ill ($n = 431$)	*P* value
Acute heart failure	131 (13.1)	43 (7.2)	88 (21.9)	<0.001
Sepsis	105 (9.5)	29 (4.3)	76 (17.6)	<0.001
Acute liver injury, %	5 (0.5)	0 (0.0)	5 (1.2)	0.009
Hyper-glycaemia, %	665 (60.7)	446 (66.9)	219 (51.0)	<0.001
Secondary bacteria infection	23 (2.1)	7 (1.0)	16 (3.7)	0.004
Treatment				
Nasal cannula	1002 (90.8)	675 (100)	427 (99.1)	0.023
High flow	399 (36.1)	163 (24.1)	236 (54.8)	<0.001
Non-invasive	46 (4.2)	10 (1.5)	36 (8.4)	<0.001
Invasive	61 (5.5)	13 (1.9)	48 (11.1)	<0.001
Extracorporeal membrane oxygenation	6 (0.5)	2 (0.3)	4 (0.9)	0.216
Renal replacement therapy	40 (3.6)	9 (1.3)	31 (7.2)	<0.001
Antiviral agents	1017 (92.0)	620 (91.9)	397 (92.1)	0.91
Antibacterial agents	759 (68.6)	424 (62.8)	335 (77.7)	<0.001
Glucocorticoids	533 (48.2)	295 (43.7)	238 (55.2)	<0.001
Immunoglobulin	220 (19.9)	97 (14.4)	123 (28.5)	<0.001

Data are median (IQR), numbers (percentages) of patients. p-values comparing Moderate and Severe+Critically ill are from χ^2-test, Fisher's exact test, or Mann–Whitney U-test. COVID-2019, coronavirus disease 2019; The severity was staged based on the guidelines for diagnosis and treatment of COVID-19 (trial seventh edition) published by Chinese National Health Commission in February 4, 2020.

and critically ill patients than in those with moderate disease [0.97 μg/ml FEU (IQR0.41–2.62) vs. 0.44 μg/ml FEU (IQR0.22–0.95), 4.71 g/L (IQR3.66–5.96) vs. 3.97 g/L (IQR3.22–5.25)]. Higher levels of serum aspartate aminotransferase, total bilirubin, direct bilirubin, albumin, alkaline phosphatase, γ-glutamyl transpeptidase, total cholesterol, and lactose dehydrogenase were more common in the severely and critically ill groups. The serum levels of creatinine kinase, high-sensitivity cardiac troponin-I (c-TnI), N-terminal pro-brain natriuretic peptide (NT-proBNP) and myoglobin were higher in severely and critically ill patients than in those with moderate disease [57.00 U/L (IQR36.00–94.50) vs. 55.00 U/L (IQR40.00–79.00), 5.70 pg/ml (IQR2.60–14.10) vs. 2.70 pg/ml (IQR1.00–6.38), 145.00 pg/ml (IQR59.00–451.00) vs. 72.00 pg/ml (IQR30.00–205.00), 46.50 ng/ml (IQR29.92–93.68) vs. 33.6 5ng/ml (IQR25.02–50.05)] (**Table 2**).

Inflammation-related indices [high-sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), serum ferritin, and procalcitonin] were significantly higher in the severely and critically ill group than in the moderate group [21.15 mg/L (IQR2.92–71.57) vs. 3.65 mg/L (IQR1.00–22.08), 28.00 mm/h (IQR13.00–47.75) vs. 14.00 mm/h (IQR6.50–38.50), 638.20 μg/L(IQR326.60–1047.20) vs. 399.00 μg/L (IQR187.62–704.17), 0.08 ng/ml (IQR0.06–0.17) vs. 0.06 ng/ml(IQR0.05–0.08)]. A comparison of cytokines levels, including IL-6, IL2R, IL-8, and TNF-α, between the two groups also showed similar trends [5.79 pg/ml (IQR2.43–20.10) vs. 3.15 pg/ml (IQR1.70–7.78), 589.00 U/ml (IQR397.00–917.00) vs. 448.50 U/ml (IQR306.00–679.75), 12.60 pg/ml (IQR7.50–22.50) vs. 8.80 pg/ml (IQR5.90–15.22), 8.80 pg/ml (IQR6.30–11.50) vs. 8.00 pg/ml (IQR6.10-9.93)] (**Table 3**).

Demographics and Baseline Characteristics of Severely and Critically Ill COVID-19 Patients With or Without Intubation

As shown in **Table 4**, 431 severely and critically ill patients were grouped according to the need for intubation. The intubated group (median age 69 years, range 44–87) was older than the group that did not require intubation (64 years, range 23–92). Fever and chronic pulmonary disease were more common in intubated patients [42 (87.5%) vs. 282 (73.6%), 9 (18.8%) vs. 30 (7.8%)]. The incidence of comorbidities including acute heart failure, sepsis, AKI, and secondary infection was higher in the intubated group than in patients that did not require intubation [41 (85.4%) vs. 47 (13.3%), 43 (89.6%) vs. 33 (8.6%), 23 (47.9%) vs. 10 (2.6%), 13 (27.1%) vs. 28 (0.8%)]. There were significant differences at baseline between the intubated patients and those not requiring intubation in terms of routine blood parameters, coagulation, liver and kidney function, myocardial enzyme spectrum, NT-proBNP, infection related indices and cytokines. The application frequency of ECMO, CRRT, antibacterial agents, glucocorticoids and immunoglobulins as significantly higher in the intubated group than that in the group that did not require intubation [4 (8.3%) vs. 0 (0.0%), 26 (54.2%) vs. 5 (1.3%), 47 (97.9%) vs. 288 (75.2), 39 (81.2%) vs. 199 (52.0%), 39 (81.2%) vs. 84 (21.9%)]. The mortality of intubated patients was significantly higher than of patients that did not require intubation (64.6 vs. 3.7%).

TABLE 2 | Laboratory findings on admission in COVID-19 patients enrolled in this study.

	Normal range	All patients	Grade		*P* value
			Moderate	Severe+ Critically ill	
Hematologic					
Leukocyte count, $\times 10^9$/L	3.5–9.5	5.81 [4.68, 7.39]	5.66 [4.62, 7.00]	6.05 [4.79, 8.14]	<0.001
Neutrophil count, $\times 10^9$/L	1.8–6.3	3.68 [2.70, 5.18]	3.46 [2.62, 4.62]	4.20 [2.83, 6.15]	<0.001
Lymphocyte count, $\times 10^9$/L	1.1–3.2	1.30 [0.89, 1.70]	1.41 [1.04, 1.83]	1.07 [0.71, 1.47]	<0.001
Platelet count, $\times 10^9$/L	125–350	234.00 [180.00, 304.00]	235.50 [187.00, 308.75]	230.00 [170.50, 301.00]	0.027
Hemoglobin, g/L	115–150	126.00 [116.00, 137.00]	127.00 [117.00, 137.75]	126.00 [115.00, 137.00]	0.163
Coagulation function					
Prothrombin time, s	11.5–14.5	13.60 [13.00, 14.10]	13.40 [12.90, 14.00]	13.80 [13.20, 14.50]	<0.001
Activated partial thromboplastin time, s	29–42	38.10 [35.50, 41.10]	37.90 [35.50, 41.00]	38.15 [35.50, 41.27]	0.734
D-dimer, ug/ml FEU	<0.5	0.59 [0.26, 1.45]	0.44 [0.22, 0.95]	0.97 [0.41, 2.62]	<0.001
Fibrinogen, g/L	2.00–4.00	4.27 [3.36, 5.58]	3.97 [3.22, 5.25]	4.71 [3.66, 5.96]	<0.001
Prothrombin activity, %	75.0–125.0	93.00 [86.00, 100.00]	94.00 [87.00, 102.00]	90.00 [81.00, 98.00]	<0.001
International standardized ratio	0.80–1.20	1.05 [0.99, 1.10]	1.03 [0.98, 1.09]	1.06 [1.01, 1.14]	<0.001
Biochemical liver function					
Alanine aminotransferase, U/L	≤41	22.00 [14.00, 37.00]	21.00 [14.00, 37.00]	23.00 [14.50, 38.00]	0.133
Aspartate aminotransferase, U/L	≤40	23.00 [17.00, 34.00]	22.00 [17.00, 31.00]	26.00 [19.00, 39.00]	<0.001
Total bilirubin, umol/L	≤21.1	8.20 [6.20, 11.88]	7.90 [5.80, 11.15]	8.70 [6.55, 12.95]	<0.001
Direct bilirubin, umol/L	≤8.0	3.50 [2.70, 4.97]	3.40 [2.55, 4.60]	3.90 [2.80, 5.60]	<0.001
Alkaline phosphatase, U/L	35–105	36.75 [32.60, 41.10]	38.30 [34.10, 42.05]	34.30 [30.75, 38.60]	<0.001
γ-glutamyl transpeptidase, U/L	6–42	26.50 [18.00, 47.00]	25.00 [17.00, 43.00]	29.00 [19.00, 55.50]	0.002
Albumin, g/L	35.0–52.0	230.00 [164.25, 273.75]	240.50 [193.50, 279.00]	198.00 [123.25, 258.25]	<0.001
Pre-albumin, mg/L	200–400	3.81 [3.24, 4.47]	3.86 [3.33, 4.50]	3.73 [3.12, 4.41]	0.003
Total cholesterol, mmol/L	<5.18	237.50 [188.00, 311.50]	219.00 [180.00, 282.00]	279.00 [211.00, 384.00]	<0.001
lactose dehydrogenase, U/L	135–214	7041.00 [5580.00, 8452.00]	7474.00 [6083.00, 8713.00]	6416.00 [4656.25, 7722.25]	<0.001
Cholinesterase, U/L	5320–12920	5.67 [5.05, 7.06]	5.45 [4.97, 6.59]	6.06 [5.23, 7.76]	<0.001
Glucose, mM		22.00 [14.00, 37.00]	21.00 [14.00, 37.00]	23.00 [14.50, 38.00]	0.133
Biochemical renal function					
Creatinine, umol/L	45–84	67.00 [56.00, 82.00]	67.00 [56.00, 80.00]	69.00 [56.00, 84.00]	0.125
Blood urea nitrogen, mmol/L	1.7–8.3	4.40 [3.50, 5.70]	4.30 [3.50, 5.35]	4.60 [3.50, 6.35]	0.001
Uric acid, umol/L	142.8–339.2	265.10 [203.07, 331.00]	269.00 [212.60, 335.20]	257.00 [188.80, 324.20]	0.008
eGFR, ml/min/1.73m^2	>90	92.25 [79.10, 101.97]	93.50 [80.25, 103.70]	90.40 [75.55, 99.30]	<0.001
Sodium, mmol/L	136–145	139.70 [137.40, 141.40]	139.90 [138.00, 141.40]	139.30 [136.20, 141.40]	0.001
Potassium, mmol/L	3.50–5.10	4.13 [3.75, 4.44]	4.17 [3.81, 4.44]	4.07 [3.69, 4.42]	0.023
Calcium, mmol/L	2.20–2.55	2.13 [2.05, 2.20]	2.15 [2.08, 2.22]	2.09 [2.01, 2.18]	<0.001

(Continued)

TABLE 2 | Continued

	Normal range	All patients	Grade		*P* value
			Moderate	Severe+ Critically ill	
Biochemical cardiac function					
Creatinine kinase, U/L	≤190	56.00 [38.50, 84.00]	55.00 [40.00, 79.00]	57.00 [36.00, 94.50]	0.483
High–sensitivity cardiac troponin I (hs-cTnI), pg/ml	≤15.6	3.85 [1.00, 9.03]	2.70 [1.00, 6.38]	5.70 [2.60, 14.10]	<0.001
N-terminal pro-brain natriuretic peptide (NT-proBNP), pg/ml	<486	96.00 [37.00, 279.50]	72.00 [30.00, 205.00]	145.00 [59.00, 451.00]	<0.001
Myoglobin, ng/ml	<70	37.00 [26.78, 63.47]	33.65 [25.02, 50.25]	46.50 [29.92, 93.68]	<0.001

Data are median (IQR), numbers (percentages) of patients. p-values comparing Moderate and Severe+Critically ill are from χ^2-test, Fisher's exact test, or Mann–Whitney U-test. COVID-2019, coronavirus disease 2019; The severity was staged based on the guidelines for diagnosis and treatment of COVID-19 (trial fifth edition) published by Chinese National Health Commission in February 4, 2020.

TABLE 3 | Laboratory findings on admission in COVID-19 patients enrolled in this study.

	Normal range	All patients	Moderate	Severe + Critically ill	*P*-value
Inflammation-related indices					
hs-CRP, mg/L	<10	7.25 [1.40, 41.32]	3.65 [1.00, 22.08]	21.15 [2.92, 71.57]	<0.001
ESR, mm/h	<15	20.00 [9.00, 45.00]	14.00 [6.50, 38.50]	28.00 [13.00, 47.75]	<0.001
Serum ferritin, ug/L	30–400	508.20 [254.60, 903.70]	399.00 [187.62, 704.17]	638.20 [326.60, 1047.20]	<0.001
IL-6, pg/ml	<7.0	3.74 [1.84, 11.37]	3.15 [1.70, 7.78]	5.79 [2.43, 20.10]	<0.001
IL-1β, pg/ml	<5.0	4.90 [4.90, 4.90]	4.90 [4.90, 4.90]	4.90 [4.90, 4.90]	0.673
IL2R, U/ml	223–710	496.00 [333.50, 748.00]	448.50 [306.00, 676.75]	589.00 [397.00, 917.00]	<0.001
IL-8, pg/ml	<62	10.30 [6.30, 17.90]	8.80 [5.90, 15.22]	12.60 [7.50, 22.50]	<0.001
IL-10, pg/ml	<9.1	4.90 [4.90, 4.90]	4.90 [4.90, 4.90]	4.90 [4.90, 5.10]	0.002
TNF-α, pg/ml	<8.1	8.20 [6.20, 10.60]	8.00 [6.10, 9.93]	8.80 [6.30, 11.50]	0.001
Procalcitonin, ng/ml	0.02–0.05	0.06 [0.05, 0.10]	0.06 [0.05, 0.08]	0.08 [0.06, 0.17]	<0.001

Data are median (IQR), numbers (percentages) of patients. p-values comparing Moderate and Severe+Critically ill are from χ^2-test, Fisher's exact test, or Mann–Whitney U-test. COVID-2019, coronavirus disease 2019; The severity was staged based on the guidelines for diagnosis and treatment of COVID-19 (trial fifth edition) published by Chinese National Health Commission in February 4, 2020.

Correlation Between SpO_2/FiO_2 and PaO_2/FiO_2

Aiming to find an index that is easy to assess and can be used to monitor blood oxygenation in real-time, we evaluated the relationship between SpO_2/FiO_2 and PaO_2/FiO_2 by fitting curve analysis, which indicated that SpO_2/FiO_2 was positively correlated with PaO_2/FiO_2 ($R^2 = 0.8683$, **Figure 1**). The cut-off of SpO_2/FiO_2 related to survival was calculated using a log-rank statistic, which yielded a value of 134.43 (**Figure 2A**). In addition, the optimal cutoff point for SpO_2/FiO_2 was also identified using ROC analysis (**Figure 2B**). In the survival curve analysis, the mortality of patients with SpO_2/FiO_2 <134.43 was significantly higher than that of patients with SpO_2/FiO_2 >134.43 (**Figure 2B**).

Characteristics of Intubated COVID-19 Patients Stratified According to the Cut-Off Value of SpO_2/FiO_2

To further assess the prognostic value of the SpO_2/FiO_2 index, intubated COVID-19 patients were stratified according to the cut-off value of SpO_2/FiO_2. The values of SpO_2/FiO_2 were measured 0.5 h before intubation. As shown in **Table 5**, days from illness onset to admission differed between the low-SpO_2/FiO_2 (<134.43) and high-SpO_2/FiO_2 (>134.43) groups [18.5 days (IRQ13.30–20.00) vs. 11days (IRQ7.75–15.25)]. The mortality of patients with low SpO_2/FiO_2 during intubation was higher than that of patients with high SpO_2/FiO_2 (72.7 vs. 33.3%). Furthermore, the median arterial pressure of patients with low SpO_2/FiO_2 was significantly lower than that of patients with

TABLE 4 | Characteristics and treatments in Severe+Critically ill COVID-19 patients.

	All patients (*N* = 431)	Intubation		*P*-value
		Yes (*N* = 48)	No (*N* = 383)	
Demographic characteristics				
Age- yr	65 [23–92]	69 [44–87]	64 [23–92]	0.001
Age≥ 65	218 (50.6)	31 (64.6)	187 (48.8)	0.046
Gender-Female	211 (49.0)	15 (31.2)	196 (51.2)	0.009
Personal history				
Smoking history	7 (1.6)	2 (4.2)	5 (1.3)	0.178
Current smoker	3 (0.7)	1 (2.1)	2 (0.5)	0.299
Former smoker	4 (0.9)	1 (2.1)	3 (0.8)	0.378
Coexisting disorder				
Cardiovascular disease	39 (9.0)	6 (12.5)	33 (8.6)	0.419
Hypertension	145 (33.6)	19 (39.6)	126 (32.9)	0.418
Diabetes	80 (18.6)	9 (18.8)	71 (18.5)	1
Cerebrovascular disease	17 (3.9)	4 (8.3)	13 (3.4)	0.108
Chronic pulmonary disease	39 (9.0)	9 (18.8)	30 (7.8)	0.027
Chronic kidney disease	13 (3.0)	1 (2.1)	12 (3.1)	1
Malignancy	36 (8.4)	4 (8.3)	32 (8.4)	1
Chronic liver disease	18 (4.2)	1 (2.1)	17 (4.4)	0.707
Signs and symptoms				
Fever	324 (75.2)	42 (87.5)	282 (73.6)	0.035
Cough	346 (80.3)	38 (79.2)	308 (80.4)	0.848
Expectoration	261 (60.6)	30 (62.5)	231 (60.3)	0.876
Shortness of breath	206 (47.8)	31 (64.6)	175 (45.7)	0.014
Pharyngalgia	44 (10.2)	5 (10.4)	39 (10.2)	1
Rhinorrhoea	27 (6.3)	0 (0.0)	27 (7.0)	0.058
Fatigue	106 (24.6)	17 (35.4)	89 (23.2)	0.075
Chest pain	36 (8.4)	3 (6.2)	33 (8.6)	0.784
Diarrhea	94 (21.8)	12 (25.0)	82 (21.4)	0.58
Abdominal pain	14 (3.2)	2 (4.2)	12 (3.1)	0.662
Anorexia	93 (21.6)	12 (25.0)	81 (21.1)	0.577
Nausea or Vomiting	48 (11.1)	4 (8.3)	44 (11.5)	0.632
Myalgia	57 (13.2)	9 (18.8)	48 (12.5)	0.256
Headache	45 (10.4)	10 (20.8)	35 (9.1)	0.021
Respiratory rate, breaths per minute	22.00 [20.00, 30.00]	22.50 [20.00, 30.00]	21.00 [20.00, 30.00]	0.452
Pulse, beat per minute	84.00 [77.00, 95.00]	90.00 [80.75, 99.00]	84.00 [76.00, 95.00]	0.021
Median arterial pressure, mmHg	97.00 [89.33, 105.67]	95.83 [87.17, 102.00]	97.33 [89.67, 105.83]	0.217
percutaneous oxygen saturation, %	96.00 [92.00, 98.00]	92.00 [87.75, 98.00]	96.00 [92.00, 98.00]	0.005
Comorbidities				
Acute respiratory distress syndrome	99 (23.0)	48 (100.0)	51 (13.3)	<0.001
Acute kidney injury	33 (7.7)	23 (47.9)	10 (2.6)	<0.001
Acute heart failure	88 (21.9)	41 (85.4)	47 (13.3)	<0.001
Sepsis	76 (17.6)	43 (89.6)	33 (8.6)	<0.001
Hyper-glycaemia, %	219 (51.0)	15 (31.2)	204 (53.5)	0.005
Secondary infection	16 (3.7)	13 (27.1)	3 (0.8)	<0.001
Treatments				
Extracorporeal membrane oxygenation	4 (0.9)	4 (8.3)	0 (0.0)	<0.001

(Continued)

TABLE 4 | Continued

	All patients (*N* = 431)	Intubation		*P*-value
		Yes (*N* = 48)	No (*N* = 383)	
Renal replacement therapy	31 (7.2)	26 (54.2)	5 (1.3)	<0.001
Antiviral agents	397 (92.1)	40 (83.3)	357 (93.2)	0.04
Antibacterial agents	335 (77.7)	47 (97.9)	288 (75.2)	<0.001
Glucocorticoids	238 (55.2)	39 (81.2)	199 (52.0)	<0.001
Immunoglobulin	123 (28.5)	39 (81.2)	84 (21.9)	<0.001
Outcomes				
In-hospital death, %	45 (10.4)	31 (64.6)	14 (3.7)	<0.001
Hematologic tests				
Leukocyte count, $\times 10^9$/L	6.05 [4.79, 8.14]	8.36 [6.16, 11.37]	5.91 [4.76, 7.90]	<0.001
Neutrophil count, $\times 10^9$/L	4.20 [2.83, 6.15]	7.19 [5.02, 9.34]	3.99 [2.79, 5.79]	<0.001
Lymphocyte count, $\times 10^9$/L	1.07 [0.71, 1.47]	0.60 [0.48, 0.88]	1.16 [0.76, 1.50]	<0.001
Platelet count, $\times 10^9$/L	230.00 [170.50, 301.00]	174.50 [109.50, 264.00]	235.00 [177.50, 303.00]	<0.001
Hemoglobin, g/L	126.00 [115.00, 137.00]	138.00 [118.50, 143.25]	125.00 [115.00, 135.00]	0.004
Coagulation function				
Prothrombin time, s	13.80 [13.20, 14.50]	15.00 [13.88, 16.10]	13.70 [13.20, 14.30]	<0.001
Activated partial thromboplastin time, s	38.15 [35.50, 41.27]	39.25 [35.82, 43.10]	38.10 [35.40, 40.90]	0.253
D-dimer, ug/ml FEU	0.97 [0.41, 2.62]	4.45 [1.54, 22.00]	0.82 [0.36, 2.10]	<0.001
Fibrinogen, g/L	4.71 [3.66, 5.96]	5.13 [4.34, 6.28]	4.64 [3.64, 5.94]	0.135
Prothrombin activity, %	90.00 [81.00, 98.00]	77.00 [67.00, 88.50]	91.00 [84.00, 98.00]	<0.001
Biochemical liver function				
Alanine aminotransferase, U/L	23.00 [14.50, 38.00]	31.00 [18.00, 46.25]	22.00 [14.00, 36.50]	0.017
Aspartate aminotransferase, U/L	26.00 [19.00, 39.00]	38.50 [24.75, 59.75]	25.00 [18.00, 36.00]	<0.001
Total bilirubin, umol/L	8.70 [6.55, 12.95]	11.65 [9.62, 18.98]	8.30 [6.30, 12.45]	<0.001
Albumin, g/L	34.30 [30.75, 38.60]	31.60 [29.10, 33.42]	34.90 [31.00, 39.45]	<0.001
Pre-albumin, mg/L	198.00 [123.25, 258.25]	101.00 [79.00, 140.00]	221.00 [150.50, 263.00]	<0.001
lactose dehydrogenase, U/L	279.00 [211.00, 384.00]	453.00 [318.75, 616.50]	266.00 [203.50, 348.00]	<0.001
Biochemical renal function				
Creatinine, umol/L	69.00 [56.00, 84.00]	81.50 [64.75, 105.50]	69.00 [56.00, 82.00]	0.001
Blood urea nitrogen, mmol/L	4.60 [3.50, 6.35]	7.65 [5.10, 10.43]	4.40 [3.40, 5.80]	<0.001
eGFR, ml/min/1.73m^2	90.40 [75.55, 99.30]	75.45 [54.80, 94.35]	91.20 [79.25, 100.15]	<0.001
Sodium, mmol/L	139.30 [136.20, 141.40]	138.15 [134.75, 140.48]	139.40 [136.25, 141.50]	0.141
Potassium, mmol/L	4.07 [3.69, 4.42]	4.25 [3.70, 4.74]	4.05 [3.69, 4.37]	0.14
Calcium, mmol/L	2.09 [2.01, 2.18]	2.03 [1.98, 2.10]	2.10 [2.02, 2.19]	0.002
Biochemical cardiac function				
Creatinine kinase, U/L	57.00 [36.00, 94.50]	92.00 [40.00, 166.50]	54.00 [36.00, 82.00]	0.002
high-sensitivity cardiac troponin I (hs-cTnI), pg/ml	5.70 [2.60, 14.10]	19.25 [7.78, 215.35]	4.80 [2.30, 12.07]	<0.001

(Continued)

TABLE 4 | Continued

	All patients (*N* = 431)	Intubation		*P*-value
		Yes (*N* = 48)	No (*N* = 383)	
N-terminal pro-brain natriuretic peptide (NT-proBNP), pg/ml	145.00 [59.00, 451.00]	774.50 [302.75, 2718.50]	127.00 [54.00, 346.00]	<0.001
Infection related indices				
hs-CRP, mg/L	21.15 [2.92, 71.57]	87.60 [54.95, 141.88]	14.90 [2.50, 61.92]	<0.001
ESR, mm/h	28.00 [13.00, 47.75]	33.50 [18.25, 54.75]	26.00 [13.00, 45.75]	0.298
Serum ferritin, ug/L	638.20 [326.60, 1047.20]	1204.10 [806.35, 2127.43]	480.40 [282.40, 792.80]	<0.001
IL-6, pg/ml	5.79 [2.43, 20.10]	32.33 [16.39, 64.16]	4.81 [2.16, 13.80]	<0.001
IL-1β, pg/ml	4.90 [4.90, 4.90]	4.90 [4.90, 6.07]	4.90 [4.90, 4.90]	0.202
IL2R, U/ml	589.00 [397.00, 917.00]	964.00 [594.75, 1376.50]	563.00 [384.00, 825.50]	<0.001
IL-8, pg/ml	12.60 [7.50, 22.50]	22.05 [15.18, 38.70]	11.80 [7.10, 20.90]	<0.001
IL-10, pg/ml	4.90 [4.90, 5.10]	6.75 [4.90, 10.05]	4.90 [4.90, 4.90]	<0.001
TNF-α, pg/ml	8.80 [6.30, 11.50]	10.80 [7.98, 14.18]	8.50 [6.20, 11.15]	0.002
Procalcitonin, ng/ml	0.08 [0.06, 0.17]	0.21 [0.14, 0.41]	0.07 [0.06, 0.13]	<0.001

Data are median (IQR), numbers (percentages) of patients. p-values comparing IMV (Invasive mechanical ventilation) and no IMV therapy are from χ^2-test, Fisher's exact test, or Mann–Whitney U-test. COVID-2019, coronavirus disease 2019; The severity was staged based on the guidelines for diagnosis and treatment of COVID-19 (trial seventh edition) published by Chinese National Health Commission in February 4, 2020.

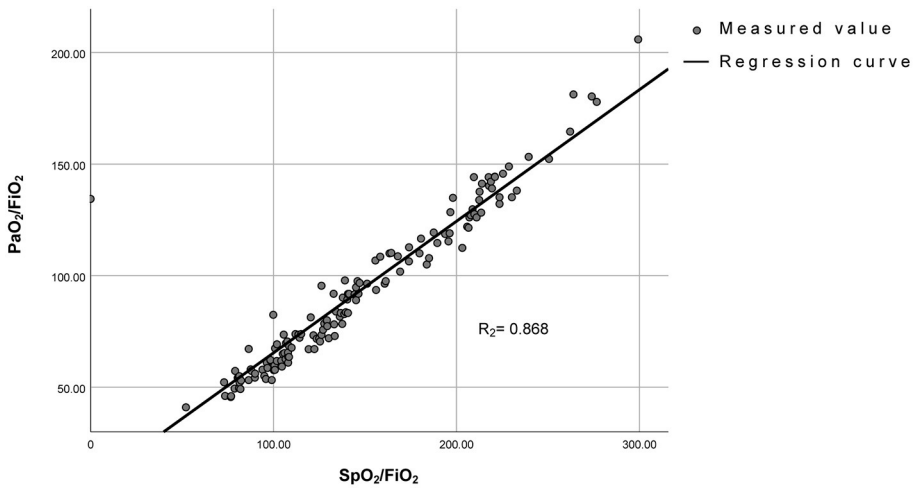

FIGURE 1 | Linear correlation between PaO_2/FiO_2 and SpO_2/FiO_2. $PaO_2/FiO_2 = 0.59^* SpO_2/FiO_2 + 6.458$ ($R^2 = 0.868$).

high SpO_2/FiO_2 [95 mmHg (IQR86.3–102.0) vs. 107.8 mmHg (IQR99.5–111.0)]. Compared to patients with high SpO_2/FiO_2, patients with low SpO_2/FiO_2 were more likely to suffer from acute heart failure [43 (97.7%) vs. 7 (58.3%)]. Cytokine levels were also analyzed, and the IL-6 levels were significantly higher in patients with low SpO_2/FiO_2 than in those with high SpO_2/FiO_2 [450.8 pg/ml (IQR182.2–5000.0) vs. 209.9 pg/ml (IQR110.6-597.7)] (**Table 5**).

Characteristics of Patients Stratified According to Glucocorticoid/CRRT /Anticoagulation Therapy

Patients were treated with glucocorticoids according to the protocols in the guidelines and references (12, 16, 17). Of the 431 severely and critically ill patients, 238 received glucocorticoid treatment (55.2%), while 47 of the 61 intubated patients received glucocorticoid treatment (77.0%).

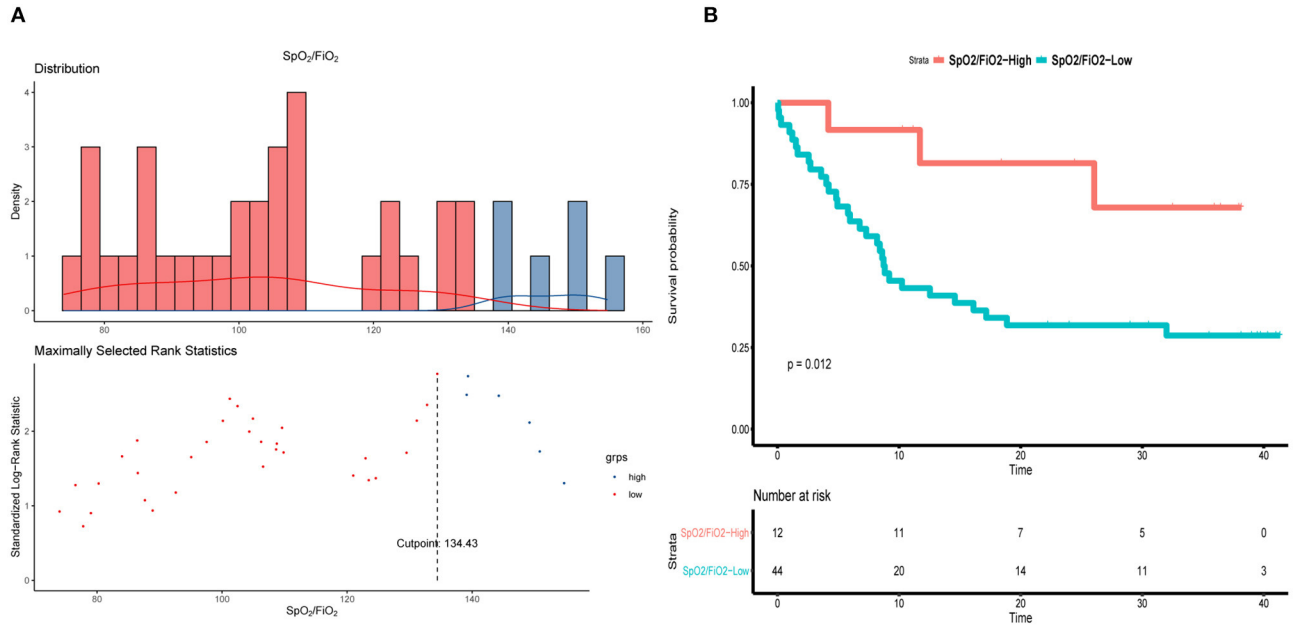

FIGURE 2 | SpO_2/FiO_2 in patients underwent intubation during hospitalization. **(A)** Distribution of SpO_2/FiO_2 and cut-off value. **(B)** Kaplan–Meier curve of overall survival by using 134.43 as the cutoff for SpO_2/FiO_2.

Patients with glucocorticoid therapy low lymphocytes at baseline, higher infection markers and cytokines, as well as higher incidence of comorbidities such as sepsis, acute heart failure, AKI, and secondary infection. Moreover, the proportion of patients receiving CRRT and immunoglobulin treatment among those receiving glucocorticoid treatment was also higher.

Of the 431 severely and critically ill patients, 31 (7.2%) were treated with CRRT, while 33 of the 61 intubated patients (54.1%) received CRRT. At baseline, patients treated with CRRT had high leukocyte and neutrophil counts, creatinine, cytokines, infection indicators, and ferritin. The proportion of patients administered glucocorticoids, immunoglobulins and ECMO among those receiving CRRT was also higher.

Anticoagulation therapy was used in 160 of the 431 severely and critically ill patients (37.1%). For patients with severe and critical COVID-19, risk assessment scales such as Welles's score can be used to prevent VTE. Medium- and high-risk patients can be subcutaneously injected with a half-dose of low-molecular-weight heparin once every 12 h or subcutaneously injected with one dose of low-molecular-weight heparin once a day for prevention. Of the 61 intubated patients, 60 received anticoagulation therapy (98.4%). Patients who required anticoagulation therapy had the baseline characteristics of higher levels of D-dimer, potassium, creatinine and blood urea nitrogen, as well as higher incidence of comorbidities such as sepsis, AKI, and acute heart failure (**Supplementary Tables 1–4**).

As detailed in **Supplementary Table 5**, 6 patients were treated with ECMO and five survived. Indications for implementing ECMO in COVID-19 patients include age < 70 years old, without known severe brain injury, unrecoverable heart damage, or uncontrollable hemorrhaging. For COVID-19 patients and ARDS, if the hypoxia is still not relieved after the mechanical ventilation settings have been optimized [low tidal volume < 6 mL/kg (ideal body weight) and airway plateau pressure < 30 cmH_2O, PEEP ≥10 cmH_2O, $FiO_2 \geq 0.8$], and prone positioning was applied for at least 12 h per day, ECMO should be considered as early as possible.

DISCUSSION

In this study, we analyzed the clinical data of 1,106 COVID-19 patients admitted to the Optical Valley Branch of Tongji Hospital between 9 February and 9 March, 2020. In the absence of effective antiviral drugs and vaccines, we adopted measures to detect potential severe cases and provide early intervention, multidisciplinary collaboration and comprehensive treatment, including improved oxygenation, multi-organ function support, maintaining water and electrolyte balance, restrictive liquid management, etc. Due to our efforts, the mortality of severely and critically ill patients could be reduced to 10.4%, and that of critically ill patients was 39.6%. Analyzing the applied treatments in this designated specialized hospital may provide crucial clues for understanding the strategy that determined the low mortality of critical COVID-19 patients.

Consistent with previous studies of COVID-19 patients in the United States and Italy, severely, critically ill and deceased patients had a higher incidence of preexisting conditions such as hypertension, diabetes, and chronic pulmonary disease (2, 5, 7–9, 18). Our results showed that the severely and critically ill patients were older, had more severe respiratory distress, lower lymphocyte counts, as well as higher levels of inflammatory indicators and cytokines. Patients with chronic pulmonary disease, hypertension and diabetes had a higher tendency to progress to severe COVID-19. Moreover, comorbidities such as

TABLE 5 | Characteristics and treatments in intubated patients who received IMV (Invasive mechanical ventilation) during hospitalization.

	All patients (*N* = 56)	Low SpO_2/FiO_2 (*N* = 44)	High SpO_2/FiO_2 (*N* = 12)	*P*-value
Demographic characteristics				
Age- yr	69 (62.8–80.3)	70 (63.8–81)	66 (60.8–71.5)	0.174
Age≥ 65	38 (67.9)	31 (70.5)	7 (58.3)	0.32
Gender–Female	14 (25)	13 (29.5)	1 (8.3)	0.13
Personal history				
Smoking history	3 (5.4)	2 (4.5)	1 (8.3)	0.522
Current smoker	1 (1.8)	1 (2.3)	0	0.79
Former smoker	2 (3.6)	1 (2.3)	1 (8.3)	0.386
Coexisting disorder				
Cardiovascular disease	6 (10.7)	5 (11.4)	1 (8.3)	0.62
Hypertension	29 (51.8)	24 (54.5)	5 (41.7)	0.32
Diabetes	12 (21.4)	10 (22.7)	2 (16.7)	0.67
Cerebrovascular disease	4 (7.1)	4 (9.1)	0	0.37
Chronic pulmonary disease	11 (19.6)	8 (18.2)	3 (25)	0.43
Chronic kidney disease	4 (7.1)	1 (2.3)	3 (25)	0.041
Malignancy	2 (3.6)	2 (4.5)	0	0.61
Chronic liver disease	4 (7.1)	3 (6.8)	1 (8.3)	0.63
Signs and symptoms				
Fever (Highest body temperature, °C)				
<37.3	10 (17.9)	10 (22.7)	0	0.098
37.3–38.0	15 (26.8)	11 (25)	4 (33.3)	0.72
38.1–39.0	25 (44.6)	19 (43.2)	6 (50)	0.75
>39.0	6 (10.7)	4 (9.1)	2 (16.7)	0.60
Cough	42 (75)	32 (72.7)	10 (83.3)	0.37
Expectoration	34 (60.7)	25 (56.8)	9 (75)	0.46
Shortness of breath	22 (39.3)	14 (31.8)	8 (66.7)	0.033
Pharyngalgia	5 (8.9)	4 (9.1)	1 (8.3)	0.71
Rhinorrhoea	1 (1.8)	1 (2.3)	0	0.79
Fatigue	20 (35.7)	13 (29.5)	7 (58.3)	0.068
Chest pain	4 (7.1)	3 (6.8)	1 (8.3)	0.41
Diarrhea	12 (21.4)	12 (27.3)	0	0.038
Abdominal pain	3 (5.4)	2 (4.5)	1 (8.3)	0.26
Anorexia	14 (25)	10 (22.7)	4 (33.3)	0.34
Nausea or Vomiting	4 (7.1)	4 (9.1)	0	0.37
Myalgia	11 (19.6)	7 (15.9)	4 (33.3)	0.17
Headache	10 (17.9)	9 (20.5)	1 (8.3)	0.31
Dizziness	3 (5.4)	3 (6.8)	0	0.48
Disorders of consciousness	3 (5.4)	2 (4.5)	1 (8.3)	0.52
Respiratory rate, breaths per minute	20.5 (20–25.3)	20 (20–25)	25 (20–32.25)	0.14
Pulse, beat per minute	88 (78–97.5)	86.5 (78–96.8)	91.5 (88–97.5)	0.78
Median arterial pressure, mmHg	97.3 (87.6–107.3)	95 (86.3–102)	107.8 (99.5–111)	0.005
percutaneous oxygen saturation, %	94.5 (89.8–98)	94.5 (90.8–98)	93.5 (88.8–97)	0.85
Comorbidities				
Acute respiratory distress syndrome	56 (100.0)	44 (100.0)	12 (100.0)	1
Acute kidney injury	28 (50)	25 (56.8)	3 (25)	0.051
Acute heart failure	50 (89.3)	43 (97.7)	7 (58.3)	0.001
Acute liver injury	4 (7.1)	3 (6.8)	1 (8.3)	1
Cardiac injury	53 (94.6)	43 (97.7)	10 (83.3)	0.11
Hyperglycaemia	12 (21.4)	10 (22.7)	2 (16.7)	0.50

(Continued)

TABLE 5 | Continued

	All patients (*N* = 56)	Low SpO_2/FiO_2 (*N* = 44)	High SpO_2/FiO_2 (*N* = 12)	*P*-value
Hypoalubminemia	17 (30.4)	14 (31.8)	3 (25)	0.47
Sepsis	51 (91.1)	40 (90.9)	11 (91.7)	0.71
Secondary infection	13 (23.2)	11 (25)	2 (16.7)	0.43
Treatments				
Extracorporeal membrane oxygenation	5 (8.9)	4 (9.1)	1 (8.3)	0.71
Renal replacement therapy	30 (53.6)	24 (54.5)	6 (50)	0.52
Antiviral agents	55 (98.2)	43 (97.7)	12 (100)	0.79
Antibacterial agents	54 (96.4)	42 (95.5)	12 (100)	0.61
Glucocorticoids	44 (78.6)	32 (72.7)	12 (100)	0.38
Immunoglobulin	48 (85.7)	38 (86.4)	10 (83.3)	0.55
Outcomes				
In-hospital death, %	36 (64.3)	32 (72.7)	4 (33.3)	0.016
Days from illness onset to first outpatient visit, days	0.5 (0–6)	1 (0–6)	0 (0–2.25)	0.3
Days from illness onset to admission, days	11.5 (8–17.3)	11 (7.75–15.25)	18.5 (13.3–20)	0.018
Duration from onset of symptoms to death, days	17.3 (27–34)	24 (14.75–34)	35.5 (31.5–38.3)	0.25
Hemoglobin concentration, g/L	137.5 (120.5–145)	134.5 (119–143.3)	142.5 (130–150)	0.43
Lymphocyte count, $\times 10^9$/L	9.1 (6.3–14.3)	9.1 (6.3–13.8)	7.1 (5.1–16)	0.87
Platelet count, $\times 10^9$/L	174.5 (123–242)	176 (126.5–242)	144.5 (108–214.5)	0.62
Prothrombin time, s	17.3 (16.1–20.3)	18 (16.4–20.6)	16.8 (15.7–18.4)	0.84
Total bilirubin concentration, μmol/L	22.2 (17.9–34.6)	25.1 (17.9–38.3)	21.6 (18.8–27.7)	0.39
Direct bilirubin concentration, umol/L	5.8 (4.3–9.7)	5.8 (4.0–9.7)		0.98
Serum creatinine concentration, μmol/L	136.5 (100.5–203.5)	146.5 (108–209)	106 (75.2–144)	0.80
Lactate concentration, mmol/L	3.66 (2.93–4.15)	4.0 (3.5–6.4)	3.2 (2.8–3.9)	0.077
hs-CRP, mg/L	80.6 (41.5–125.6)	102.3 (47.3–142.4)	59 (24.1–77.9)	0.21
ESR, mm/h	30 (14–54.8)	29 (14–62.3)	40.5 (11.3–53.8)	0.70
Serum ferritin, ug/L	1,678 (1,042–3,300)	1,182 (1,046–3,896)	1,678 (675–2,713)	0.56
Interleukin−6, pg/ml	379 (144.8–3,723)	450.8 (182.2–5,000)	209.9 (110.6–597.7)	0.015
Interleukin-2R, U/mL	1,610 (1080.3–3049.3)	1770.5 (1,173–3125.3)	1,036 (816.3–1691.3)	0.32
D-dimer, ug/ml FEU	3.4 (1.3–19.5)	3.1 (1.3–17.5)	12.3 (0.6–21.0)	0.28
Fibrinogen, g/L	5.14 (3.96–6.41)	5.30 (3.96–6.77)	4.6 (3.4–5.3)	0.11
Prothrombin activity, %	77.5 (67–90.5)	76 (67–90.5)	85 (77–95.3)	0.29
Alkaline phosphatase, U/L	68.5 (62.3–88.3)	67.5 (61.3–85.8)	81 (67.3–92.8)	0.89
lactose dehydrogenase, U/L	461.5 (295–600.8)	464 (304.8–645.5)	403.5 (255.8–575.5)	0.48
Cholinesterase, U/L	5,192 (4,149–6,027)	4,918 (4,091–5,861)	5,740 (4,175–6,528)	0.31
Blood urea nitrogen, mmol/L	7.1 (4.9–10.1)	7.6 (4.9–10.1)	6.1 (4.6–9.7)	0.65
uric acid, umol/L	266.1 (179.1–348.5)	262.5 (179.1–354)	275.1 (176.1–333.2)	0.81
eGFR, ml/min/1.73m^2	76.1 (58.8–93.5)	78.2 (58.8–91.5)	71.1 (53.3–96.3)	0.89

Cut-off value: $SpO_2/FiO_2 = 134.43$.

Data are median (IQR), numbers (percentages) of patients. p-values comparing SpO_2/FiO_2 high and low are from χ^2-test, Fisher's exact test, or Mann–Whitney U-test. COVID-2019, coronavirus disease 2019; The severity was staged based on the guidelines for diagnosis and treatment of COVID-19 (trial seventh edition) published by Chinese National Health Commission in February 4, 2020.

sepsis, myocardial injury, heart failure, acute liver and kidney injury, or vascular embolism were significantly more likely to occur in severely and critically ill patients, with potentially fatal outcomes. According to these results, treatment for multi-organ dysfunction, including intubation, glucocorticoid treatment, CRRT, anticoagulation therapy and ECMO should be emphasized in reducing the mortality of severely and critically ill COVID-19 patients.

Since immune-cell infiltration, diffuse alveolar damage and small airway blockage by mucus plugs all contribute to the development of COVID-19 (19, 20), the severely and critically ill patients suffered from sustained and severe hypoxemia, resulting in a rapid deterioration of the patients' condition, and even sudden death. Therefore, it is of great importance to evaluate the level of hypoxia and rectify hypoxemia in time. Although the oxygenation index was applied in assessment of hypoxemia (12, 21), PaO_2 requires an invasive operation and cannot be monitored in real time. In comparison, the SpO_2/FiO_2 measurement addressed in the WHO COVID-19 guidance is non-invasive, and the screening and monitoring of SpO_2/FiO_2 is more flexible when the medical practitioners have to wear full protective gear (13, 21). It was also defined by the Kigali modification of the Berlin definition and showed a correlation with the diagnosis of ARDS (22). Importantly, our results demonstrated that SpO_2/FiO_2 showed a positive relationship with PaO_2/FiO_2, indicating that SpO_2/FiO_2 can potentially be used as an alternative index for hypoxia. Interestingly, it seems a better correlation of SpO_2/FiO_2 and PaO_2/FiO_2 in previous study reported by Bilan et al. (23) compared to our study, which may be due to differences of sample sizes and characteristics of ARDS caused by COVID-19. Then, we calculated 134.43 as a cut-off value of SpO_2/FiO_2 according to the prognosis of intubated patients. When the intubated patients were stratified according to the cut-off value of SpO_2/FiO_2, we further found that the mortality of patients with SpO_2/FiO_2 <134.43 during intubation (72.7%) was much higher than that of patients with SpO_2/FiO_2 >134.43 (33.3%), suggesting the degree of hypoxemia was correlated with mortality of intubated patients. Considering that no specific values of oxygenation index for evaluating the timing of intubation were reported in previous studies (13, 21, 24) our results provide an real-time index for early warning and timely mechanical ventilation, which might improve the outcomes to some extent.

There is increasing evidence that the rapid deterioration of critically ill COVID-19 patients may be caused by a cytokine storm characterized by explosive and potentially fatal hyper-cytokinemia and multiple organ failure, especially involving the lungs (2, 25). Previous clinical studies reported that high cytokine levels are a risk factor for mortality in critically ill COVID-19 patients (2, 18). Therefore, we analyzed the cytokine levels of intubated patients stratified according to the cut-off value of SpO_2/FiO_2. Interestingly, the levels of cytokines, and especially IL-6, in patients with low SpO_2/FiO_2 were significantly higher than in the high SpO_2/FiO_2 group, indicating that cytokine levels may be related to the degree of hypoxia and may also potentially offer a timely warning sign.

Glucocorticoids and CRRT are well-established as effective treatments against runaway inflammation and cytokine storms. However, the use of glucocorticoids in COVID-19 remains controversial (26). Dequin et al. reported that low-dose hydrocortisone did not significantly reduce treatment failure at day 21 compared with the placebo group (27). In contrast, Sterne et al. reported that systemic administration of corticosteroids was associated with lower 28-day all-cause mortality compared with usual care or placebo (28), while Horby et al. reported that the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization, but not among those receiving no respiratory support (29). Also, Derek et al. reported that treatment with a 7-day fixed-dose course of hydrocortisone or shock-dependent dosing of hydrocortisone resulted in 93 and 80% better odds of not requiring organ support within 21 days (30). Indeed, benefits of glucocorticoid therapy and decreased cytokine levels were observed in some severely and critically ill patients in our study. Importantly, there seems to be a downward trend in the mortality of intubated patients with glucocorticoid treatment. Our study was consistent with current reports at least to a certain extent. In particular, the proportion of glucocorticoid usage in severely and critically ill patients was higher than in other studies from the same period (4, 5). Thus, our results showed that a high proportion of glucocorticoid treatment may be correlated with lower mortality of severely and critically ill patients. Current studies recommend that glucocorticoid therapy should be given at an appropriate dose and course at the right time (16, 17). Therefore, the timing of glucocorticoid treatment and the COVID-19 patient's own condition can determine the prognosis to a certain extent, but multi-center, random, double-blind studies with larger cohorts may be required in the future. At least but not last, a part of patients with higher cytokines, and progressive deterioration of SpO_2/FiO_2 may have benefited from glucocorticoid treatment.

There is accumulating evidence that CRRT is associated with lower mortality in patients with sepsis. Moreover, the removal of endotoxins and cytokines by CRRT could improve the prognosis of patients with ARDS (31). Since severe ARDS is the fundamental pathophysiology of severe viral pneumonia, CRRT was also performed in a proportion of the intubated COVID-19 patients in our cohort, which was higher than that in previously published studies (5, 32). Continuously elevated cytokine levels are regarded as announcing the onset of a cytokine storm (5). Once started, hyper-inflammation can trigger a cascade reaction leading to multiple organ failure (33). Our study showed a large increase in the expression of inflammatory makers in the intubated COVID-19 patients, and cytokine removal by CRRT was linked with a favorable prognosis. Hence, CRRT should be considered as an adjunct therapy for early treatment of critically ill COVID-19 patients, especially those with hyper-inflammation.

Although the incidence of venous thromboembolism (VTE) events in COVID-19 patients is unknown, the relationship between pneumonia and VTE is well-described (34). The activated leukocytes and cellular adhesion molecules on the vein walls contribute to the development of VTE (35). For example, H1N1 ARDS patients had high risk for pulmonary embolism

and VTE (36). Given that ARDS occurred in more than half of the critically ill COVID-19 patients (5), we concluded that anticoagulation therapy should be considered in patients at high risk of trombosis. In fact, anticoagulation therapy was applied in 37.1% (160/431) of the severely and critically ill patients, as well as practically all intubated patients (60/61). There were 3 cases of mild upper gastrointestinal hemorrhage in our study. However, fatal intracranial hemorrhage was also found to be connected with the use of anticoagulants (36). The prevention of pulmonary embolism and VTE should therefore be weighed against the risks of hemorrhagic complications.

ECMO was also applied in our study. Five of the six patients who received ECMO survived until the end of the follow-up period. Early initiation of ECMO was associated with better outcomes. Although this sample was small, and the specific baseline characteristics as well as the disease courses were different, it raises concerns about potential benefits of ECMO therapy for critically ill COVID-19 patients.

Our study has several limitations. Firstly, the representativeness of study may be limited by its single-center nature and resulting data bias. Secondly, due to the retrospective nature of the study, not all laboratory indicators were available for all patients, including lactate, lymphocyte subsets, etc. Thirdly, interpretation of our result might be limited by the sample size. Finally, retrospective and observational study cannot make causal relationship between treatments and outcome. Therefore, further studies are needed to provide a better understanding of treatment options and mortality of COVID-19 patients, which may help guide efforts aimed at reducing the mortality.

In summary, we recommend the real-time tracking of early warning signs, multidisciplinary collaboration, multi-organ function support and personalized treatment, which may play key role in the prognosis of severely and critically ill COVID-19 patients.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the Ethics Commission of Tongji hospital (Approval No.: TJ-IRB20200334), and the written informed consent requirement was waived for anonymized data in view of the rapidly emerging infectious disease.

AUTHOR CONTRIBUTIONS

JL, HW, and ZT made substantial contributions to the study concept and design. ZD, HF, YR, BL, JJ, NZ, FH, and YL collected the epidemiological and clinical data. ZD, ZW, HF, DW, BZ, GX, JZ, and GL summarized and analyzed all data. WZ, HZ, YL, ZL, YR, and ZD drafted the manuscript. JL, HW, ZT, HZ, and WZ revised the final manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.582764/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CASE REPORT
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Case Report: Administration of Amniotic Fluid-Derived Nanoparticles in Three Severely Ill COVID-19 Patients

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Rationale/Objectives: A human coronavirus (HCoV-19) has caused the novel coronavirus disease (COVID-19) outbreak worldwide. There is an urgent need to develop new interventions to suppress the excessive immune response, protect alveolar function, and repair lung and systemic organ damage. Zofin (previously known as Organicell Flow) is a novel therapeutic that is derived from the soluble and nanoparticle fraction (extracellular vesicles and exosomes) of human amniotic fluid. Here within, we present the clinical outcomes after Zofin treatment in three critically ill patients suffering from severe, multi-organ complications induced by COVID-19 infection. All patients were diagnosed with COVID-19, developed respiratory failure, and were hospitalized for more than 40 days.

Methods: Zofin was administered to patients concurrently with ongoing medical care who were monitored for 28-days post-therapy. SOFA score assessment, chest X-rays, and inflammatory biomarker testing was performed.

Main Results: There were no adverse events associated with the therapy. The patients showed improvements in ICU clinical status and experienced respiratory improvements. Acute delirium experienced by patients completely resolved and inflammatory biomarkers improved.

Conclusions: Primary outcomes demonstrate the therapy was safe, accessible, and feasible. This is the first demonstration of human amniotic fluid-derived nanoparticles as a safe and potentially efficacious therapeutic treatment for respiratory failure induced by COVID-19 infection.

Keywords: COVID-19, critical care, ARDS (acute respiratory distress syndrome), exosomes, amniotic fluid (AF), extracellular vesicles

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BACKGROUND

A human coronavirus (HCoV-19) has caused the novel coronavirus disease (COVID-19) outbreak worldwide. The main symptoms of COVID-19 include fever, fatigue, and cough that can progress rapidly to severe and critical conditions resulting in pulmonary edema leading to the most common complications: acute lung injury (ALI) and acute respiratory distress syndromes (ARDS) (1–5).

The majority of cases result in mild symptoms, but some can progress into pneumonia and multi-organ failure. According to severity, it is divided into mild, normal, severe, and critically ill, the last of which is associated with ICU admission and mortality (6). Immune activation in some patients and the appearance of cytokine storm syndrome is one of the most potent causes of severe damage to lungs and other organs, which may lead to death.

In the early stages of the COVID-19 pandemic, treatment for COVID-19 patients included non-specific anti-viral, anti-inflammatory medication, oxygen therapy, mechanical ventilation, and blood pressure medications. A definitive antiviral therapy or ALI treatment for patients with or recovering from COVID-19 infections continues to be in development. Furthermore, as the number of COVID-19 infections continues to rise, severe cases continue to result in organ failure and long-term impairments. As a result, there remains an urgent need to develop new interventions to suppress the excessive immune response in a timely manner during the course of disease, protect alveolar function, and repair the pulmonary and systemic organ damage caused after the infection (7).

One hallmark feature of critical COVID-19 patients is the extremely high expression of pro-inflammatory markers, including C Reactive protein (CRP) and cytokines IL-6, TNFα, and IL8 (8). Anti-inflammatory and immune modulatory therapies have risen as strong therapeutic candidates because inflammatory cytokine storm is common in severe cases and is the highest amongst non-survival patients (8). Exaggerated immune response, the secretion of pro-inflammatory cytokines, and marked pulmonary infiltration are lethal components of viral infections (9). Therefore, traditional anti-inflammatory treatments, such as the anti-interlukin-6 receptor monoclonal antibody Tocilizumab and corticosteroids, are actively being used to suppress cytokine storms and prevent further injury. However, current standard of care anti-inflammatory medications are not optimal due to the concern that they may delay the elimination of the virus and risk secondary infection (8). Furthermore, severe COVID-19 cases continue to persist despite the incorporation of these current treatment options. Cell-based therapies are actively being tested for COVID-19 infections due to the observed immunomodulatory and anti-inflammatory effects (10). However, cell therapies are often limited due to cell delivery challenges and inadequate cell survival post-infusion (11). Furthermore, research has uncovered that cell-beneficial effects are mainly paracrine-mediated via the release of growth factors, cytokines, and extracellular vesicles such as exosomes rather than engraftment and differentiation (12, 13). Therefore, our proposed therapeutic intervention utilizes cell- and tissue-secreted paracrine factors, rather than the cells themselves, as the active drug components.

Zofin (previously known as Organicell Flow) is a novel biologic that is derived from the soluble and nanoparticle fraction of human amniotic fluid. The manufactured Zofin therapeutic is an acellular product characterized to contain over 300 growth factors, cytokines, and chemokines as well as other extracellular vesicles and exosomes secreted from perinatal tissues. Amniotic fluid sourced biologics have been studied for the therapeutic use of orthopedic repair due to the abundance of anti-inflammatory and tissue healing components (14–16). However, the use of amniotic fluid-derived paracrine factors, including proteins and nanoparticles, have not been tested for the treatment of COVID-19-induced systemic organ damage and respiratory failure.

Here within, we present three case reports of critically ill patients suffering from severe, multi-organ complications induced by COVID-19 infection who were treated with Zofin in addition to the authorized standard of care available at that time. These patients represent the subset of COVID-19 patients most effected by the virus. These three patients tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using a real-time reverse transcriptase polymerase chain reaction assay, were diagnosed with ARDS, and suffered from severe organ damage and respiratory failure. At the time of hospital admission there was no emergency authorized standard of care for COVID-19 infection. These patients were treated with supplemental oxygen, anti-inflammatories, antibiotics, antiviral medication, and other medications required to manage their multiorgan failure symptoms. Prior to enrollment for investigational treatment at the study site ICU (Landmark Hospital of Athens), these patients had been hospitalized for over 40 days and were transferred from the initial hospital sites to appropriately manage multiple comorbidities. The physicians explored all authorized pharmacological options available to them at that time. Due to the concern for declining and irreversible injury, the treating physician requested single patient emergency, compassionate use IND (eIND) to administer Zofin.

The first patient (de-identified subject CU#1) approved for Zofin was a 74-year-old Caucasian female with multiple comorbidities including obesity, hypertension (HTN), type 2 diabetes, depression, hyperlipidemia (HLD), and vitamin D deficiency. This patient was initially admitted to the hospital 44 days prior to treatment at the study site. Initial diagnosis was acute hypoxemic respiratory failure with positive COVID-19 infection. The patient was orally intubated after 6 days in the hospital and treated for COVID-19 with pneumonia. COVID-19+ tests were reported for 20 days post-admission. Tracheostomy placement was performed prior to transfer to the study site. Patient CU#1 continued to require mechanical ventilation prior to treatment and developed acute metabolic encephalopathy with ICU delirium along with acute kidney injury and anemia. The initial COVID-19 treatment upon admission included a 10-day course of Hydroxychloroquine, three doses of Ribavarin, and Kaletra. Inclusion of additional medication was ongoing to manage complications induced by the multiple comorbidities. Ten days after transfer to the study site, Zofin infusion was initiated in addition to ongoing medical treatment. Due to the patient's high BMI, it was decided to administer a total of four doses instead of the originally planned three. FDA approval was obtained prior to this protocol change.

The second patient (de-identified subject CU#2) was a 79-year-old Caucasian female with multiple chronic comorbidities including obesity, HTN, HLD, Hodgkin's disease, hypothyroidism (HYT), and status post-left carotid endarterectomy. This patient was admitted to the hospital 47 days prior to treatment at the study site. Her initial diagnosis

included septic syndrome and hypoxemic respiratory failure with positive COVID-19 infection. The initial treatment reports did not indicate if this patient received any anti-viral medication to target the COVID-19 infection; instead, the treatment included a wide range of medications to manage the severe symptoms associated with comorbidities, antibiotics (Cefepime and Vancomycin), and hemodialysis. Due to the severity of the patient upon admission, mechanical ventilation was immediately required after 2 days. The patient was extubated and then reintubated, followed by tracheostomy placement. COVID-19+ tests were reported for 16 days post-admission. Hospital course was complicated by acute kidney injury, anemia requiring blood transfusion, encephalopathy, and septic shock. The patient underwent PEG placement a few days prior to transfer to the study site. Transfer of the patient to the study site was completed for ventilator liberation and management of other comorbidities. Like the previous patient, the high BMI of CU#2 qualified this patient for four doses of Zofin, as approved by the FDA.

The third patient (de-identified subject CU#3) was a 66-year-old Hispanic male with comorbidities that included type 2 diabetes and HTN. This patient was admitted to the hospital 42 days prior to treatment at the study site. Initial diagnosis was hypoxemic respiratory failure secondary to COVID-19 pneumonia. Initial COVID-19 treatments included Hydroxychloroquine as an outpatient, followed by Tocilizumab on admission. Patient CU#3 required intubation that was followed by extubation and reintubation. Hospital course was complicated by hypoxemic cardiac arrest, acute kidney injury that required renal replacement therapy, acute DVT, and encephalopathy. The patient underwent tracheostomy prior to transfer to the study site. Transfer to the study site was completed for ventilator liberation, management of hemodialysis, continuation of nutritional support, and management of other comorbidities. COVID-19+ tests were reported for 8 days post-admission. Additional medication and antibiotics were incorporated throughout treatment as the patient's condition evolved. The patient received three doses of Zofin beginning 9 days after transfer to the study site.

The primary objective of these three eINDs was to demonstrate safety, feasibility, and accessibility of Zofin for the treatment of these severely ill patients. Secondarily, we aimed to observe post-treatment changes in clinical status improvement and inflammatory biomarker improvement that may suggest potential therapeutic efficacy. Our underlying hypothesis suspected that Zofin treatment would improve patient outcomes and promote lung and organ failure assessment recovery. This report demonstrates the first use of an amniotic fluid-derived product in humans as a potential therapeutic to aid in the recovery from severe organ injuries induced by COVID-19 infection.

METHODS

Ethics

This study involving human participants was reviewed and approved by the FDA and the Independent Review Board Western Institutional Review Board. The patient's consent to participate in the study and for data publication was obtained at the treatment site by the patient's proxy using an IRB approved informed consent form. These single patient INDs were submitted under the approved parent IND #19881 and FDA approval was issued with the following IND numbers: CU#1 IND#22370, CU#2 IND#22371, and CU#3 IND#22897. IRB approval was issued by letters of acknowledgment from the Western Institutional Review Board.

Therapeutic Intervention

The therapeutic intervention studied in these case reports was an acellular biologic called Zofin. Zofin was manufactured by Organicell Regenerative Medicine, Inc. in Miami, FL. The Zofin product was derived from human amniotic fluid donated from consenting adults during routine, planned cesarean sections under IRB approved donor screening (IRB approval agency: IRCM). Donor qualification was performed under FDA CFR 1271. Donor qualification was certified following the review of the mother's medical history, social history, physical examination, and raw product recovery information. Relevant communicable disease testing was completed, and the mother was reported to have negative/non-reactive results for CMV total Ab, Hepatitis B core total Ab, Hepatitis B surface Ag, Hepatitis C virus Ab, HIV-1/HIV-2 Plus O, HTLV I/II Ab, Syphilis screening—non-treponemal, Ultrio Elite HBV, Ultrio Elite HCV, Ultrio Eliter HIV-1/2, and WNV. Upon receipt, the collected amniotic fluid was subjected to centrifugation and proprietary filtration to remove large particle debris and preserve the natural protein, nanoparticle, and exosome composition of amniotic fluid. The final Zofin product was released by Organicell Regenerative Medicine, Inc. after meeting the release criteria requirements. The specific release criteria parameters for the product administered in these treatments were: sterility (14-day cultures: no growth for aerobic, anaerobic, and fungal contamination), endotoxin (<0.05 EU/mL), nanoparticle composition (concentration $= 3.26 \times 10^{11}$/mL, mode particle size $= 90.2$ nm), protein concentration (2.83 mg/mL), and hyaluronic acid concentration (261 ng/mL). Zofin was stored frozen and shipped on dry ice to the treatment location following validated storage and shipping methods.

Patient Standard Care and Administration of Therapeutic Intervention

Patient care and product infusion throughout the study period was performed at Landmark Hospital Athens, in Athens, GA. Standard care was followed along with Zofin administration under approved single patient eIND by the FDA and under IRB oversight. The patient care was defined by the treating physician in accordance with the authorized standard of care practices ongoing at the study site at the time of patient enrollment. The care was focused on treating the multiple ongoing organ failure issues induced by the COVID-19 infection. At the time of hospital admission, there was no standardized or authorized therapy for COVID-19 infection. These patients were treated with available anti-viral, anti-inflammatory, antibiotics, and other medication required to manage their occurring symptoms. Supplemental oxygen therapy and ventilation was provided

TABLE 1 | Clinical status of compassionate use patients.

Patient ID	CU#1	CU#2	CU#3
Age	74	79	66
Gender	F	F	M
Weight (kg)	118.75	100.24	60.36
BMI (kg/m^2)	38.43	40.18	22.14
Prior comorbidities	Obesity, HTN, T2DM, depression, HLD, Vit. D deficiency	Obesity, HTN, HLD, Hodgkin's disease, HYT, status post left carotid endarterectomy	T2DM, HTN
Pre-treatment complications	Hyperglycemia Acute lung injury (ARDS) Anemia with normocytic indices	Hyperglycemia Acute renal failure Anemia requiring blood transfusion Acute lung injury (ARDS)	Acute renal injury Acute renal failure Acute lung injury (ARDS) Hyperglycemia
Days hospitalized Prior to treatment	44	48	42
Respiratory status	Base: 21% T-Collar Day 4: 21% T-Collar Day 6: 21% T-Collar Day 8: 21% T-Collar Day 14: 21% T-Collar Day 21: PMV room air Day 28: room air	Base: CPAP 5 PS 10 30% Day 4: CPAP 5 PS 10 35%. Weaned PS to 8 and FiO_2 to 30% Day 6: CPAP PS 40 % Day 8: Patient placed on 40% ATC at 0811 and the PMV at 1531 Day 14: Patient placed on 40% ATC at 0811 and the PMV at 1531 Day 21: 40% T-Collar Day 28: 30% T-Collar	Base: PS/CPAP 8/5 24% Day 4: Patient tolerates trial cap and is successfully decannulated Day 8: Placed on 2L of O2 Day14: Weaned down to room air Day 21: Remains in room air Day 28: Discharged 26 days after baseline
Status after 28-day follow up period	Decannulated, discharged	Step-down unit, remained in ventilation and hemodialysis	Decannulated, not in hemodialysis, discharged

HTN, hypertension; T2DM, type-2 diabetes; HLD, hyperlipidemia; HYT, hypothyroidism.

as determined by the physicians. Zofin was administered intravenously at a dose of 1 mL diluted in 100 mL of normal saline. Intravenous infusion was performed at a rate of 2 mL/min. Product thawing and dilution occurred immediately before administration. Patients CU#1 and CU#2 received a total of four doses administered on day 0, day 4, day 6, and day 8. Patient CU#3 received a total of three doses administered on day 0, day 4, and day 8.

SOFA Score Assessment

ChartPad Software (Technomad), a cloud-based electronic data capture platform, was used to collect patient data. SOFA score was calculated as reported in the literature (17) and was assessed on 0, 4, 6, 8, 14, 21, and 28 days after the initiation of Zofin therapy. The SOFA score was derived from clinical and laboratory results obtained for respiration (PaO_2/FiO_2, mmHg), coagulation (platelets, $\times 10^3/\mu L$), liver (bilirubin, mg/dL), cardiovascular (mean arterial pressure), neurologic (Glasgow coma score), and renal (creatinine, mg/dL).

Chest X-Ray

A portable chest x-ray (CXR) was used to acquire imaging at baseline and throughout treatment to evaluate, identify, and monitor lung abnormalities (18). After images were acquired, analysis was performed by the radiologist at Landmark Hospital and CXR reports were generated to outline the clinical findings.

Biomarker Testing

Biomarker collection occurred at 0, 4, 6, 8, 14, 21, and 28 days after initiation of Zofin therapy to assess for concentration of D-Dimer, CRP, IL2, IL6, and TNFα. D-Dimer and CRP measurements were performed at the Athens Regional Labs, while IL2, IL6, and TNFα were measured by Quest Diagnostics.

RESULTS

Follow up of ICU Clinical Status

The clinical status of the patients was monitored for 28 days post-initiation of Zofin therapy. After treatment, the respiratory status of the patients improved and stabilized. CU#1 respiratory status improved throughout the 28 days, changing from a 21% oxygen T-collar to room air with no oxygen therapy requirement, CU#2 respiratory status improved during the 28 days with a transition from mechanical ventilation to non-mechanical ventilation, and the respiratory status of CU#3 improved 4 days post-treatment with decannulation and subsequent removal from oxygen therapy by day 14. Furthermore, all patients were transferred out of ICU status to the step-down unit within the 28-day period (**Table 1**). Patient CU#1 was discharged from the hospital 29 days post-treatment initiation and patient CU#3 was discharged from the hospital 26 days post-treatment initiation. Patient CU#2 remained in the hospital as she had experienced setbacks due to aspiration but was controlled and stable in the step-down unit with ventilation and hemodialysis.

TABLE 2 | SOFA score parameters.

Patient	SOFA Score	PaO_2/FiO_2	Platelet Count ($\times 10^3$)	Bilirubin (mg/dL)	Glasgow score	MAP(mmHg)	Creatinine (mg/dL)
CU#1	Day 0: 3	Day 0: 342	Day 0: 310	Day 0: 0.5	Day 0: 10–12	Day 0: 77–103	Day 0: 0.78
	Day 4: 2	Day 4: 457	Day 4: 364	Day 4: 0.7	Day 4: 10–12	Day 4: 65–86	Day 4: 1.10
	Day 6: 1	Day 6: 466	Day 6: 340	Day 6: 0.6	Day 6: 13–14	Day 6: 92–96	Day 6: 0.89
	Day 8: 1	Day 8: 476	Day 8: 329	Day 8: 0.6	Day 8: 13–14	Day 8: 74–94	Day 8: 0.98
	Day 14: 0	Day 14: 462	Day 14: 405	Day 14: 0.6	Day 14: 15	Day 14: 79	Day 14: 0.89
	Day 21: 0	Day 21: 471	Day 21: 423	Day 21: 0.7	Day 21: 15	Day 21: 75	Day 21: 0.94
	Day 28: 0	Day 28: 471	Day 28: 342	Day 28: 0.6	Day 28: 15	Day 28: 95	Day 28: 0.97
CU#2	Day 0: 7	Day 0: 242	Day 0: 183	Day 0: 0.4	Day 0: 10–12	Day 0: 62–94	Day 0: 3.55
	Day 4: 7	Day 4: 268	Day 4: 204	Day 4: 0.3	Day 4: 10–12	Day 4: 76–92	Day 4: 3.74
	Day 6: 4	Day 6: 280	Day 6: 190	Day 6: 0.5	Day 6: 15	Day 6: 85–95	Day 6: 1.98
	Day 8: 3	Day 8: 232	Day 8: 201	Day 8: 0.4	Day 8: 15	Day 8: 73–96	Day 8: 1.79
	Day 14: 4	Day 14: 245	Day 14: 214	Day 14: 0.3	Day 14: 15	Day 14: 93	Day 14: 3.28
	Day 21: 4	Day 21: 240	Day 21: 201	Day 21: 0.3	Day 21: 15	Day 21: 82	Day 21: 2.29
	Day 28: 4	Day 28: 271	Day 28: 269	Day 28: 0.3	Day 28: 15	Day 28: >70	Day 28: 2.27
CU#3	Day 0: 4	Day 0: 350	Day 0: 428	Day 0: 0.3	Day 0: 15	Day 0: 90	Day 0: 3.96
	Day 4: 3	Day 4: 466	Day 4: 540	Day 4: 0.3	Day 4: 15	Day 4: 89	Day 4: 4.16
	Day 6: –	Day 6: –	Day 6: –	Day 6: –	Day 6: –	Day 6: –	Day 6: –
	Day 8: 3	Day 8: 471	Day 8: 723	Day 8: 0.6	Day 8: 15	Day 8: 99	Day 8: 5.2
	Day 14: 2	Day 14: 471	Day 14: 507	Day 14: 0.3	Day 14: 15	Day 14: 85	Day 14: 2.73
	Day 21: 0	Day 21: 467	Day 21: 294	Day 21: 0.3	Day 21: 15	Day 21: 84	Day 21: 1.24
	Day 28: –	Day 28: –	Day 28: –	Day 28: –	Day 28: –	Day 28: –	Day 28: –

–, sample not taken.

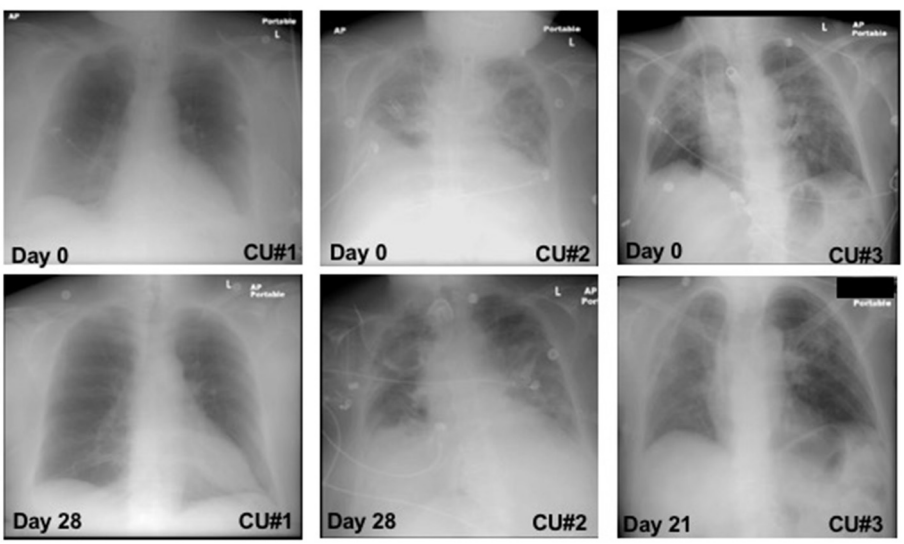

FIGURE 1 | Chest-X ray images. Chest-X ray images of patient CU#1 at day 0 and day 28 (Left). Chest-X ray images of patient CU#2 at day 0 and day 28 (Middle). Chest-X ray images of patient CU#3 at day 0 and day 21 (Right).

Effect of Zofin on SOFA Score

Improvement in SOFA score was found in all patients. SOFA score calculations decreased from 3 to 0 in CU#1 within 28 days, from 7 to 4 in CU#2 within 28 days, and from 4 to 0 in CU#3 within 21 days (**Table 2**). Assessment of the individual parameters used to calculate SOFA score showed improvements in PaO_2/FiO_2 and Glasgow score for CU#1, improvements in Glasgow score and creatinine levels for CU#2, and improvements in PaO_2/FiO_2 and creatinine levels for CU#3 (**Table 2**). Platelet count, bilirubin, and MAP measurements remained stable throughout the treatment course.

TABLE 3 | Inflammatory biomarkers.

Patient	D-Dimer (ng/mL)	CRP(mg/dL)	IL6 (pg/mL)	IL2(pg/mL)	TNFα (pg/mL)
CU#1	Day 0: 1,033	Day 0: 2.66	Day 0: 19.39	Day 0: <38.0	Day 0: 0.95
	Day 4: 1,113	Day 4: >8.00	Day 4: 50.83	Day 4: <38.0	Day 4: 2.06
	Day 6: 1,069	Day 6: >8.00	Day 6: 51.95	Day 6: <38.0	Day 6: 2.08
	Day 8: 1,165	Day 8: >8.00	Day 8: 40.29	Day 8: <38.0	Day 8: 2.29
	Day 14: 1,122	Day 14: 1.28	Day 14: 8.23	Day 14: <38.0	Day 14: 2.58
	Day 21: 963	Day 21: 0.93	Day 21: 7.70	Day 21: <38.0	Day 21: 2.97
	Day 28: 599	Day 28: 0.70	Day 28: 6.43	Day 28: <38.0	Day 28: 1.36
CU#2	Day 0: 5,871	Day 0: 1.74	Day 0: 23.62	Day 0: <38.0	Day 0: 1.77
	Day 4: 4,305	Day 4: 1.79	Day 4: 22.17	Day 4: <38.0	Day 4: 1.99
	Day 6: 2,377	Day 6: 2.49	Day 6: –	Day 6: –	Day 6: –
	Day 8: 1,980	Day 8: 4.19	Day 8: 32.82	Day 8: <38.0	Day 8: 1.69
	Day 14: 3,444	Day 14: 1.04	Day 14: 17.79	Day 14: <38.0	Day 14: 2.13
	Day 21: 3,627	Day 21: 0.59	Day 21: 16.57	Day 21: <38.0	Day 21: 1.90
	Day 28: 4,468	Day 28: 0.35	Day 28: 13.58	Day 28: <38.0	Day 28: 2.21
CU#3	Day 0: 1,098	Day 0: 6.48	Day 0: 29.78	Day 0: <38.0	Day 0: 7.85
	Day 4: 1,130	Day 4: 2.15	Day 4: 28.71	Day 4: <38.0	Day 4: 6.51
	Day 6: –	Day 6: –	Day 6: –	Day 6: –	Day 6: –
	Day 8: 1,082	Day 8: 1.98	Day 8: 1,259	Day 8: <38.0	Day 8: >10
	Day 14: 1,647	Day 14: 2.79	Day 14: 7.9	Day 14: <38.0	Day 14: 6.53
	Day 21: 828	Day 21: 0.18	Day 21: 7.12	Day 21: <38.0	Day 21: 4.67
	Day 28: –	Day 28: –	Day 28: –	Day 28: –	Day 28: –

–, sample not taken.

Effect of Zofin on Lung Imaging

CXR images were collected throughout the treatment and the changes from baseline to day 21 and 28 were observed and reported (**Figure 1**). CXR analysis of patient CU#1 displayed at baseline show an infiltrate present in the left lower lobe with no defined pleural fluid. After 28 days, CXR showed basilar, infrahilar air space opacity present bilaterally in the base of the lungs. CXR analysis of patient CU#2 displayed bilateral pulmonary disease at baseline. At day 28, CXR analysis showed small pleural effusions. CXR analysis of patient CU#3 displayed bilateral upper lobe infiltrate at baseline. At day 21, CXR analysis showed residual consolidation present in the left perihilar region. There was partial interval resolution of right upper lobe pneumonic consolidation.

Inflammatory Biomarker Assessment

Quantification of inflammatory biomarkers was completed at each testing time point (**Table 3**). There was a slight increase in TNFα for CU#1 within 28 days. CU#1 had an elevation in CRP and IL-6 that was attributed to bacteremia from an infected vein port at day 4, 6, and 8. However, levels of CRP and IL-6 began to drop below baseline by day 14 through day 28. Additionally, D-Dimer concentration decreased in this patient on day 28. CU#2 also showed a decrease in CRP and IL-6 levels by day 14 through day 28, however, TNFα and D-Dimer remained elevated. CU#3 showed high levels of inflammatory markers TNFα, IL-6, and D-Dimer up to day 8, however, declines in all markers were reported by day 21. Furthermore, CRP levels in CU#3 declined dramatically by day 21. IL-2 levels were below the detection level in all patients at all-time points.

DISCUSSION

These completed case studies are the first demonstrations of human amniotic fluid-derived nanoparticles as a safe and potentially efficacious therapeutic treatment to recover from complications induced by COVID-19 infection. The multi-dose administration of Zofin as a therapeutic approach for patients severely ill from COVID-19 was safe and well-tolerated, without the report of any serious adverse events. The molecular composition of Zofin, particularly the nanoparticle population that includes perinatal secreted extracellular vesicles and exosomes, has strong potential as a COVID-19 therapeutic (19). Extracellular and exosome-based therapeutics are beginning to be explored in the clinic and have quickly emerged as a promising therapeutic candidate due to the anti-inflammatory and tissue regenerative effects shown across various pre-clinical models (20–22). For example, the delivery of exosomal cargo to recipient macrophages stimulates M2 polarization that leads to the reduction of pro-inflammatory cytokine secretion (23). Similarly, exosome-mediated transfer of miRNA between immune cells may contribute to immune response at various cellular pathway levels, such as the suppression of pro-inflammatory response initiated in the presence of endotoxins (24). Based on this pre-clinical data, it is hypothesized that the immune modulatory effect of exosomes is particularly

useful in mitigating symptoms associated with COVID-19 infection, and to promote the induction of endogenous tissue repair (25).

In these three cases, we are limited by the absence of experimental controls. First, the absence of a placebo control group and administration of the therapy as open label does not allow for scientific proof of efficacy. Similarly, the combination of ongoing care with Zofin treatment makes it difficult to determine the extent of therapeutic efficacy derived solely from the therapeutic. Therefore, the precise therapeutic value of Zofin can only be speculated based on the collected data post-treatment. With these limitations in mind, the primary take-away from these single patient cases is focused on safety, accessibility, and feasibility. As a new biologic, the primary objective of small, single patient studies is to demonstrate therapeutic safety. Safety was strictly monitored during product infusion and throughout the following days by the treating physician and onsite nurses. There was no reported appearance of any adverse reactions or adverse events. Therefore, Zofin was determined to be safe for the treated patients. Furthermore, these first completed studies support the accessibility and feasibility of the therapeutic. Zofin is an acellular biologic that requires minimal training and specialized equipment to ship, prepare for infusion, and administration. The product can be stored in standard medical freezers (below -20°C) and can be prepared for infusion by the onsite hospital pharmacist. There were no issues with drug handling and preparation at the hospital site. This experience is an important step toward the development of a therapy with wide-spread distribution potential and rapid incorporation into clinics.

Despite the experimental limitations, analysis of the collective data in all patients showed a reduction of SOFA score, improvement in ICU clinical status, and respiratory improvements. To date, the patient's laboratory results have shown improvements with decreased inflammatory biomarkers. Because of the small patient population and the lack of a placebo control, it is premature to determine the potential mechanism of action for the observed clinical effects. However, inflammatory biomarkers CRP and IL-6 decreased in all patients, similarly to other reported cases utilizing cell therapies, thus allowing for the further investigation of an anti-inflammatory effect (26, 27). All data was reported by the treating physician and nursing staff. Patients were not asked to share their perspective of the treatment outcome.

The clinical features of patient CU#1 improved considerably with lungs improving on CXR and both mental status and kidney function returning to normal. Respiratory function of this patient improved 21 days post-treatment, transitioning from a 21% T-collar to room air PMV and decannulation on day 26, representing a considerable achievement for this patient demographic. Inflammatory marker status of this patient, IL6 and CRP, improved after the 14-day time point. The patient further improved to hospital discharge after 29 days post-treatment initiation.

The clinical features of patient CU#2 systemically improved, including respiratory function, during the treatment time course. The patient transitioned from CPAP 5 PS 10 30% ventilation to 30% T-Collar ventilation by day 28 and the acute delirium improved. This patient sustained acute kidney injury and required regular hemodialysis during the study period.

After receiving Zofin, patient CU#3 displayed rapid improvement in respiratory function, with a complete decannulation from oxygen therapy by day 4. The patient had a complete recovery of renal function, had decreased creatinine concentration levels, and was removed from hemodialysis by day 17. CU#3 was discharged 26 days post-treatment initiation.

Our positive experience with these three patients further warrants placebo-controlled testing to determine the therapeutic effects of Zofin in this patient population. Organicell Regenerative Medicine is currently conducting the first multicenter, randomized, double-blinded, placebo-controlled phase I/II clinical trial to test Zofin in COVID-19 patients with moderate to severe Acute Respiratory Distress Syndrome.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by letters of acknowledgment by Independent Review Board-Western Institutional Review Board. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MM: study design, data interpretation, writing, figures. MB: study design, data interpretation, writing, data analysis, literature search, figures. AS and MS: patient care, data collection, data interpretation. WK and AM: study design. KV: data collection. GH: data collection, data analysis, figures, writing. DS: study design, writing, product manufacturing. ZA, IS, and JM: study design, product manufacturing. GS: study design, data analysis, data interpretation, writing. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: MM, AM, and GS reports personal fees and other from Organicell Regenerative Medicine, Inc., outside the submitted work. In addition, MM has a patent COMPOSITIONS COMPRISING NANOPARTICLES, METHOD OF MAKING AND USES THEREOF pending. MB, GH, DS, ZA, IS, and JM report personal fees from Organicell Regenerative Medicine, Inc., outside the submitted work. WK is a medical advisor to Organicell Regenerative Medicine.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Clinical Characteristics of Severe COVID-19 Patients Admitted to an Intensive Care Unit in Lombardy During the Italian Pandemic

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Italy was one of the worst affected European countries during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. More than 50% of Italian cases occurred in the northern region of Lombardy, where the saturation of health services between March and April 2020 forced hospitals to allocate patients according to available resources. Eighteen severe coronavirus disease 2019 (COVID-19) patients were admitted to our hospital needing intensive support. Given the disease fatality, we investigated the patients' characteristics to identify mortality predictors. We counted seven deaths from multiple organ failure, two from septic shock, and two from collapsed lungs. The maximum case fatality was observed in patients who contracted SARS-CoV-2 in hospitals. The fatal outcome was associated with the following baseline characteristics: polymorbidity (OR 2.519, $p = 0.048$), low body mass index (OR 2.288, $p = 0.031$), low hemoglobin (OR 3.012, $p = 0.046$), and antithrombin III (OR 1.172, $p = 0.048$), along with a worsening of PaO_2/FiO_2 ratio in the first 72 h after admission (OR 1.067, $p = 0.031$). The occurrence of co-infections during hospitalization was associated with a longer need for intensive care (B = 4.511, $p = 0.001$). More information is needed to inform intensive care for patients with severe COVID-19, but our findings would certainly contribute to shed some light on this unpredictable and multifaceted disease.

Keywords: SARS-CoV-2, COVID-19, infection, intensive care, intubation, systemic inflammatory response syndrome, sepsis, anesthesia

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a respiratory virus that primarily affects the lungs of the human host and that causes, in susceptible individuals, an unrestrained response of the immune system, respiratory failure, cardiovascular system damage, neuropsychiatric manifestations, and multiple organ injuries (1–4). Since the first outbreak testimony in China at the end of the year 2019, the apparent disease termed coronavirus disease 2019 (COVID-19) had a large-scale spread within a few months. Among the European countries, Italy was the first to confront the worst infection situation, and it has been for many weeks the

nation most affected, with hundreds of deaths being testified every day. About 60,000 total deaths have been presently confirmed (WHO weekly epidemiological update, 8 December 2020) and over half of all losses having occurred in the northern region of Lombardy, in many respects considered the epicenter of the Italian economic and industrial activity. The number of new cases has been progressively decreasing since May 2020, but at the peak of the emergency scenario in March–April 2020, all the major hospitals in northern Italy were forced to cope with this infection, rapidly corroborating the saturation of the health services (5). Along with the consistent traumatic injuries, patients with severe COVID-19 overflowing from the surrounding clinics were transferred to our hospital in Lombardy (6). In critically ill COVID-19 patients, it is a fact that respiration support saves lives, but reports from the United States, Canada, United Kingdom, and China have observed survival rates ranging from 15 to 97% (7–11), with the dissimilar signs and biochemical fluctuations possibly depending upon the variety of environmental factors and ethnicity (12, 13). Given the need for better characterization of severe COVID-19 patients in our Italian context, the aim of this study is to describe albeit retrospectively the clinical and biochemical characteristics of the COVID-19 patients admitted to the intensive care unit (ICU) of our hospital.

MATERIALS AND METHODS

Patients admitted to our hospital who resulted positive for SARS-CoV-2 have been categorized according to a 4-level classification: level 0 (asymptomatic, the patient should not be hospitalized), level 1 (mild symptoms, pharyngodynia, dry cough, fever), level 2 (moderate symptoms, high fever, persistent dry cough, asthenia, dyspnea, requires non-invasive oxygen support, may require intensive care), and level 3 (severe symptoms, invasive oxygen therapy, requires access to intensive care). This COVID-19 classification, together with the score of the Sequential Organ Failure Assessment (SOFA), the Charlson Comorbidity Index (CCI) (14), and the other clinical data, was extracted from the electronic case report form for all patients admitted to the ICU between March and April 2020. Biochemical parameters comprised routine coagulation parameters (activated partial thromboplastin activity and ratio, prothrombin activity and international normalized ratio, antithrombin III, thrombocyte count), inflammatory markers (fibrinogen, C-reactive protein, procalcitonin), injury factors (amylase, creatine phosphokinase, lactate dehydrogenase, γ-glutamyl transpeptidase, aspartate aminotransferase, alanine aminotransferase), immune response cells (neutrophils, lymphocytes, monocytes, eosinophils, basophils), proteins (hemoglobin, albumin, creatinine, urea, bilirubin), and minerals (calcium, chloride, phosphorus, magnesium, potassium, sodium). For each parameter, the value at ICU admission, the 72-h mean (the mean in the first 3 days), the 48-h trend (the difference between the value on day 2 and 1), and the 72-h trend (the difference between the value on day 3 and 1) were calculated. The presence of any infection from bronchial aspirates/bronchoalveolar lavage, blood, or urine was arbitrarily coded 1 point, with the co-occurrence of infections in multiple districts being coded as the sum of points (e.g., the presence of a urinary tract infection = 1 point, whereas a urinary tract infection plus lung infection = 2 points).

At baseline, the potential difference between biochemical and respiratory features of patients with hospital-acquired vs. parental-acquired infection was investigated by using paired samples *t*-test for normally distributed continuous values or Mann–Whitney–Wilcoxon (MWW) signed-rank test for skewed continuous values. Skewness was defined by the Shapiro–Wilk test $p < 0.05$, with the 72-h trend of amylase and potassium being the only variables with no normal distribution. Subsequently, the CCI, the body mass index (BMI), the respiratory parameters (PaO_2/FiO_2 ratio = P/F; the positive end-expiratory pressure), and all biochemical variables at the 1st day of ICU admission, the 72-h means, and the trends in the first 72 h were associated with the binary clinical outcome (survival:death) in the whole cohort through logistic regression. The length of ICU stay combined with the survival in each outcome group was analyzed through separated linear regressions with the occurrence of infections and with the 72-h mean, the 48-h trend, and the 72-h trend of respiratory parameters. All tests were 2-tailed and performed by using IBM SPSS Statistics 22. The raw data used to support the findings of this study are included within the **Supplementary Material** as a Microsoft Excel worksheet.

RESULTS

Thirteen males and five females with severe COVID-19 aged 67.77 ± 9.92 years old were admitted to the ICU of our hospital in March–April 2020 for intensive care support, and 11 of them were deceased for COVID-19-associated complications. At admission, 17 patients were categorized as level 3 COVID-19 severity and were all subjected to invasive oxygen therapy with either oropharyngeal tube or tracheostomy, whereas one patient was classified as an upper level 2 patient since he maintained respiratory autonomy through the helmet. Most patients suffered from co-existing conditions, with five patients being classified as nosocomial infected patients (see **Table 1** for details).

Compared with parental-acquired infections, the hospital-acquired infection patients had higher CCI at admission (5.60 vs. 3.46, *t*-test $p = 0.033$), lower baseline positive end-expiratory pressure (11.00 vs. 14.87 cm H_2O, *t*-test $p = 0.012$), lower 72-h mean of positive end-expiratory pressure (10.87 vs. 14.81 cm H_2O, *t*-test $p = 0.014$), higher 72-h mean of thromboplastin activity (35.2 vs. 28.46, *t*-test $p = 0.013$), higher 72-h mean of thromboplastin ratio (1.25 vs. 1.02, *t*-test $p = 0.006$), lower antithrombin III at 48-h and 72-h trends (−1.00 vs. 8.77%, *t*-test $p = 0.005$ and −5.40 vs. 9.08%, *t*-test $p = 0.021$), lower baseline fibrinogen (441.40 vs. 647.00 mg/dl, *t*-test $p = 0.040$), lower 72-h trend of amylase (−34.60 vs. −11.00 IU/l, MWW $p = 0.035$), lower hemoglobin at admission and 72-h mean (9.50 vs. 11.75 mg/dl, *t*-test $p = 0.0004$ and 9.26 vs. 11.71 mg/dl, *t*-test $p = 0.0002$), lower 48-h trend of albumin (−0.22 vs. −0.01 g/dl, *t*-test $p = 0.046$), lower potassium at admission and 72-h mean (3.84 vs. 4.44 mmol/l, MWW $p = 0.009$ and 3.93 vs. 4.45 mmol/l, *t*-test $p = 0.006$).

TABLE 1 | Baseline and outcome data of severe COVID-19 patients admitted to our hospital for intensive care support during the Italian pandemic of 2020.

Descriptors	Severe COVID-19 patients (*N* = 18)
Demographics	
Ethnicity	Caucasian
Age (years)	67.77 ± 9.92 (43.66; 81.10)
Gender (male:female)	13:5
Admission (month)	March–April
Disease severity	
SOFA	6.67 ± 2.22
CCI	4.06 ± 1.95
Hospital-acquired	5
Parental-acquired	14
Level 0	–
Level 1	–
Level 2	1
Level 3	17
Clinical outcome	
ICU stay (days)	17.17 ± 7.18 (7.00; 35.00)
Discharged (*n*)	7
Deceased (*n*)	11

SOFA, Sequential Organ Failure Assessment; CCI, Charlson Comorbidity Index (scores 1–2 = mild; scores 3–4 = moderate; scores ≥5 = severe), COVID-19 level of severity (level 0 = asymptomatic, the patient should not be hospitalized; level 1 = mild symptoms, pharyngodynia, dry cough, fever; level 2 = moderate symptoms, high fever, persistent dry cough, asthenia, dyspnea, requires non-invasive oxygen support, may require intensive care; level 3 = severe symptoms, invasive oxygen therapy, requires access to intensive care); ICU, intensive care unit.

Concerning the survival prediction in the whole cohort, the higher was the baseline BMI (OR 0.437, $p = 0.031$), antithrombin III (OR 0.853, $p = 0.048$), and hemoglobin (OR 0.332, $p = 0.046$), the lower was the risk of death. Conversely, the higher was the polymorbidity represented by a high CCI, the greater was the risk for adverse outcome (OR 2.519, $p = 0.048$). Those patients who survived vs. those who deceased had these baseline predictors of 30.11 ± 3.89 vs. 24.50 ± 2.31 kg/m^2 for BMI (t-test $p = 0.001$), a circulating antithrombin III of 96.71 ± 14.99 vs. 72.73 ± 13.14% (t-test $p = 0.003$), hemoglobin of 12.03 ± 1.09 vs. 10.55 ± 1.30 mg/dl (t-test $p = 0.024$), and a CCI of 2.71 ± 1.89 vs. 4.91 ± 1.51 (t-test $p = 0.015$). No other baseline variables were found to be associated with the survival.

Considering the 48-h and 72-h trends of the collected variables, only the negative 72-h trend of P/F was found to be predictive of fatal outcome (OR 1.067, $p = 0.031$). Patients who survived had a 72-h trend of P/F of +25.34 ± 25.14 vs. −13.23 ± 24.02 for those who deceased (t-test $p = 0.005$). Concerning the length of ICU stay, the non-survivors needed intensive support for 16.00 ± 5.31 days, whereas the survivors stayed in the ICU for 19.00 ± 9.63 days. No respiratory parameters were found to be associated with the days of ICU stay. Conversely, the occurrence of infections resulted to be predictive of the length of ICU stay in the whole cohort (see **Figure 1** for details), with B being 4.656 ($p = 0.0004$; 95% CI 2.466:6.846).

DISCUSSION

We have presented the main clinical and biochemical features of 18 patients with severe COVID-19 that were managed in our ICU during the SARS-CoV-2 pandemic in Italy. The demographic descriptors were in line with the literature evidence, being older males the individuals more prone to both being infected and encountering severe consequences of COVID-19 (15). In addition, we found the highest potential for casualty from nosocomial infections, meaning that the infectious cross-contamination affecting already critical patients, for example, surgical patients, could represent an exponential risk for fatal consequences (16).

The baseline clinical descriptor CCI was found to be associated with ICU death. Undeniably, a common denominator of patients with SARS-CoV-2 is known to be the co-existence of multiple conditions, especially cardiovascular diseases (17). The common underlying conditions in the totality of casualties in Italy have been hypertension in 66.8%, type 2 diabetes in 30.0%, and ischemic heart disease in 27.6% (Italian SARS-CoV-2 Surveillance Group, 25 June 2020). Similarly, our cohort comprised hypertension in 11 (61.11%), type 2 diabetes in 5 (27.8%), and other cardiovascular conditions, such as arrhythmia and vascular diseases, in four cases (22.2%). The BMI, antithrombin III, and hemoglobin at admission resulted to be associated with the risk of death. However, the small sample size of our patients limits the generalization of these parameters beyond the context of our study group. Nevertheless, some evidences in the literature are in line with our observations. A high BMI in older adults is known to be protective against adverse events (18), and the human host is known to face a protracted inflammatory status along with a rapid emptying of body reservoirs during any infective complication (19). As a result, a lower BMI in COVID-19 was associated with ICU mortality in a multiethnic population from the United States (7). Furthermore, decreased hemoglobin in non-survivors is suggested to be associated with SARS-CoV-2 interference with iron metabolism and mimicking of hepcidin roles (20, 21), the latter being an important regulator of oxygen supply (22). Concerning antithrombin III, low plasma concentrations were found in Chinese patients who deceased for COVID-19-associated complications (23). Importantly, the intensive care for our patients comprised equivalent respiration, hydration, nutritional, and pharmacological support with antiviral, anti-inflammatory, antiplatelet, and immunosuppressive drugs, but contrariwise covered a different anticoagulant therapy with low-molecular-weight-heparin (LMWH). The anticoagulant therapy was in fact increased from 4,000 to 6,000 IU of enoxaparin every 12 h after the first literature sheds evidence highlighting the importance of thromboembolic prevention in COVID-19. Antithrombin III is known to be crucial for heparin activity and Xa binding, and low circulating levels are associated with a high risk of thromboembolic events. Still, there

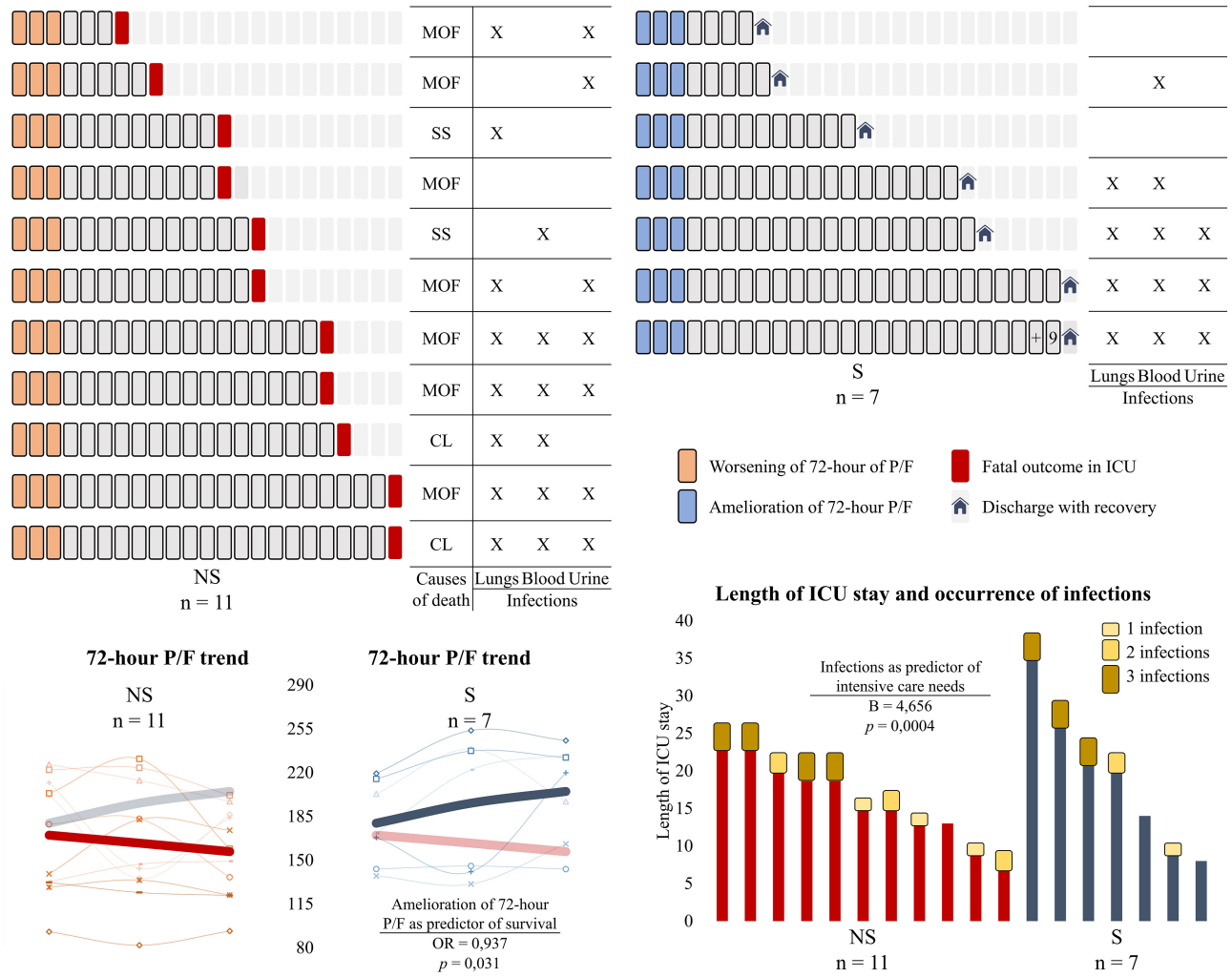

FIGURE 1 | Days of intensive care, survival outcomes, the occurrence of infections, and the 72-h trend of PaO_2/FiO_2 in severe COVID-19 patients admitted to the intensive care unit (ICU). Above are represented the length of ICU stay for each patient, with a square corresponding to a day. Patients have been divided into two groups according to the clinical outcome (non-survivors on the left and survivors on the right). The causes of death for the non-survivors are shown in the columns on the left, with the occurring infections being represented for both groups. Below are depicted the line graphs of the 72-h trend of PaO_2/FiO_2 ratio and the bar graphs of the days of ICU stay combined with the occurrence of infections. The bold trends in the line graphs represent the average trend of the parameter of interest, with the variable of the other group being represented as nuanced for easier comparison. In our cohort of severe COVID-19 patients admitted to the ICU, the amelioration of the PaO_2/FiO_2 in the first 3 days was predictive of survival (OR and *p*-value are shown), whereas the occurrence of infections during the hospitalization was predictive of intensive care needs (B and *p*-value are shown). NS, non-survivors; S, survivors; MOF, multiple organ failure; SS, septic shock; CL, collapsed lungs; PaO_2/FiO_2 ratio, P/F.

is no consensus about the proper pharmacological therapy for COVID-19, but narrow indications support the use of high pharmacological doses of LMWH and treatment with hyperimmune serums (24–26).

The trend of P/F in the first 72 h was a good predictor of clinical outcome, with the negative trend among the non-survivors possibly being ascribed to a late disease stage and therefore to increased alveolar damage. The positive trend in survivors could have also mirrored a good adaptive response to mechanical ventilation and intensive care that hence allowed a discharge with recovery. A significantly better P/F ratio at admission was also observed in patients from the United States who survived in the ICU (7), and its early improvement was associated with discharge with recovery in another Italian cohort (27). Elevated markers of liver injury, high C-reactive protein, and low lymphocytes at admission were associated with adverse outcomes in Chinese patients with COVID-19 (28, 29), but we found no significant changes of the abovementioned parameters possibly associated with medication concealing. The occurrence and the cumulative value of identified co-infections during hospitalization were positively associated with longer ICU stay in both survivors and non-survivors, and this may be linked with the disruption of host defenses that are no longer able to prevent pathogen migrations (30, 31).

Although our patients were relatively young individuals (mean age 67.77 ± 9.92 years), the incidence of mortality of 61.11% was higher than some previous reports, thus certainly contributing to reducing the ICU stay of non-survivors of 3 days less than the average survivors' length of stay. The great case fatality rate could be due to the co-existence of negative prognostic factors, such as polymorbidity, low BMI, and low hemoglobin. Furthermore, both the respiratory features (worsening of 72-h P/F) and the coagulation abnormalities (low antithrombin III) at admission could be indicative of an advanced stage of the disease. More information will be needed to inform intensive care for these challenging patients and therefore characterize both the unpredictable nature of SARS-CoV-2 and the multifaceted features of COVID-19.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MB, TC, FP, and MM collected the clinical data and managed the database. MB analyzed the data and wrote the first draft of the manuscript. TC, FP, MM, MP, EDV, GB, and PP revised the first draft and contributed to the manuscript sections. All authors contributed to the manuscript revision and read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.582896/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association Between Respiratory Alkalosis and the Prognosis of COVID-19 Patients

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Aim: The aim of the study was to describe the clinical characteristics of patients with or without respiratory alkalosis, and analyze the relationship of respiratory alkalosis and the outcome of adult coronavirus disease 2019 (COVID-19) patients.

Methods: Clinical and laboratory data of adult COVID-19 patients in a single center in China, were retrospectively collected and analyzed. The Kaplan-Meier (KM) curve and cox regression were adopted to analyze the association between respiratory alkalosis and prognosis of COVID-19 patients.

Results: Of 230 adult COVID-19 patients, 66 patients (28.7%) had respiratory alkalosis on admission. Of 66 patients, the median age was 53 years old (range, 21–84 years), and 43 (65.2%) were female. Compared with those without respiratory alkalosis, patients with respiratory alkalosis were significantly older ($P = 0.002$), had a higher proportion of female ($P = 0.004$), and showed higher ratios of underlying diseases including hypertension ($P = 0.023$) and cardiovascular disease ($P = 0.028$). Moreover, they demonstrated higher proportion of severe events ($P = 0.001$). Patients with respiratory alkalosis had a higher possibility of developing severe events compared with those without respiratory alkalosis (Log Rank $P = 0.001$). After adjusting for gender, age, and comorbidities, patients with respiratory alkalosis still showed significantly elevated risks of developing to severe cases (HR 2.445, 95% CI 1.307–4.571, $P = 0.005$) using cox regression analyses.

Conclusions: Respiratory alkalosis as a common acid—base disorder in COVID-19 patients, was associated with a higher risk of developing severe event.

Keywords: COVID-19, respiratory alkalosis, acid-base disorder, severity, biomarker

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was first reported in Wuhan, China, at December 2019 (1–5), has spread widely and rapidly around the world (6, 7). The World Health Organization (WHO) has declared COVID-19 as a global pandemic (8). How to decrease mortality and improve the prognosis of COVID-19 has become a global problem.

Respiratory alkalosis as the most common acid—base imbalance in clinical practice, is generally induced by a process involving hyperventilation, which include hypoxemic causes, pulmonary diseases and central diseases. Pulmonary diseases include pneumonia, acute asthma and chronic obstructive pulmonary disease (COPD) exacerbations (9, 10). Furthermore, respiratory alkalosis is considered to be associated with adverse outcomes (11). Some COVID-19 patients showed hypoxemia and dyspnea, but the incidence of respiratory acid-base disorders and their relations with the prognosis of COVID-19 remained unknown. To address this question, we sought to present the clinical characteristics of COVID-19 patients with or without respiratory alkalosis, and analyze the association between respiratory alkalosis and the outcomes of COVID-19 patients.

MATERIALS AND METHODS

Study Design and Participants

This case series was approved by The Institutional Ethics Board of The Second Xiangya Hospital of Central South University (No. 2020001). Adult laboratory-confirmed COVID-19 patients admitted to Public Health Treatment Center of Changsha, China from January 17 to March 14, 2020, were enrolled.

Primary and Second Endpoints

The primary endpoint was the severity of COVID-19, and the second endpoints were the mortality, virus shedding time, and length of hospital stay. Severe cases of COVID-19 were defined as meeting any of the following criteria: (1) respiratory rate $\geq$ 30 /min; (2) oxygen saturation $<$ 93%; (3) $PaO_2/FiO_2 \leq 300$ mmHg; (4) lung lesions progressed >50% within 24–48 h; (5) mechanical ventilation was implemented; (6) shock; (7) intensive care was required because of other organ dysfunction (12). At least two consecutive nucleic acid tests were performed after remission. Virus shedding duration was defined as time between symptom onset (or the diagnosed date for asymptomatic patients) and the first negative sample of SARS-CoV-2 without any positive sample thereafter.

Data Collection

The medical records of patients were carefully collected by two authors, separately. Demographic, symptoms, underlying disease, laboratory, and outcome data were collected. All patients underwent blood gas analysis within the first day after admission and the first blood gas analysis results after admission were collected. In case of PH $>$ 7.45, $PaCO_2 < 35$ mmHg in arterial blood gas was considered as respiratory alkalosis, and in case of pH $<$ 7.35, $PaCO_2 > 45$ mmHg was defined as respiratory acidosis (13).

Statistical Analysis

We used median with range and Mann-Whitney-test to depict and analyze the data. The χ^2-test or Fisher's exact-test was utilized to compare the differences of the categorical variables. Baseline variables with significant differences between respiratory alkalosis and no respiratory alkalosis groups were included in the univariate and multivariate analyses. The Kaplan-Meier (KM) curve and the Log Rank-test were applied to estimate the cumulative proportion of severe events in non-severe patients after admission according to the respiratory alkalosis groups. Multivariate analysis was performed using the cox regression model to determine the association between respiratory alkalosis and the severe event with the hazards ratio (HR) and 95% confidence interval (95% CI) being reported. All analyses were performed using IBM SPSS version 26 software.

TABLE 1 | Baseline characteristics of COVID-19 patients with or without respiratory alkalosis.

	Respiratory alkalosis (n = 66)	No respiratory alkalosis (n = 164)	P-value
Sex (male/female)	23/43	92/72	**0.004**
Age, median (range), y	53 (21–84)	42 (19–82)	**0.002**
Comorbidity			
Hypertension (*n*, %)	16 (24.2)	20 (12.2)	**0.023**
Cardiovascular disease (*n*, %)	6 (9.1)	3 (1.8)	**0.028**
Diabetes (*n*, %)	6 (9.1)	9 (5.5)	0.480
Cerebrovascular disease (*n*, %)	3 (4.5)	3 (1.8)	0.358
Symptoms			
Fever (*n*, %)	58 (87.9)	117 (71.3)	**0.008**
Fatigue (*n*, %)	41 (62.1)	66 (40.2)	**0.003**
Cough (*n*, %)	55 (83.3)	134 (81.7)	0.771
Anorexia (*n*, %)	40 (60.6)	75 (45.7)	0.041
Chills (*n*, %)	9 (13.6)	20 (12.2)	0.766
Myalgia (*n*, %)	10 (15.2)	14 (8.5)	0.138
Dyspnea (*n*, %)	33 (50.0)	49 (29.9)	**0.004**
Expectoration (*n*, %)	34 (51.5)	72 (43.9)	0.295
Pharyngalgia (*n*, %)	9 (13.6)	21 (12.8)	0.756
Diarrhea (*n*, %)	16 (24.2)	37 (22.6)	0.784
Nausea (*n*, %)	12 (18.2)	18 (11.0)	0.142
Dizziness (*n*, %)	13 (19.7)	16 (9.8)	**0.040**
Headache (*n*, %)	12 (18.2)	19 (11.6)	0.185
Vomiting (*n*, %)	14 (21.2)	12 (7.3)	**0.003**
Abdominal pain (*n*, %)	4 (6.1)	4 (2.4)	0.338
Chest CT positive rate (*n*, %)	64 (97.0)	156 (95.1)	0.792
Chest CT with ground-glass change (*n*, %)	32 (48.5)	77 (47.0)	0.833
Severe cases (*n*, %)	22 (33.3)	23 (14.0)	**0.001**
Length of hospital stay, median (range), days	16 (5–40)	16 (5–41)	0.553
Virus shedding duration, median (range), days	17 (6–43)	19 (3–59)	0.458
Mortality (*n*, %)	2 (3.0)	0 (0)	0.081

$P < 0.05$ was considered statistically significant (marked in bold).
COVID-19, coronavirus disease 2019.

TABLE 2 | Laboratory findings of COVID-19 patients with or without respiratory alkalosis.

	Respiratory alkalosis ($n = 66$)	No respiratory alkalosis ($n = 164$)	*P*-value
White blood cell count, $\times 10^9$/L, median (range)	4.2 (0.8–10.4)	4.6 (1.5–13.4)	0.164
Lymphocyte count, $\times 10^9$/L, median (range)	0.9 (0.1–3.7)	1.2 (0.2–3.2)	**0.001**
Lymphocyte %, median (range)	24.0 (5.5–46.6)	27.5 (2.1–61.1)	**0.015**
Alanine aminotransferase, U/L, median (range)	22.4 (8.1–93.7)	18.8 (2.6–87.7)	**0.007**
Aspartate aminotransferase, U/L, median (range)	27.7 (15.1–82.1)	23.2 (2.0–78.8)	**0.000**
Total bilirubin, μmol/L, median (range)	10.4 (5.1–162.1)	11.0 (4.0–38.2)	0.873
C-reactive protein, mg/L, median (range)	24.0 (0.2–101.9)	12.0 (0.1–101.9)	**0.000**
Erythrocyte sedimentation rate, mm/h, median (range)	53.0 (3.0–143.0)	37.0 (1.0–114.0)	**0.012**
Procalcitonin, ≥0.05 ng/ml, No. (%)	24 (36.4)	39 (23.8)	0.053
Creatinine, μmol/L, median (range)	46.8 (20.6–110.3)	53.4 (21.9–255.7)	0.058
Creatine kinase, U/L, median (range)	68.4 (11.3–986.4)	76.1 (17.4–599.6)	0.882
Creatine kinase-MB, U/L, median (range)	10.1 (1.0–221.7)	9.5 (0.3–82.8)	0.758

P < 0.05 was considered statistically significant (marked in bold).
COVID-19, coronavirus disease 2019.

TABLE 3 | Multivariate Cox regression analysis for severe events of adult COVID-19 patients.

Variables	HR	95% confidence interval	*P*-value
Respiratory alkalosis	2.445	1.307–4.571	**0.005**
Age (≥60 y)	1.021	0.999–1.044	0.062
Gender (male)	1.973	1.056–3.588	**0.033**
Hypertension	1.927	0.946–3.924	0.071
Cardiovascular disease	1.355	0.493–3.719	0.556

P < 0.05 was considered statistically significant (marked in bold).
COVID-19, coronavirus disease 2019; HR, Hazard Ratio.

RESULTS

Two hundred and thirty adult patients with laboratory-confirmed SARS-CoV-2 infection by March 14, 2020, in Changsha, China, were included in our study, of whom none had respiratory acidosis and 66 patients (28.7%) had respiratory alkalosis on admission.

Of the 66 patients with respiratory alkalosis, the median age was 53 years old (range, 21–84 years), and 43 (65.2%) were women. Hypertension, diabetes and cardiovascular disease were the most common comorbidities. The most common symptoms were fever, cough, anorexia and fatigue. Most (97.0%) patients showed pulmonary exudative lesion in chest computed tomographic (CT) scan, of which 32 (48.5%) patients showed ground glass opacity in the lungs (**Table 1**).

Laboratory findings for patients with respiratory alkalosis were shown in **Table 2**. On admission, the medium number of white blood cell count, lymphocyte percentage and lymphocyte count were in the normal range. C-reactive protein and erythrocyte sedimentation rate significantly elevated. Median levels of indicators of liver, kidney and myocardial injury were not obviously abnormal.

Compared with patients without respiratory alkalosis, patients with respiratory alkalosis were significantly older and had a higher proportion of female. They also showed higher ratios of underlying diseases including hypertension and cardiovascular diseases. Additionally, they had lower lymphocyte proportion, decreased lymphocyte counts, as well as higher levels of C-reactive protein and erythrocyte sedimentation rate (**Table 2**). Most importantly, patients with respiratory alkalosis showed significantly higher proportion of severe events (**Table 1**).

Furthermore, patients with respiratory alkalosis had a higher possibility of developing severe events compared with those without respiratory alkalosis (Log Rank $P = 0.001$, **Figure 1**). After adjusting for gender, age and common comorbidities (cardiovascular disease and hypertension), patients with respiratory alkalosis still showed significantly elevated risks of developing to severe cases than those without respiratory alkalosis (HR 2.445, 95% CI 1.307–4.571, $P = 0.005$) (**Table 3**).

However, in terms of virus shedding duration and length of hospital stay, patients with respiratory alkalosis showed no obvious differences (**Table 1**). Because hyperventilation reactions due to hypoxia may be different from gender, age and comorbidities (14), we performed a subgroup analysis on these factors for virus shedding duration and length of hospital stay. Respiratory alkalosis seemed to have no effect on virus shedding duration and length of hospital stay in both men and women, as well as subgroups of common comorbidities. Moreover, subgroup analysis on age showed in non-elderly ($P = 0.045$) but not elderly patients demonstrated shorter virus shedding duration in patients with respiratory alkalosis than those without (**Table 4**).

DISCUSSION

To our knowledge, this is the first article to explore the respiratory acid-base situation of COVID-19 patients and evaluate the effect of respiratory alkalosis on the prognosis. About 28.7% patients presented respiratory alkalosis on admission, who were more likely to be severe and die. Meanwhile, respiratory alkalosis was significantly associated with the risk for severe events of COVID-19 patients.

Most (65.2%) COVID-19 patients with respiratory alkalosis were female, which is consistent with other studies. Previous studies showed PCO_2 was lower in women than men (15).

TABLE 4 | Subgroup analysis of influence of respiratory alkalosis on the virus shedding duration and length of hospital stay.

	Virus shedding duration (days)		*P*-value	Length of hospital stay (days)		*P*-value
	Respiratory alkalosis (*n* = 66)	No respiratory alkalosis (*n* = 164)		Respiratory alkalosis (*n* = 66)	No respiratory alkalosis (*n* = 164)	
Gender						
Male	15 (10–39)	18 (6–59)	0.369	13 (5–36)	16 (5–41)	0.221
Female	17 (6–43)	19 (3–53)	0.824	17 (5–40)	15.5 (5–40)	0.830
Age						
Elderly*	22 (9–43)	19.5 (4–43)	0.326	19 (6–40)	17 (6–37)	0.349
Non-elderly#	15 (6–39)	18 (3–59)	**0.045**	13 (5–35)	15 (5–41)	0.091
Hypertension						
No	16 (6–43)	19 (3–59)	0.473	15.5 (5–40)	15 (5–41)	0.665
Yes	18 (12–38)	18 (6–45)	0.648	16.5 (5–37)	19.5 (7–41)	0.336
Diabetes						
No	16.5 (6–43)	19 (3–59)	0.521	15.5 (5–40)	16 (5–41)	0.477
Yes	16.5 (9–34)	23 (6–43)	0.776	18 (6–32)	17 (7–30)	1.000
Cardiovascular diseases						
No	16 (6–43)	18 (3–59)	0.210	16 (5–40)	16 (5–41)	0.458
Yes	31 (21–39)	22 (19–29)	0.250	22 (12–35)	23 (19–27)	0.786

*P < 0.05 was considered statistically significant (marked in bold). *≥60 years, #<60 years.*
COVID-19, coronavirus disease 2019.

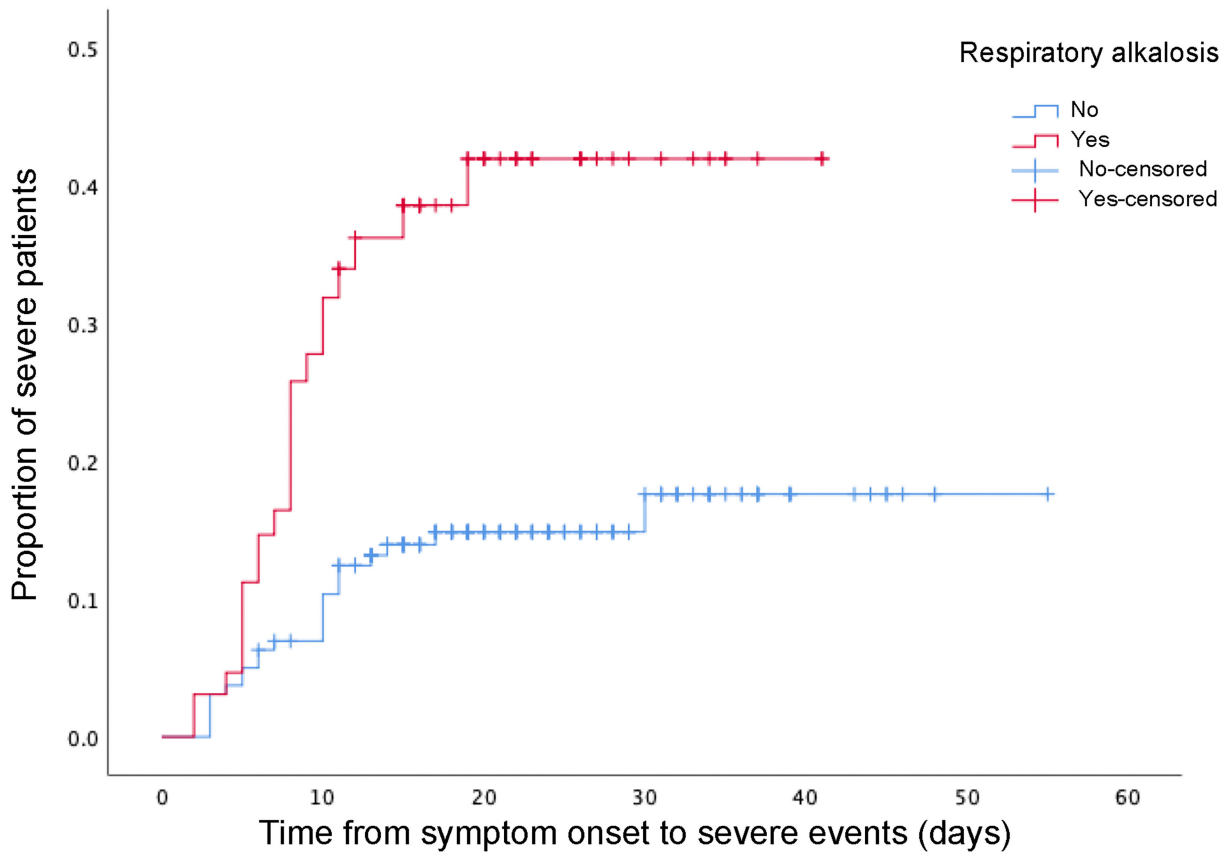

FIGURE 1 | The time-dependent risk of reaching to severe events in COVID-19 patients with or without respiratory alkalosis using Kaplan-Meier analysis and log rank-test. COVID-19, coronavirus disease 2019.

Compared to men, women were more prone to have a compensated respiratory alkalosis, which may be the role of hormones such as progesterone (14, 16). However, respiratory alkalosis was associated with severe events of COVID-19 patients both in male and female in this study.

In this study, COVID-19 patients with respiratory alkalosis had a higher risk of severe events, but the reason is not very clear. Generally, hypoxic stimulation leads to hyperventilation in an attempt to correct hypoxia at the expense of a CO_2 loss in pulmonary diseases (17). Although some patients did not show significant hypoxemia at the early stage, if respiratory alkalosis occurred, they may already have a compensatory hyperventilation and deteriorate soon. Therefore, we believe that COVID-19 patients with respiratory alkalosis need to be given adequate monitoring even though they did not show hypoxemia yet.

According to current reports (4, 18), deaths of COVID-19 patients mainly occur in severe cases, which indicates that the mortality of COVID-19 patients is closely related to the disease severity. Since there were only 2 deaths in this study, we did not perform association analysis on respiratory alkalosis and mortality, but the risk of developing severe event and respiratory alkalosis were significantly related. It suggests that respiratory alkalosis may be also a risk factor for death, but larger sample size studies are needed to verify this conclusion.

Our study has several limitations. First, some patients with respiratory alkalosis coexisted with other acid-base imbalances, which may lead some bias to the outcomes. In the future research, other acid-base imbalances also need to be studied in greater detail. Second, this study only focused on the acid-base status at the time of admission, and further analysis of the dynamic acid-base status may be needed in the future. Third, in general, most cases of respiratory alkalosis are secondary to hypoxia. However, this study did not include oxygenation index data, due to lack of some data, which may affect the analysis of the causes of respiratory alkalosis. Forth, this was a retrospectively single center study with a small sample size. Therefore, well-designed studies with large sample size were needed to demonstrate the conclusion.

CONCLUSIONS

To the best of our knowledge, this is the first report about respiratory acid-base imbalance in COVID-19 patients. As a common acid-base disorder in COVID-19 patients, respiratory alkalosis was associated with a higher possibility of developing severe events.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because they need permission from local health and disease control authorities. Requests to access the datasets should be directed to zhongyanjun@csu.edu.cn.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Institutional Ethics Board of The Second Xiangya Hospital of Central South University (No. 2020001). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

GWa and CW developed the study design and conducted the analyses. YZ interpreted the results, reviewed the study design, and performed the statistical analyses. QZ and BY acquired patient demographic and clinical data. JL, GWu, SW, and SZ participated in interpreting the clinical results and reviewed the manuscript. All authors have read and approved the final version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Medicine

BRIEF RESEARCH REPORT
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Mortality and Life-Sustaining Therapy Decisions in Patients With Cancer and Acute Respiratory Failure Due to COVID-19 or Other Causes: An Observational Study

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It is unknown if patients with cancer and acute respiratory failure due to COVID-19 have different clinical or cancer-related characteristics, decisions to forgo life-sustaining therapies (LST), and mortality compared to patients with cancer and acute respiratory failure due to other causes. In a cohort study, we tested the hypothesis that COVID-19 was associated with increased in-hospital mortality and decreased decisions to forgo LST in patients with cancer and acute respiratory failure. We employed two multivariate logistic regression models. Propensity score matching was employed as sensitivity analysis. We compared 382 patients without COVID-19 with 65 with COVID-19. Patients with COVID-19 had better performance status, less metastatic tumors, and progressive cancer. In-hospital mortality of patients with COVID-19 was lower compared with patients without COVID-19 (46.2 vs. 74.6%; $p < 0.01$). However, the cause of acute respiratory failure (COVID-19 or other causes) was not associated with increased in-hospital mortality [adjusted odds ratio (OR) 1.27 (0.55–2.93; 95% confidence interval, CI)] in the adjusted model. The percentage of patients with a decision to forgo LST was lower in patients with COVID-19 (15.4 vs. 36.1%; $p = 0.01$). However, COVID-19 was not associated with decisions to forgo LST [adjusted OR 1.21 (0.44–3.28; 95% CI)] in the adjusted model. The sensitivity analysis confirmed the primary analysis. In conclusion, COVID-19 was not associated with increased in-hospital mortality or decreased decisions to forgo LST in patients with cancer and acute respiratory failure. These patients had better performance status, less progressive cancer, less metastatic tumors, and less organ dysfunctions upon intensive care unit (ICU) admission than patients with acute respiratory failure due to other causes.

Keywords: cancer, respiratory insufficiency, COVID-19, intensive care unit, critical care outcomes

INTRODUCTION

Intensive care unit (ICU) admissions, acute respiratory failure (ARF), and poor outcomes are more common in patients with COVID-19 and cancer than in patients with COVID-19 without cancer (1, 2). Furthermore, patients with cancer are also susceptible to ARF due to other causes (3). It is unknown if patients with cancer and ARF due to COVID-19 (COVID-19 ARF) have different clinical characteristics, cancer-related characteristics, and in-hospital mortality compared to patients with cancer and ARF due to other causes (non-COVID-19 ARF).

Severe COVID-19 in patients with cancer could increase decisions to forgo life-sustaining therapies (LST) because COVID-19 is perceived as a high-mortality disease. By contrast, COVID-19 acute presentation and the worldwide commotion to save patients with COVID-19 might decrease the decision to forgo LST. COVID-19 impact on the decision to forgo LST is unknown in patients with cancer.

We tested the hypothesis that COVID-19 was associated with increased in-hospital mortality and decreased decisions to forgo LST in patients with cancer and ARF. We also compared clinical and cancer-related characteristics between cancer patients with COVID-19 ARF and non-COVID-19 ARF.

METHODS

Study Design and Patients

We designed a cohort study using data collected from a cancer center with 490 beds (AC Camargo Cancer Center, São Paulo, Brazil), with 50 being ICU beds. The sample size calculation demanded, at least, 65 patients with and 195 without COVID-19 ARF (1:3 ratio) (see **Supplementary Material**).

The study compared a prospective cohort of patients with cancer and COVID-19 ARF with a historical control group of patients with cancer and non-COVID-19 ARF. In both groups, we included all adult patients with solid tumors or hematologic malignancies and unplanned ICU admission due to ARF, and we excluded patients with cancer remission >5 years, decision to forgo LST prior to ICU, and admissions for post-operative care. Patients with COVID-19 were included during the pandemic (March until August 2020), while patients without COVID-19 were included before the pandemic (March until August, in the years 2012 until 2017, respectively). If a patient had multiple ICU admissions, only the first was considered.

Data were collected and maintained in a structured electronic spreadsheet designated to the present study. In the hospital, COVID-19 was confirmed by a positive SARS-CoV-2 RT-PCR in a patient with compatible symptoms or image of COVID-19.

According to Brazilian regulations, the forgoing of LST requires a consensual decision of the patient (or a next of kin) and the attending team. In our ICU, the forgoing of life-sustaining therapies requires a consensual decision of intensivists, oncologists, and patients (or a next of kin).

The local ethics committee approved this study (2521/18L) and waived the need for informed consent.

Data Collection

Upon ICU admission, patient's demographic characteristics, Simplified Acute Physiology Score (SAPS 3) (4); Eastern Cooperative Oncology Group (ECOG) performance status (5); the Sequential Organ Failure Assessment Score (SOFA) and the respiratory parameters of the SOFA score (respiratory SOFA) (6); Charlson Comorbidity Index (7); specific comorbidities [arterial hypertension, diabetes, chronic pulmonary disease (chronic obstructive pulmonary disease or chronic restrictive pulmonary disease), heart diseases (chronic arrhythmia needing treatment or systolic or diastolic heart failure), overweight or obesity (body mass index > 25 kg/m^2)]; type of cancer (non-metastatic solid tumor, metastatic solid tumor, or hematologic malignancies); recent systemic cancer treatment (chemotherapy or immunotherapy in the last month); site of the solid tumors; and response to cancer treatment (newly diagnosed without treatment, partial or complete response, or progressive cancer despite treatment) were recorded.

During the ICU stay, the use of invasive mechanical ventilation (>24 h), the use of non-invasive mechanical ventilation, the use of vasopressors (defined as any use of noradrenaline, dobutamine, vasopressin, or adrenaline), the need of hemodialysis, and any decision to forgo life-sustaining therapies (withholding or withdrawing of treatment) were recorded. According to Brazilian regulations, the forgoing of life-sustaining therapies requires a consensual decision of the patient (or a next of kin) and the attending team. In our hospital, the forgoing of life-sustaining therapies requires a consensual decision of intensivists and oncologists.

Finally, the in-hospital mortality was recorded.

Statistical Analysis

Categorical and continuous data were presented as percentages and median [25–75% interquartile range (IQR)] values, respectively. Categorical variables were compared using the chi-square test or Fisher's exact-test, as appropriate. Continuous variables were compared with the Mann–Whitney-test.

To test the hypothesis that COVID-19 was associated with increased in-hospital mortality and decreased decisions to forgo LST in patients with cancer and ARF, we employed two multivariate logistic regression models. We used a directed acyclic graph to identify confounders (8), and the following confounders were included in the both models: age, sex, type of cancer, response to cancer treatment, ECOG, Charlson Comorbidity Index, and the ARF cause (COVID-19 or non-COVID-19) (**Supplementary Figures 1**, **2**).

As a sensitivity analysis, we employed propensity score matching, with balance checking (absolute standardized mean difference), to match COVID-19 ARF to non-COVID-19 ARF patients (9).

We depicted (Kaplan–Meier) and compared (log-rank-test) the 28-day mortality curves of patients with COVID-19 ARF and non-COVID-19 ARF.

Statistical analyses were performed by SPSS software (Version 23.0. Armonk, NY: IBM Corp). P-values ≤ 0.05 were considered significant. We followed the recommendations of the STROBE statement that guides the report of observational studies (10).

TABLE 1 | Characteristics of patients with cancer and acute respiratory failure due to COVID-19 and non-COVID-19 causes.

Variable	Non-COVID-19 ($n = 382$)	COVID-19 ($n = 65$)	p
Age (years)	64 (56–74)	62 (55–70)	0.26
Male	199 (52.1)	37 (56.9)	0.50
Charlson comorbidity index	7 (6–9)	4 (2–6)	<0.01
Comorbidities			
Hypertension	150 (39.3)	32 (49.2)	0.13
Diabetes	61 (16.0)	17 (26.2)	0.05
Chronic pulmonary disease	46 (12.0)	9 (13.8)	0.68
Cardiovascular disease	37 (9.7)	8 (12.3)	0.50
BMI > 25 kg/m^2	144 (38.4)	41 (63.1)	<0.01
ECOG performance status			<0.01
0–1	102 (26.7)	47 (72.3)	
2–4	280 (73.3)	18 (27.7)	
Cancer type			<0.01
Non-metastatic solid	86 (22.5)	31 (47.7)	
Metastatic solid	247 (64.7)	17 (26.2)	
Hematologic malignancies	49 (12.8)	17 (26.2)	
Solid tumor site			0.05
Breast	52 (15.6)	12 (25.0)	
Lung	83 (24.9)	5 (10.4)	
Prostate	10 (3.0)	6 (12.5)	
Head and neck	25 (7.5)	2 (4.2)	
Colorectal	38 (11.4)	6 (12.5)	
Pancreas	8 (2.4)	3 (6.3)	
Other	117 (35.1)	14 (29.2)	
Response to treatment			<0.01
Newly diagnosed	41 (10.7)	5 (7.7)	
Complete or partial	138 (36.1)	39 (60.0)	
Progressive disease	203 (53.1)	21 (32.3)	
Cancer treatment			
Chemotherapy last month	205 (53.7)	18 (27.7)	<0.01
Immunotherapy last month	13 (3.4)	3 (3.9)	0.28
Bone marrow transplant	12 (3.1)	4 (6.2)	0.26
SAPS3 at ICU admission	69 (62–77)	58 (49–70)	<0.01
SOFA at ICU admission	5 (4–7)	3 (1–4)	<0.01
Respiratory SOFA at ICU admission	3 (2–3)	3 (2–3)	0.52
During ICU stay			
Invasive MV	141 (36.9)	38 (58.5)	0.02
Non-invasive MV	142 (37.2)	19 (29.2)	0.26
Vasopressors	63 (16.5)	37 (56.9)	<0.01
Hemodialysis	32 (8.4)	18 (27.7)	<0.01
ICU length of stay	4 (2–7)	9 (3–18)	<0.01
ICU mortality	196 (51.3)	27 (41.5)	0.17
Decision to forgo LST	138 (36.1)	10 (15.4)	0.01
Hospital length of stay	7 (3–14)	22 (13–35)	<0.01
In-hospital mortality	285 (74.6)	30 (46.2)	<0.01

ICU, intensive care unit; SAPS 3, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment Score; Respiratory SOFA, the value of respiratory parameter of the SOFA score; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; LST, life-sustaining therapies; MV, mechanical ventilation; Invasive MV, invasive mechanical ventilation for more than 24 h. Chronic pulmonary disease is chronic obstructive pulmonary disease or chronic restrictive pulmonary disease; heart diseases are chronic arrhythmia needing treatment and systolic or diastolic heart failure; vasopressors are defined as any use of noradrenaline, vasopressin or adrenaline. Categorical and continuous data are presented as absolute counts (percentages) and median (25–75% interquartile range), respectively. Categorical variables were compared using the chi-square test or Fisher's exact-test, as appropriate. Continuous variables were compared with the Mann–Whitney-test.

TABLE 2 | Multivariate analysis for in-hospital mortality and decisions to forgo life-sustaining therapies of critically ill patients with cancer admitted to ICU with acute respiratory failure.

Variable	Survivors ($n = 315$)	Non-survivors ($n = 132$)	*Adjusted OR	Forgo LST ($n = 148$)	Not forgo LST ($n = 299$)	*Adjusted OR
Age	64 (56–73)	64 (55–73)	1.97 (0.99–3.62)	64 (56–73)	64 (56–72)	1.01 (0.98–1.04)
Male	176 (55.8)	60 (45.5)	0.97 (0.94–1.00)	79 (53.4)	157 (52.5)	0.86 (0.50–1.49)
Charlson comorbidity index	7 (6–9)	6 (4–8)	0.87 (0.71–1.07)	7 (6–9)	6 (4–8)	0.96 (0.78–1.18)
ECOG performance status						
0–1	44 (14.0)	105 (79.5)	REF	19 (12.8)	130 (43.5)	REF
2–4	271 (86.0)	27 (20.5)	47.48 (22.17–101.69)	129 (87.2)	169 (56.5)	5.08 (2.57–10.07)
Cancer type						
Non-metastatic solid tumor	53 (16.8)	64 (48.5)	REF	22 (14.9)	95 (31.8)	REF
Metastatic solid tumor	218 (69.2)	46 (34.8)	7.37 (2.69–20.17)	117 (79.1)	147 (49.2)	2.19 (0.83–5.78)
Hematological malignancies	44 (14.0)	22 (16.7)	3.59 (1.49–8.63)	9 (6.1)	57 (19.1)	0.64 (0.22–1.87)
Response to cancer treatment						
Newly diagnosed	15 (11.4)	31 (9.8)	REF	1 (0.7)	45 (15.1)	REF
Complete or partial response	79 (59.8)	98 (31.1)	0.87 (0.34–2.23)	8 (5.4)	169 (56.5)	2.35 (0.28–19.67)
Progressive disease	38 (28.8)	186 (59.0)	2.56 (0.95–6.92)	139 (93.9)	85 (28.4)	73.63 (9.75–555.77)
COVID-19 as cause of ARF	30 (9.5)	35 (26.5)	1.27 (0.55–2.93)	10 (6.8)	55 (18.4)	1.21 (0.44–3.28)

ARF, acute respiratory failure; SOFA, Sequential Organ Failure Assessment Score; ECOG, Eastern Cooperative Oncology Group; ICU, intensive care unit; LST, life-sustaining therapies; OR, odds ratio. Categorical and continuous data are presented as frequencies (percentages) and median (25–75% interquartile range), respectively.

**The confounders included in the model (age, male, Charlson, ECOG, cancer type, and response to cancer treatment) serve exclusively to control for confounding. The observed associations between these confounders and the outcome (in-hospital mortality or decision to forgo life-sustaining therapies) have not been subject to the same control of confounding as the exposure (COVID-19). Therefore, residual confounding and other biases often heavily influence these associations.*

RESULTS

During the pre-pandemic period, we included all 382 patients with non-COVID-19 ARF. During the pandemic, 107 patients with confirmed COVID-19 diagnosis were admitted to the ICU and 65 patients were included. Forty patients were excluded because they were admitted to post-operative care, 19 patients had cancer remission >5 years, and three patients had readmissions.

Clinical and Cancer-Related Characteristics

Patients with COVID-19 ARF had better performance status, less metastatic tumors, and progressive cancer. They had lower Charlson Comorbidity Index but more overweight/obesity. Upon ICU admission, patients with COVID-19 ARF had less severe acute organ dysfunctions. However, during ICU stay, they needed more life-sustaining therapies and had longer ICU and hospital lengths of stay than patients with non-COVID-19 ARF (**Table 1**). Among the hospital survivors, the hospital length of stay of the patients with COVID-19 [24 days (16–42)] was higher than the patients without COVID-19 [12 days (7–19)] ($p < 0.01$).

In-Hospital Mortality

In-hospital mortality of patients with COVID-19 ARF was lower compared with patients with non-COVID-19 ARF (46.2 vs. 74.6%; $p < 0.01$) [unadjusted odds ratio 0.29 (0.17–0.50; 95% confidence interval, CI)] (**Table 1** and **Supplementary Figure 3**). However, adjusting for age, sex, type of cancer, response to cancer treatment, ECOG, Charlson Comorbidity Index, and the ARF cause (COVID-19 or non-COVID-19), COVID-19 as the cause of ARF was not associated with increased in-hospital mortality [adjusted odds ratio 1.27 (0.55–2.93; 95% CI)] (**Table 2**).

Decision to Forgo Life-Sustaining Therapies

The percentage of patients with a decision to forgo LST was lower in patients with COVID-19 ARF than in patients with non-COVID-19 ARF (15.4 vs. 36.1%; $p = 0.01$) [unadjusted odds ratio 0.32 (0.16–0.65; 95% CI)] (**Table 1**). However, adjusting for age, sex, type of cancer, response to cancer treatment, ECOG, Charlson Comorbidity Index, and the ARF cause (COVID-19 or non-COVID-19), COVID-19 as the cause of ARF was not associated with decisions to forgo LST [adjusted odds ratio 1.21 (0.44–3.28; 95% CI)] (**Table 2**).

Sensitivity Analyses

As the primary analyses, sensitivity analysis also showed that COVID-19 was neither associated with in-hospital mortality nor with decision to forgo LST (**Table 3**).

DISCUSSION

Patients with cancer and COVID-19 ARF had different cancer-related and clinical characteristics from their non-COVID-19 counterparts, such as better performance status and less progressive cancer. These differences probably occurred because patients with poor performance status and progressive cancer had low mobility and were less exposed to COVID-19. Additionally, patients with a high probability of survival might be

TABLE 3 | Comparison of patients with cancer and COVID-19 acute respiratory failure with matched patients with non-COVID-19 acute respiratory failure.

Variable	*Matched Non-COVID-19 (*n* = 50)	COVID-19 (*n* = 50)	*p*	ASMD
Age (years)	61 (48–69)	60 (54–68)	0.93	0.00
Male	27 (54.0)	25 (50.0)	0.84	0.08
Charlson comorbidity index	5 (3–6)	6 (3–6)	0.64	0.07
Comorbidities				
Arterial hypertension	15 (30.0)	24 (48.0)	0.99	
Diabetes	5 (10.0)	13 (26.0)	0.07	
Chronic pulmonary disease	6 (12.0)	6 (12.0)	0.99	
Cardiovascular disease	2 (4.0)	6 (12.0)	0.27	
BMI > 25 kg/m^2	19 (38.0)	29 (58.0)	0.07	
ECOG performance status			0.84	0.08
0–1	31 (62.0)	33 (66.0)		
2–4	19 (38.0)	17 (34.0)		
Cancer type			0.71	0.12
Non-metastatic tumor	26 (52.0)	22 (44.0)		
Metastatic tumor	13 (26.0)	16 (32.0)		
Hematologic malignancies	11 (22.0)	12 (24.0)		
Solid tumor site			0.24	
Breast	9 (23.1)	10 (26.3)		
Lung	9 (23.1)	4 (10.5)		
Prostate	1 (2.6)	4 (10.5)		
Head and neck	5 (12.8)	1 (2.6)		
Colorectal	5 (12.8)	4 (10.5)		
Pancreas	1 (2.6)	3 (7.9)		
Other	9 (23.1)	12 (31.6)		
Cancer treatment response			0.94	0.03
Newly diagnosed	5 (10.0)	4 (8.0)		
Complete or partial	27 (54.0)	28 (56.0)		
Progressive disease	18 (36.0)	18 (36.0)		
Chemotherapy last month	24 (48.0)	16 (32.0)	0.15	
Immunotherapy last month	1 (3.0)	2 (6.0)	0.62	
Bone marrow transplant	4 (8.0)	4 (8.0)	1.00	
SAPS3 at ICU admission	67 (56–76)	58 (48–74)	0.05	
SOFA at ICU admission	4 (1–6)	3 (1–5)	0.52	0.06
Respiratory SOFA at ICU admission	3 (2–3)	3 (2–3)	0.22	
During ICU stay				
Invasive MV	19 (38.0)	28 (56.0)	0.11	
Non-invasive MV	23 (46.0)	13 (26.0)	0.06	
Vasopressors	8 (16.0)	28 (56.0)	<0.01	
Hemodialysis	4 (8.0)	15 (30.0)	<0.01	
ICU length of stay	5 (3–11)	7 (4–18)	0.08	
ICU mortality	17 (34.0)	21 (42.0)	0.54	
Decision to forgo LST	11 (22.0)	8 (16.0)	0.61	
Hospital length of stay	10 (6–18)	22 (13–35)	<0.01	
In-hospital mortality	22 (44.0)	23 (46.0)	0.99	

ASMD, absolute standardized mean difference; ICU, intensive care unit; SAPS 3, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment Score; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; LST, life-sustaining therapies; MV, mechanical ventilation. Respiratory SOFA is the value of respiratory parameter of the SOFA score; chronic pulmonary disease is chronic obstructive pulmonary disease or chronic restrictive pulmonary disease; cardiovascular diseases are chronic arrhythmia needing treatment and systolic or diastolic heart failure; invasive MV is invasive mechanical ventilation for more than 24 h; vasopressors are defined as any use of noradrenaline, vasopressin, or adrenaline. Categorical and continuous data are presented as absolute counts (percentages) and median (25–75% interquartile range), respectively. Categorical variables were compared using the chi-square test or Fisher's exact-test, as appropriate. Continuous variables were compared with the Mann–Whitney-test.

[*] Patients with COVID-19 and non-COVID-19 acute respiratory failure were matched for age, sex, type of cancer, response to cancer treatment, SOFA, ECOG, and Charlson Comorbidity Index. The propensity score was calculated using logistic regression and pairs were matched by the nearest neighbor with a caliper distance ≤0.05.

preferentially admitted to the ICU, as part of the effort to improve ICU resource allocation during the pandemic.

Upon ICU admission, patients with COVID-19 ARF had less severe organ dysfunctions than patients with non-COVID-19 ARF; however, during ICU stay, they needed more invasive mechanical ventilation, vasopressors, and hemodialysis. These results probably occurred because at presentation, severe COVID-19 is predominantly a respiratory disease; however, its typically long course led to progressive clinical deterioration and increased use of life-sustaining therapies (11, 12). Confirming the long COVID-19 course, in our study, patients with COVID-19 ARF had a significantly longer ICU and hospital lengths of stay than patients with non-COVID-19 ARF.

The observed clinical and cancer-related differences explain the lower mortality found in patients with cancer and COVID-19 ARF because the severity of organ dysfunctions upon ICU admission (13, 14), poor performance status (13, 14), progressive cancer (14), hematologic malignancies, and metastatic tumors (15) are associated with in-hospital mortality of critically ill patients with cancer.

Patients with COVID-19 required more hemodialysis, probably due to a direct impact of COVID-19 on the kidney, because the standard of care was similar between groups. Patients without COVID-19 presented a higher percentage of lung cancer than patients with COVID-19, probably reflecting a direct thoracic cancer involvement as a cause of ARF in patients without COVID-19.

It has been shown that poor performance status and progressive cancer are associated with more decisions to forgo LST (16), while hematological malignancies was associated with less decisions to forgo LST (17). In the present study, patients with COVID-19 ARF had better performance status, less progressive cancer, and more hematological malignancies compared to non-COVID-19 patients. These differences probably determined the lower percentage of decisions to forgo LST in patients with COVID-19 ARF.

The present study has limitations. It was conducted at a single dedicated cancer center and physicians must carefully evaluate the results of single-center trials within the context of their clinical experience and the preferences of their patients to determine how best to translate research to the bedside (18). The causes of ARF in non-COVID-19 patients were unknown for several patients, and some causes probably were non-infectious, such as cancer spread and idiopathic alveolar hemorrhage. However, only 5 to 20% of ARF causes are non-infectious (19–21), around 10% of patients have more than one cause (19), and even with the best efforts ∼20% of causes are impossible to be established in patients with cancer (20, 21). We did an extensive characterization of lung injury and clinical status upon ICU admission, but some relevant variables were not recorded, such as previous thoracic radiation therapy, presence of pulmonary and pleural metastasis to characterize lung injury, and absolute neutrophil count and hemoglobin level to characterize the patient upon ICU admission. Finally, patients with non-COVID-19 ARF were included during a 6-year period (2012 until 2017) while patients with COVID-19 were included in 2020, and improvements in overall ICU care along this period (22) should be considered in interpreting the results.

In conclusion, COVID-19 was not associated with increased in-hospital mortality or decreased decisions to forgo life-sustaining therapies in patients with cancer and acute respiratory failure. Patients with cancer and COVID-19 acute respiratory failure had better performance status, less progressive cancer, less metastatic tumors, and less organ dysfunctions upon ICU admission than patients with non-COVID-19 acute respiratory failure.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by AC Camargo Cancer Center Ethics Committee (2521/18L). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

RT, AP, and PC made substantial contributions to the conception of the work, acquisition, and interpretation of data. ANJ and RC made substantial contributions to the design of the study and interpretation of data. PS and VO made substantial contributions to acquisition and interpretation of data. PC drafted the manuscript. All authors revised the manuscript critically for important intellectual content and gave final approval of the version to be published.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.620818/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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The Role of Dysbiosis in Critically Ill Patients With COVID-19 and Acute Respiratory Distress Syndrome

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In late December 2019, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) quickly spread worldwide, and the syndrome it causes, coronavirus disease 2019 (COVID-19), has reached pandemic proportions. Around 30% of patients with COVID-19 experience severe respiratory distress and are admitted to the intensive care unit for comprehensive critical care. Patients with COVID-19 often present an enhanced immune response with a hyperinflammatory state characterized by a "cytokine storm," which may reflect changes in the microbiota composition. Moreover, the evolution to acute respiratory distress syndrome (ARDS) may increase the severity of COVID-19 and related dysbiosis. During critical illness, the multitude of therapies administered, including antibiotics, sedatives, analgesics, body position, invasive mechanical ventilation, and nutritional support, may enhance the inflammatory response and alter the balance of patients' microbiota. This status of dysbiosis may lead to hyper vulnerability in patients and an inappropriate response to critical circumstances. In this context, the aim of our narrative review is to provide an overview of possible interaction between patients' microbiota dysbiosis and clinical status of severe COVID-19 with ARDS, taking into consideration the characteristic hyperinflammatory state of this condition, respiratory distress, and provide an overview on possible nutritional strategies for critically ill patients with COVID-19-ARDS.

Keywords: microbiota, dysbiosis, ARDS, critical care, infection, COVID-19

INTRODUCTION

In late December 2019, a novel coronavirus able to induce an acute respiratory syndrome was identified in Wuhan, China (1). This virus, since named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), quickly spread worldwide, and the syndrome it causes, coronavirus disease 2019 (COVID-19), was declared a pandemic by the World Health Organization on March 11, 2020. The standard presentation of COVID-19 includes fever, dry cough, respiratory distress, fatigue, myalgia, dyspnea, headache, and diarrhea (1, 2). Fecal samples collected from patients with COVID-19 remained positive for about 11 days, raising concerns about the possible fecal-oral transmission of the virus and gastrointestinal symptoms (3, 4).

Several patients with COVID-19 are admitted to the intensive care unit (ICU) due to severe respiratory distress, with a clear status of typical or atypical acute respiratory distress syndrome (ARDS), requiring critical care support (2, 5). The rate of patients admitted to ICU depends on the diversity of cares within countries and the pandemic global situation. Indeed, compared with the first wave of the pandemic, during the second wave 50% less of all hospitalized patients with COVID-19 were admitted to the ICU (6). Traditional critical care includes respiratory and cardiovascular support, management of renal, hepatic, infectious, and neurologic status, and nutritional management (2). Patients with severe COVID-19 often experience an enhanced immune response with a hyperinflammatory state characterized by a "cytokine storm" (7), with fever and respiratory distress considered to represent increased dysbiosis. During critical illness, the multitude of therapies administered, including antibiotics, sedatives, analgesics, invasive mechanical ventilation, and nutritional support, may enhance the inflammatory response and impact on the patients' microbiota, leading to dysbiosis. In turn, this status may lead to hyper vulnerability in patients and an inappropriate response to critical circumstances (8).

In this context, the aim of our narrative review is to provide an overview of possible interaction between patients' microbiota dysbiosis and the clinical status of severe COVID-19 with ARDS, taking into consideration the characteristic hyperinflammatory state of this condition, respiratory distress, and provide an overview of possible nutritional strategies for critically ill patients with COVID-19-ARDS.

PATHOPHYSIOLOGY OF THE MICROBIOTA GUT-LUNG AXES

The gut-lung axis is bidirectional, which means that metabolites derived from the gut or lung bacteria can affect each other. Gut microbiota is often altered as early as the first days of ICU admission (9), altering both susceptibility to and severity of infections (10). Mechanisms implied in microbiota-lung-gut-axis alteration in COVID-19 include: (1.1) Direct lung damage (1.2) ACE2 expression; (1.3) gut microbiota as lungs' defense against SARS-CoV-2; and (1.4) immune response.

Direct Lung Damage in COVID-19

ARDS is a common complication of COVID-19. After binding to angiotensin-converting enzyme-2 receptors (ACE2) and transmembrane protease serine 2 (TMPRSS2), SARS-CoV-2 enters the host cells and causes pneumonia with possible ARDS in the most severe cases. The histologic presentation of severe COVID-19 pneumonia includes a progressive thickening of the alveolar wall with infiltrates of mononuclear cells and macrophages, associated with endotheliitis (11). Edema, fibroblasts, and myofibroblasts thicken the alveolar septa, with interstitial inflammatory cell infiltrates. In the late and organizing stage, the lungs become consolidated, and fibroblasts and myofibroblasts proliferate and migrate, forming granulation tissue and fibrosis by accretion, with possible thickening of interlobular septum and bronchial walls, thus leading to diffuse alveolar damage (DAD) (11). In this state, patients with severe COVID-19 may need to be admitted to the ICU for endotracheal intubation and mechanical ventilation. The evolution to COVID-19-ARDS is characterized by pulmonary edema, hypoxemia and inflammation, which are associated with changes in the lung microbiome (12). The microbiota is defined as the overall community of microbes included in a population (13), and the genetic content of the microbiota is known as the microbiome. In healthy conditions, the composition of the microbiota is generally characterized by high abundance and diversity of microorganisms with preponderance of potentially beneficial species, a condition known as eubiosis (13).

The microbiota is primarily involved in the immune response and host defense against pathogens, as well as in gut maturation, nutrient uptake and metabolism, mucosal barrier function, intestinal motility, and modulation of the enteric nervous system (14). Moreover, mechanical ventilation, decreased bowel transit time, reduced oxygenation, multiple antibiotic usage, sedatives, analgesics, muscle relaxants, gastric protectors, and abnormal nutritional intake may affect the composition of microbiota, which may increase the risk of dysbiosis and inflammation (15–17). Mice treated with broad spectrum or targeted antibiotics impaired their response to systemic and respiratory infections (18). Most prominent among these are gram-negative bacteria (e.g., *Proteobacteria*), which can lead to severe gut-lung dysbiosis (9, 19).

ACE2 Expression

Once affected the lungs' tissue, COVID-19 may extend to other organs by binding to ACE2 and TMPRSS2 (20, 21), which are broadly expressed in various tissues (22, 23). ACE2 are involved in the regulation of inflammation and microbial community, while regulating the host intestinal metabolism of tryptophan, which plays a key role in the composition of gut microbiota (24–26). Thus, ACE2 expression may alter both the lung and gut microbiomes in certain disease conditions (24–26). In fact, a down-regulation of ACE2 reduces the absorption of tryptophan in the gut, while reducing the secretion of antimicrobial peptides and triggering dysbiosis (27). *Bacterioides dorei* and other bacterial species down-regulate the expression of colonic ACE2, thus supporting the appearance of intestinal symptoms in some COVID-19 patients (28). SARS-CoV-2 infection of the intestinal

tract impairs the absorption of nutrients altering the intestinal function and activation of the enteric nervous system, causing gastrointestinal manifestations (29). Recent findings confirmed the role of gut dysbiosis in the induction of ARDS and its importance in possibly determining tissue damage in SARS-CoV-2 infection (16, 30).

Gut Microbiota as Lungs' Defense Against SARS-CoV-2

The gut microbiota regulates the function of the immune system and cellular homeostasis of both gut and lung tissues due to antimicrobial peptides and metabolites derived from intestinal commensals (18, 31). The enteric nervous system is composed of the myenteric plexuses, which control fluid movement and intestinal motility; and is influenced by the activation pattern recognition receptors (PRRs), especially toll-like receptors (TLRs) which recognize pathogens (32).

SARS-CoV-2 infection may promote intestinal inflammation, epithelial barrier disruption, and decreased production of antimicrobial peptides (AMPs), until developing secondary enteric infections. An increased inflammatory status of the gut induced by SARS-CoV-2 may alter gut permeability causing epithelial leakage, which may enhance bacterial translocation and trigger systemic inflammation and inflammatory response to other organs (22). Additionally, over-expression of fecal calprotectin is implied in gut inflammation in COVID-19 (33). The passage of gut bacteria from the intestinal to the lung tissues is regulated by the ability of gut tight junctions in maintaining epithelial permeability, and intestinal bacteria in preserving the intestinal barrier. Among the proposed mechanisms of alteration, products of commensal bacteria fermentation like butyrate and other short-chain-fatty-acids (SCFAs) are responsible of intestinal barrier function and regulation of tight junctions' permeability (34). Additionally, the alteration in the secretion of mucin by goblet cells can lead to impaired mucus layer, increasing susceptibility to increased gut permeability (35). Dysbiosis results in diminished production of microbial-associated molecular patterns including TLRs and nucleotide oligomerization domain (NOD)-like agonists and microbial metabolites such as SCFAs, thus reducing antibacterial pulmonary immunity (18). Hence, by altering the gut immune homeostasis, respiratory viral superinfection may occur. Gut bacteria were found in lung microbiome, suggesting possible translocation from the intestinal tract to the lungs via the hematic circulation (36). The abundance of gut-associated pathogens in the lungs is increased in non-COVID-19 ARDS patients, but little is known regarding ARDS associated with COVID-19. Patients with ARDS revealed a higher prevalence of *Lechnospiraceae* as a strong predictor of reduced survival (37). Some authors investigated the lung bacterial burden and diversity of patients with non-COVID-19 ARDS, concluding that the lung microbiota is reduced in term of diversity and is increased in terms of bacterial burden (38).

Immune Response

The multifunctional SARS-CoV-2 Envelope (E) protein, which interact with host tight junction protein ZO1, showed great contribution to virus assembly, while contributing to epithelial barrier damage, pathogenesis (binding to ACE2 receptor), and disease severity (39). Human intestinal epithelial cells (in the esophageal upper epithelia, gland cells, enterocytes of the ileum and colon) are potential target of viral replication, also promoting spreading of SARS-CoV-2 and immune response mediated by type III interferon (IFN) (40, 41). At lungs level, studies have highlighted the impact of gut microbiota on the lungs' production of type I IFN, which is implied in the control of viral infections (42, 43). Microbial metabolites such as desaminotyrosine and SCFAs are critical for microbiota homeostasis. For example, significant changes in the composition of gut microbiota have been identified in an experimental model of pulmonary influenza (44). Desaminotyrosine is produced by an anaerobe clostridium called *Clostridium orbiscindens* to protect the lungs and activate the innate immune response passing through the blood system against influenza infection. Desaminotyrosine implements type I IFN signaling of lungs' phagocytes by promoting genes transcription (45). Similarly, SCFAs result important in priming the pulmonary immune innate system (18, 31). The subsequent inflammatory response can promote and encourage local inflammation followed by endothelial and epithelial injury (**Figure 1**).

The inflammatory response of SARS-CoV-2 infection is very complex. In fact, SARS-CoV-2 may interfere with the innate antiviral immune response that is made up two different antiviral pathways.

Phagocytes are recruited to fight against local infections and to repair and regenerate the epithelium. As aforementioned, the manipulation of cytokines and IFNs may play an important role in the prevention of infections and mucosal protection. Particularly, IL-22 and IFN-λ act as mucosal defenders and upregulate antimicrobial peptides (46). The IFN regulatory factors increase transcription of type I and III IFNs, which stimulate natural killer cells and cluster differentiation (CD)8+ T lymphocytes, whereas the nuclear factor-kB (NF-kB) promotes the activation of monocytes and their differentiation into macrophages (type M1). Cytokines are therefore released, and T-cells activated (inflammatory T-cells Th1 and Th17). Notably, a "cytokine storm" appears to occur in cases of severe COVID-19, as demonstrated by increased levels of interleukin (IL)-2, IL-17, granulocyte-colony stimulation factor, IFN-γ, inducible protein 10, monocyte chemoattractant protein-1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α (7). Previous studies found that IL-22 is substantially expressed during viral infections, and animals with deficiency of IL-22 were unable to repair and regenerate epithelial tissues (47). Moreover, IL-22 usually enhance the recruitment of other inflammatory cells, thus amplifying the systemic inflammatory response (46, 48), which along with the local damage may predispose COVID-19 patients to secondary bacterial infections, capillary leakage syndrome, and systemic bacterial translocation (49), thus enhancing the risk of multiple organ damage (20–22). Nevertheless, in the COVID-19 era the role of cytokines and interferons on epithelial integrity and systemic reaction is still not clear, and IL-22 and IFN-λ might be considered as further promising targets to maintain the COVID-19 lungs' integrity, but more evidences are urgently needed (50). This

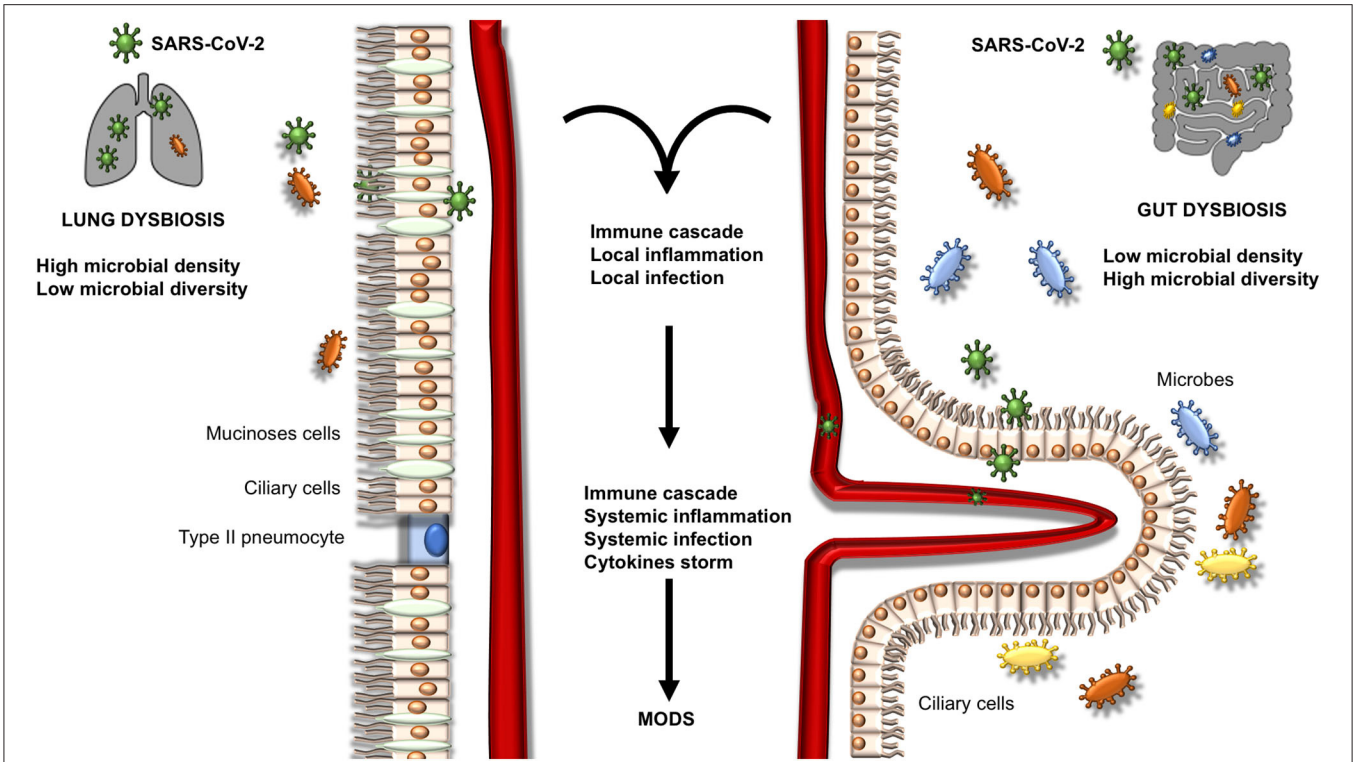

FIGURE 1 | Mechanisms of microbiota gut-lung axis dysbiosis. This figure represents the possible evolution of dysbiosis in the lungs and intestine. A local inflammatory process is activated, thus converting in a systemic inflammatory process with possible infection and multiorgan disease syndrome (MODS).

exaggerates cytokines and interleukins release may increase the expression of markers like programmed death-1, T-cell immunoglobulin, mucin domain-containing protein-3 while favoring lymphocyte apoptosis and necrosis. Lymphopenia is frequent and is associated with disease severity and inflammation (51). Lymphopenia in COVID-19 may be induced by several mechanisms, including direct infection of lymphocytes, viral aggression of lymphatic organs, or continuous inflammation with cytokines release that could induce lymphocyte deficiency (52–54). Additionally, lymphopenia may be associated with glucocorticoids treatment (51). Since gut microbiota is one of the key components of the host immune system, and primary responses to infections and other immune insults, lymphopenia due to SARS-CoV-2 infection may interfere and predispose to changes in the normal flora by opportunistic germs (52–55).

COMPOSITION OF THE GUT-LUNG MICROBIOTA IN CASES OF SEVERE COVID-19 PNEUMONIA

The gut represents the largest microbial environment in humans. The healthy (eubiotic) intestinal microbiota represents a highly heterogeneous ecosystem including eukaryotic organisms (including *Yeast*), *Virus, Archaea* and *Bacteria*. The latters are the most represented members and include nine different phyla, of which *Bacteroidetes* and *Firmicutes* represent the most common populations (13, 32). Differently from the gut, the microbiota is scarcely represented in the lung, being mainly associated with mucosal surfaces. The gut microbiota of patients with COVID-19 demonstrated a high prevalence of opportunistic pathogens over commensals that persisted after negative swabs and resolution of respiratory symptoms. The abundance of *Coprobacillus*, *Clostridium ramosum*, and *Clostridium hathewayi* correlated with the severity of COVID-19 (33). Another study confirmed a high prevalence of opportunistic pathogens in patients with COVID-19, including *Streptococcus*, *Rothia*, *Veillonella*, and *Actinomyces* with a reduced relative abundance of symbionts (56).

The high prevalence of gastrointestinal disorders associated with acute infection by SARS-CoV-2 (anorexia, dysgeusia, ageusia, diarrhea, nausea, and hematemesis) (57) might be associated with the damage to the intestinal ecosystem that may be modified (58). In fact, SARS-CoV-2 infection can impact on some tight junction proteins (like PALS1), that compose the intestinal and lung epithelium. However, definitive confirmation on the impact of SARS-CoV-2 on tight junctions and intestinal permeability while potentially damaging to enterocytes are still limited and warrants further molecular researches (59). Gastrointestinal symptoms have been also associated with reduced number of circulating lymphocytes, and the circulating lymphocytes were inversely associated with virus discharge in stool (58). Moreover, a recent meta-analysis on gastrointestinal symptoms of SARS-CoV-2 infection concluded that gastrointestinal symptoms on admission were associated

more with complications, including ARDS, acute cardiac injury, and acute kidney injury (57).

The main difference between gut and lung microenvironments is the higher turnover of lung bacteria with regard to the gut counterpart. This characteristic of the lung microbiota is due to the high rate of immigrated and eliminated pathogens (aspiration and mucosal dispersion vs. cough and muco-ciliary clearance). The gut microbiota, which is usually enriched in nutrients, makes tough competition with dense resident communities. In contrast, the lung microbiota is enriched in pharyngeal microbes (60, 61), as demonstrated in numerous studies (62, 63).

The oral cavity is the second largest microbiota in humans, and *Neisseria*, *Corynebacterium*, *Leptotrichia*, *Streptococcus*, *Veillonella*, *Prevotella*, *Fusobacterium*, and *Capnocytophaga* are among the most common bacterial taxa (64). Similarly, the healthy lung microbiota is predominantly composed of *Streptococcus*, *Fusobacterium*, *Pseudomonas*, *Veillonella*, *Prevotella*, and *Capnocytophaga* (65). In a recent study of eight patients with SARS-CoV-2 infection, samples of bronchoalveolar lavage fluid (BALF) were sequenced for meta-transcriptome. The host variants varied from 0 to 51 due to a high rate of evolution of the virus. Differences in microbiota composition between healthy controls and those with SARS-CoV-2 were observed, although the variation was not specific (65). Opportunistic bacteria have been found in BALF of patients with COVID-19, particularly *Veillonella* and *Capnocytophaga*, which are commensal of the oral cavity (66). Another study on BALF of patients with COVID-19 revealed predominance of *Leptotrichia buccalis*, *Veillonella parvula*, *Capnocytophaga gingivalis*, and *Prevotella*, whereas *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Aspergillus flavus*, *Candida glabrata*, and *Candida albicans* were detected in nasal swabs (67, 68). Several studies demonstrated a higher incidence of ventilator-associated pneumonia (VAP) in patients with ARDS due to SARS-CoV-2 infection. In a multicentric study in 586 patients admitted to ICU, VAP incidence resulted as high as 29%, being *Pseudomonas aeruginosa* and *Staphylococcus aureus* the most involved microorganisms. Septic shock at VAP onset and ARDS were associated with fatality (69). Another study which compared 81 COVID-19 and 144 non-COVID-19 patients, concluded that those with SARS-CoV-2 infection were significantly more likely to develop VAP (Cox proportional hazard ratio 2.01, 95%CI 1.14–3.54, $p = 0.0015$). The organisms responsible of VAP and microbiome were similar between groups, but COVID-19 patients were more susceptible to *Aspergillus* and *Herpes* infections than general ICU patients (70). Again, data extracted by Rouzé et al. (71) from an European multicentric cohort of 1,576 patients concluded that lower respiratory tract infections associated to ventilation were significantly higher in patients with COVID-19 as compared to influenza patients, and those without viral infections. The most common causative pathogens included *Pseudomonas aeruginosa*, *Enterobacter spp*, and *Klebsiella spp*. Further studies are warranted to confirm the real incidence of lung dysbiosis and VAP in cases of severe COVID-19 pneumonia. **Figure 2** depicts differences in lung and gut microbiota composition in patients with severe COVID-19 pneumonia and patients with typical ARDS.

RISK FACTORS AND PREVENTION OF DYSBIOSIS IN SEVERE COVID-19-ARDS

Recognizing the causes of dysbiosis in critical illness is challenging (16). Literature confirm that hospital admission may only partially alter patients' ecosystem, while increasing severity is commonly seen when implementing the level of cares. Indeed, several and impacting iatrogenic forces are applied during ICU care, thus affecting the physiology of the host, which in turn alters the community structures of resident microbes. In healthy or minimally ill individuals the elimination of pathogens is normally rapid and mediated by the passage through the intestinal tract via defecation. During critically illness, glucose and electrolyte disturbances, endogenous and exogenous opioids, sedatives and catecholamines, myorelaxants, poor oral hygiene, endotracheal or nasotracheal intubation, cuff pressure balance, body position, patients' transport and mobilization represent only few of the possible risk factors that may influence dysbiosis (72, 73). The consequent systemic response includes a lowering of the stomach and intestinal transit-time, drops in bile salt production, impairment of immunoglobulin type A production, and loss of the mucosal barrier. Moreover, the intestinal wall is often hypoperfused, leading to mucosal inflammation, altered oxygen gradient and increased nitrate concentration, while reducing the commensal bacteria in favor of the pathogens, and lowering the transit-time and pathogens' elimination. Additionally, when mechanical ventilation is applied, the ecological system of the lungs is highly stressed with possible impaired muco-ciliary clearance, depressed cough reflex and pathogens' overgrowth (16). If to these important grounds typical COVID-19 patients' comorbidities are added, the risk of dysbiosis is dramatically increased.

Comorbidities of Patients With Severe COVID-19-ARDS and Their Role in Dysbiosis

The age of patients with severe COVID-19 is commonly high, and populations of gut bacteria normally change with age. In the gut of the elderly, less *Bifidobacteria* have been identified, maybe because of reduced gut epithelial barrier function, reduced immune function, and increased inflammation (74). In addition, obesity seems to be a typical characteristic of COVID-19, and it is associated with higher levels of pro-inflammatory cytokines and a poorer gut barrier. These mechanisms may favor the passage of gram-negative bacteria with possible endotoxemia (75). Intestinal bacteria along with their products (like SCFAs) play a key role in the protection of the mucosal intestinal barrier, and in the maintenance of adequate permeability through tight junctions, that may be down-regulated by pro-inflammatory cytokines and chemokines (76). Low-grade systemic inflammation is also present in those with chronic cardiovascular disease, type II diabetes mellitus, arthritis, and cancer. This may increase the risk of infection and altered

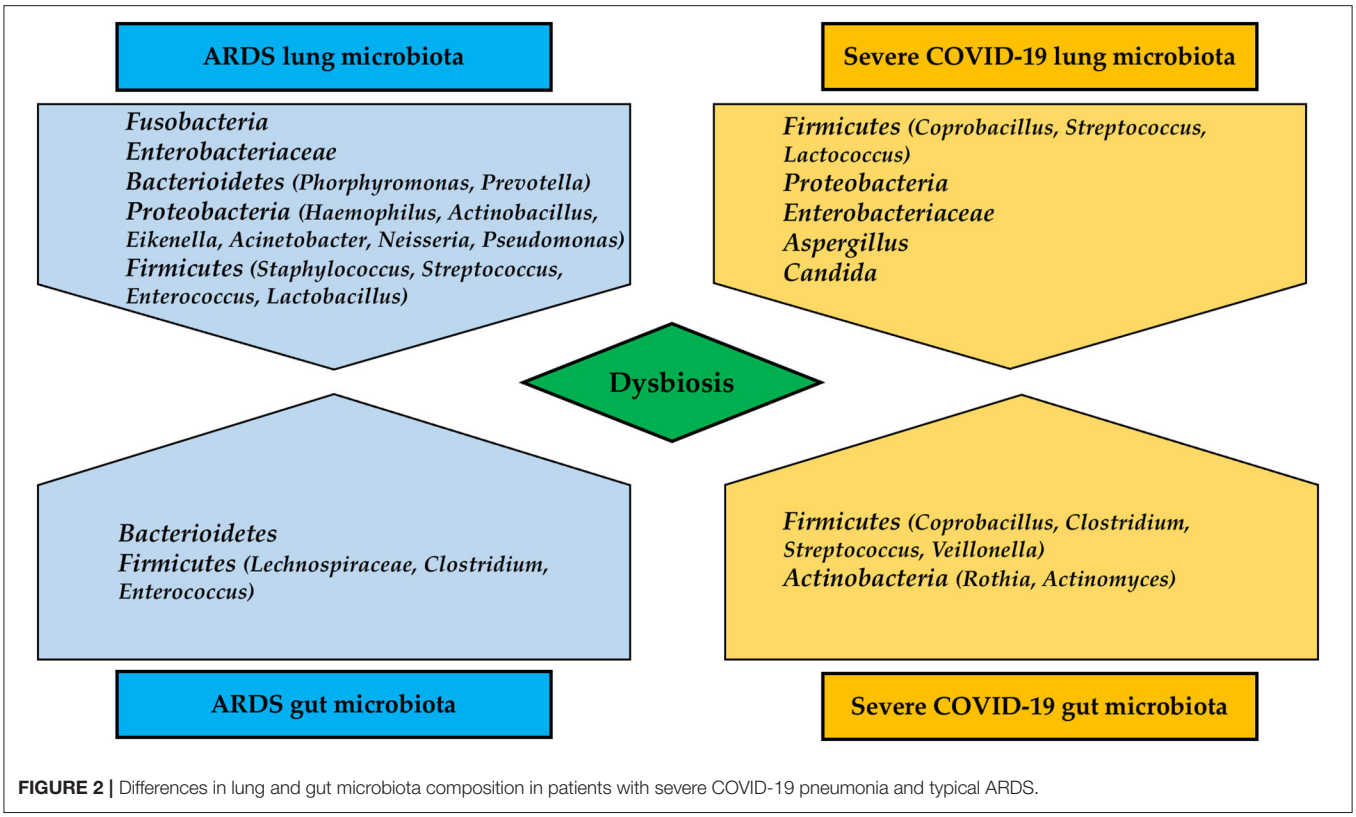

FIGURE 2 | Differences in lung and gut microbiota composition in patients with severe COVID-19 pneumonia and typical ARDS.

microbiota (77). A great proportion of COVID-19 patients has hypertension (78). SCFAs has a crucial role in regulating blood pressure, while trimethyl amine-n-oxide (TMAO) is involved in atherosclerosis, hypertension, and coronary artery diseases' pathogenesis (79).

COVID-19 patients who present type II diabetes mellitus are around 30%. *Lactobacilli* are higher in diabetic patients, while the abundance of *Firmicutes* is correlated with inflammation (80). This basal diversity should be kept in mind when approaching dysbiosis in a COVID-19 patient with both SARS-CoV-2 infection and type II diabetes mellitus. Finally, according to the CDC's weekly report, around 35% of critically ill COVID-19 patients have an underlying chronic lung disease, such as asthma (81). As previously explained, the direct lung damage may be responsible for microbiota dysbiosis and over-infections. The airway mucosal barrier may lose the critical defense against SARS-CoV-2 and other infections (46).

Indirect Risk Factors of Dysbiosis Associated With Mechanical Ventilation in COVID-19

Oral Hygiene and Aseptic Mouthwashes

Poor oral hygiene has been associated with increased incidence of pneumonia and dysbiosis in critically ills (82), and no scientific evidence exists yet to recommend mouthwashes to control the SARS-CoV-2 load in the oral cavity. Some antiseptic mouth rinses have antiviral ingredients able to decrease the viral load, but conclusive evidences are still limited. Besides, changes in the normal oropharyngeal flora as a consequence of poor oral hygiene could be related, not only to a greater ease of infection by SARS-CoV-2 with consequent higher viral load and greater severity (83), but also to secondary superinfections (84).

Common periodontal pathogens have been identified in the lungs of ICU patients, including *Treponema denticola*, *P. gingivalis*, *Fusobacterium nucleatum*, *Actinobacillus actinomycetemcomitans,* and *Veillonella parvula* (85, 86). In a cohort of 122,251 patients, the risk of pneumonia increased in those who did not engage in good oral care, including the presence of dental caries and missing teeth (87). The use of mouthwashes to prevent pneumonia is still debated. A randomized controlled trial (RCT) on 80 ICU patients who were randomized to receive Nanosil mouthwashes and chlorhexidine 0.12% for 5 days demonstrated that the pneumonia rate was reduced in the Nanosil group (2.7 vs. 23.7%, $p = 0.008$), but mortality was similar in both groups (88). Another trial investigating the role of peroxide hydrogen over normal saline in the prevention of pneumonia concluded that patients treated with peroxide hydrogen had a lower risk of contracting VAP (relative risk [RR], 2.6; 95% confidence interval [CI], 1.04–6.49, $p = 0.0279$) (89). Although no data on patients infected with SARS-CoV-2 are available, mouthwashes containing cetylpyridinium chloride reduced *in vitro* SARS-CoV-2 infectivity. The reduction of SARS-CoV-2 infectivity may reduce lung dysbiosis, but the novelty of this study is limited by the fact that, being *in vitro*, it cannot reproduce the real

condition of an *in-vivo* oral flora (90). Moreover, the efficacy of mouthwashes with hydrogen peroxide has not been in doubt, especially their capacity to inactivate corona and influenza viruses (91, 92). In conclusion, irrespective of the mouthwash agent, maintaining good oral hygiene is an effective strategy to reduce the rate of over-infections in all ICU patients, especially in those with COVID-19 and ARDS which may present higher risk of superinfections (70, 71).

Endotracheal Intubation, Cuff Pressure Control, and Chest Physiotherapy

Unfortunately, no specific study in severe COVID-19 pneumonia is actually available and current suggestions come from ICU patients. The choice of nasal intubation over the endotracheal route should be weighed against several factors, including a higher level of comfort, less use of sedatives and analgesics, but also the higher incidence of sinusitis and possible translocation of nasal bacteria to the lungs (93). A study comparing patients intubated endotracheally with polyurethane tubes with continuous assessment of cuff pressure and subglottic drainage with patients intubated with PVC and intermittent cuff pressure measurements and intermittent subglottic drainage, demonstrated that prevention of VAP could be performed by using polyurethane tubes, performing continuous subglottic drainage, and continuous cuff pressure measurement (94). The use of chest physiotherapy maneuvers such as subglottic secretion drainage has been identified as a valuable adjuvant for the prevention of VAP in ICU patients. This technique is currently in use in several ICUs during the COVID-19 pandemic, although with limited resources and higher risks. A modified technique has recently been proposed by our group to limit airborne exposure (95). A recent meta-analysis investigated the real benefits of this maneuver, concluding that subglottic secretion drainage is effective but not significant in reducing VAP (RR, 0.56; 95%CI, 0.48–0.63, $p = 0.841$) (96). A recent RCT compared chest physiotherapy with controls for the prevention of VAP, and found that VAP occurred in 39% of the intervention group vs. 8% of the control group (odds ratio, 14; 95% CI, 0.03–0.56; $p = 0.002$); no differences were found in terms of mortality and length of ICU stay (97). However, a meta-analysis concluded that chest physiotherapy does not reduce the incidence of VAP, although these results should be viewed cautiously due to the heterogeneity of the studies and poor evidence (98).

Body Position

As understood by decades of research, body position plays a pivotal role in the development of pneumonia and lungs' dysbiosis (99). The lateral position is known to be effective for improving oxygenation in monolateral pneumonia (100), but severe COVID-19 pneumonia seems to interest both lungs (101). Besides, lateral position in COVID-19 is applied (102, 103). Despite the confirmed application of lateral position in COVID-19, its effects on possible superinfections and subsequent dysbiosis has not been investigated yet. The majority of literature concerning the effects of body position on superinfections and possible dysbiosis come from non-COVID-19 setting. A meta-analysis from 10 RCTs compared a semi-recumbent position (30°-60°) and a supine position (0°-10). The semi-recumbent position, with the higher elevation of the head of the bed, reduced the risk of VAP (14 vs. 40%; RR, 0.36; 95% CI, 0.25–0.5) (104). The lateral Trendelenburg position and a semi-recumbent position were compared in a recent RCT, which concluded that the semi-recumbent position was associated with a higher incidence of VAP than the lateral Trendelenburg (4 vs. 0.5%; RR, 0.13; 95% CI, 0.02–1.03; $p = 0.04$), with no differences in mortality and other secondary outcomes (105). Finally, the prone position, which assumes a pivotal role for severe COVID-19 with ARDS (101), did not seem to increase the incidence of VAP (incidence rate per 100 days of mechanical ventilation of 1.18 vs. 1.54 for supine and prone positions, respectively, $p = 0.1$) (106), as confirmed by a previous similar RCT (107). Similar results were obtained from a multicentric study on 586 COVID-19 patients (69). In conclusion, as stressed above, few studies investigating the role of body position on lung dysbiosis in severe COVID-19 pneumonia are currently available. We suggest that body position may play a role in the development of dysbiosis.

Medications as Possible Risk Factors of Dysbiosis

Antibiotics

Numerous medications are administered in the ICU. Antibiotic consumption in ICUs is almost doubled that in non-ICU wards. During the COVID-19 pandemic, severely ill ICU patients received more antibiotics (66, 108). Antibiotic use is associated with important changes in gut microbial communities with a subsequent loss of the colonization resistance, a hallmark feature of the healthy gut microbiota, thus increasing the susceptibility to gastrointestinal infections by nosocomial pathogen (109, 110). Antibiotic exposure seems to increase the phyla of *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, and *Proteobacteria* (111). The COVID-19 pandemic is associated with a higher and often unnecessary use of antibiotics in the early phases of the disease, in older people, and in mechanically ventilated patients (112, 113). Azithromycin is one of the largely used antibiotics in COVID-19 due to its antiviral and immunomodulatory effects *in vitro*, which include the interference with receptor mediated binding, viral lysosomal escape, intracellular pathways and enhancement of type I and III interferon expression (20). Besides, recent trials on the use of azithromycin combined or not with hydroxychloroquine in critically ill COVID-19 patients tended toward non-routine use (114). Similar results were obtained from a large observational study (115, 116). Another RCT on the use of azithromycin in hospitalized patients with COVID-19 is currently ongoing (117).

Sedatives, Analgesics, and Myorelaxants

Sedation and analgesia in mechanically ventilated COVID-19 patients are important pieces of this complex multisystemic puzzle. Patients with severe COVID-19 pneumonia and multiorgan disease are often kept sedated and curarized for longer periods than non-COVID-19 patients (median 10 days vs. 1 day) (118). Moreover, stopping sedatives, analgesics, and myorelaxants a greater proportion of COVID-19 patients

experienced delirium (119). Growing evidence confirm the role of sedatives, analgesics opioids and myorelaxants on gut microbiota composition. Opioids receptors are located both in the digestive tract and central nervous system, and its effects on dysbiosis have been largely reported by literature. Moreover, some bacterial components can modify the expression of opioids receptors, changing the tolerance to pain (120). Larger studies are needed to confirm the effect of these medications on gut microbiota composition and outcome.

Inotropes and Vasopressors

Critically ill mechanically ventilated COVID-19 with ARDS frequently report the need of vasopressors and inotropes for treating septic shock or other multisystemic diseases (69, 121). Insights from animal models concluded that catecholamines may increase the growth of bacteria, virulence-associated factors, adhesions, and biofilm formation, while influencing the outcome of infections in many hosts (122). Inotropes have been associated with the growth of pathogens, and vasopressors inhibit growth (123, 124). To date, no evidence concerning the effects of inotropes and vasopressors on gut dysbiosis have been described.

Proton Pump Inhibitors (PPI) and H-2 Receptor Antagonists (H2RA)

PPI and H2RA are largely used in ICU for stress ulcer prophylaxis, and likely increases mortality but with low certainly evidence (125–127). The effect of PPI on gut microbiome has been largely investigated in animal studies. PPI showed increased intestinal permeability when compared to non-treated animals, thus changing the microbial composition, impairing colonization resistance, and inducing dysbiosis (128) and pneumonia in humans (129). This was also confirmed by other evidences in humans (130), but few specific investigations on COVID-19 are available yet. In a small monocentric study in 152 COVID-19 patients the impact of PPI was tested (131). Sixty-two patients were treated with PPI, of whom 48.4% without clear reason. Forty-eight percentage of patients treated with PPI, and only 20% of those non-treated presented with secondary infection. Forty-eight percentage of PPI treated patients and 12% of non-treated developed ARDS. The development of secondary infections remained significant after adjusting for other potential confounding (131). Although the sample size of this study is small, we believe that an association between the use of PPI and H2RA and superinfections in COVID-19 who are -per se- at higher risk of superinfections should be considered. Moreover, another study concluded that the pre-hospital use of PPI was associated with worse clinical outcome in hospitalized COVID-19 (132, 133).

Steroids

The Surviving Sepsis Campaign Coronavirus Disease 2019 recently published the first update of their known guidelines (134). High-quality evidence showing reduction in death and minimal adverse effects with short course of corticosteroids. Thus, the guidelines strongly recommended the use of a short course of systemic corticosteroids over not using corticosteroids. There are no trials comparing different corticosteroids with each other, but dexamethasone was associated with good treatment effect compared to no corticosteroids (135, 136). On one hand, corticosteroids reduce death and severity of COVID-19; on the other hand, corticosteroids remain mediators of the stress response that may enhance the hypothalamus-pituitary-adrenal axis which is implied in the control of immune response to stressor agents and intestinal microenvironment. Glucocorticoids may be therefore be involved in the alteration of gastrointestinal microbiota by enhancing the translocation of aerobe and gram negative enteric bacteria to extraintestinal tissues (137). A recent RCT reported no substantial differences in infections among critically ill COVID-19 patients treated with dexamethasone (21.9%) and those not treated (29.1%). However, few conclusive studies are warranted to confirm the real effects of corticosteroids on superinfections in severe COVID-19 pneumonia (138).

TREATMENT PROPOSALS

Prebiotics and Probiotics

Probiotics are living micro-organisms which confer benefits to the host when administrated in adequate dose, and most used organisms include bifidobacteria, lactic acid bacteria, enterococci, and yeast (139). Probiotics usually have distinctive characteristics such as the ability of surviving under intestinal conditions, stimulating the immune system and acting against pathogens, also preventing health-care associated pneumonia (140). Furthermore, probiotics exert interesting properties by modulating cytokines production, interacting with TLRs, antagonizing pathogens in cell adhesion and mucin homeostasis, and by stimulating SCFAs production (141).

Probiotics act by enhancing epithelial barrier function and are anti-inflammatory, improving gut diversity and competing against opportunistic pathobionts for the same ecological niches in the gut (including competition for nutrients or cellular receptors on the mucosal surface). Specifically, they act by blocking or activating multiple signaling pathways (such as NF-kB and STAT1) and producing protective metabolites such as SCFAs. Gastrointestinal symptoms (including diarrhea) appear to be common in COVID-19, possibly reflecting alterations in the composition of gut microbiota (dysbiosis), inflammation and disruption of the epithelial barrier. In this context, administration of probiotics and/or prebiotics might be considered. As an example, Lactobacilli are well-known modulators of intestinal inflammation and immune response, so that their administration is recommended to counteract high level of inflammation, in prevention of diarrhea, and during infections sustained by enteric pathogens (139). Additionally, *Bifidobacteria*, are able to produce vitamins, enzymes, acetic and lactic acids, lowering the pH in the colon microenvironment and inhibiting (potential) pathogens (142). Evidence of beneficial effects, such as decreased infections frequency, shortening of the duration of episodes by 1–1.5 days, reduced shedding of rotaviruses or an increase in the production of rotavirus-specific antibodies, have been demonstrated for *Lactobacillus rhamnosus* GG (LGG), *L. casei* Shirota, *L. reuteri*, *Bifidobacterium animalis* ssp. lactis Bb-12, and a number of other probiotic strains (143).

Probiotics, prebiotics (formulation of nutrients exploited by probiotic bacteria), and symbiotics (a synergistic combinations of pro- and prebiotics) are currently used to improve gut dysbiosis, by favoring the proliferation of healthy protective bacteria in the intestine, ameliorating or preventing inflammation (balancing proinflammatory and immunoregulatory cytokines) and other intestinal diseases (144). The use of probiotics has also been associated with a reduction in the incidence and severity of VAP. Probiotics reduced the duration of mechanical ventilation in critically ill patients (145, 146). Specifically, use of the probiotic *Streptococcus salivarius* K12 has been proposed for patients with COVID-19 (146). Also, the presence of ACE2 was identified in certain probiotics strains. Oral delivery of human ACE2 through the probiotic species *Lactobacillus paracasei* increased ACE activity in the serum and tissues of mice. Similar results can be obtained with the bacteria-derived B38-CAP enzyme (147, 148). Recent research highlighted the role of mucin biopolymers as pivotal in regulating mucin production, which is implied in viral replication in the gut. Lactobacilli are known implementors of the mucus layer and glycocalyx, and inhibitors of pathogenic adherence, thus preventing intestinal inflammation (149). A recent network meta-analysis provided a rationale for the implementation of probiotics in preventing and treating COVID-19. They identified 90 genes potentially implicated in COVID-19 probiotics treatment. Moreover, the clearly shown that the application of probiotics could play a pivotal role on ACE2-mediated virus entry, activation of the systemic immune response, immunomodulatory pathways, lung tissue damage, cardiovascular complications, and altered metabolic pathways in the disease outcome (150). There are currently multiple lines of research with probiotics and numerous potential therapeutic indications, however studies with strong scientific evidence of therapeutic benefits are required.

Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) is gaining ground as a treatment option for certain changes in the gut microbiota. The mechanism of action of FMT requires a fecal suspension from a healthy donor deposited into the gastrointestinal tract of a patient by using an endoscope, nasal tube, or capsule. However, FMT is still considered "off label" except for recurrent or refractory *Clostridium difficile* infections, where reconstitution of the intestinal microbiota by FMT has proved extremely successful and has definitively confirmed the role of dysbiosis in the pathogenesis such infection. Only one study reported FMT in COVID-19 population (151). Because COVID-19 frequently presents with gastrointestinal symptoms (such as diarrhea), fecal transplantation could potentially contribute to spreading the virus. Therefore, the authors suggested careful identification of donors, considering typical symptoms and history of possible contacts, as well as donor testing for SARS-CoV-2 by real-time PCR (152). Eleven COVID-19 patients who received fecal microbiota transplantation resulted in altered peripheral lymphocyte subset, restored gut microbiota and alleviated gastrointestinal disorders (151). FMT efficacy may be affected by some microbial metabolites as primary bile acids (such as cholic acid and chenodeoxycholic acid), that are conjugated by the gut microbiota and bile salt hydrolase to form secondary bile acids (such as deoxycholic acid, lithocholic acid, and ursodeoxycholic acid) (153). The post-antibiotic expansion of *C. difficile* population was shown to be strongly associated with the depletion of secondary bile salts, consequently to an antibiotic-mediated depletion of microbial taxa mediating the conversion of primary into secondary bile acids (154). Primary and secondary bile acids may also exert anti-inflammatory properties and inhibit several viruses by modulating the cytokine-storm via NF-kB (influenza A, and other viruses) (155).

Most intriguingly, while the treatment's success of FMT mostly revolves around intestinal viable healthy bacteria that are transferred through fecal suspensions, it should be considered that the viable bacteria fraction may not be the only factor affecting the recipient's biology. Viruses, archaea, fungi, donor's colonocytes, immunoglobulin, protists, and a number of metabolites, made by the donor's commensal bacteria (as SCFAs) or intestinal cells, can be implanted, potentially triggering a plethora of functionally different effects (156).

Dietary Composition

In the acute phase of ICU admission, inflammation, energy expenditure, and catabolic metabolism are enhanced (157). During their stay in the ICU, patients often develop post-ventilation-acquired dysphagia and ICU-acquired weakness, which mean nutritional support has a pivotal role in maintaining the necessary muscular strength to help wean patients from the ventilator (158–160). Moreover, critical illness is considered to be a major environmental factor in influencing gut homeostasis and dysbiosis, and nutritional therapy could play an essential role in these processes. Among the various environmental factors, indeed, diet is a source of dominant variation of the whole gut microbial community (161). As an example, nutritional models based on plant-based foods were shown to promote a more favorable gut microbiota profile based on the high amount of dietary fiber and SCFA (162). Therefore, nutrition may exert different indirect effect on intestinal function by modulating the gut microbial composition. A recent study on fecal samples of patients with COVID-19 revealed a high abundance of bacterial species *Collinsella aerofaciens*, *Collinsella tanakaei*, *Streptococcus infantis*, *Morganella morganii,* and higher nucleotide *de novo* biosynthesis, amino acid biosynthesis, and glycolysis. These were distinct from fecal samples of patients without COVID-19 who had higher abundance of SCFAs-producing bacteria, including *Parabacteroides merdae*, *Bacteroides stercoris*, *Alistipes onderdonkii*, and *Lachnospiraceae bacterium 1_1_57FAA* (163). It is now well-recognized that SCFAs exert several beneficial effects, influencing a number metabolic (as the lipids, cholesterol and glucose metabolism) and inflammatory (as the butyrate-mediated inhibition of macrophagic NF-κB or inhibition of the LPS-induced cytokines IL-6 and IL-12p40) responses (164).

Colon bacteria respond to fermentable substrates provided by the diet to produce SCFAs and gases through anaerobic metabolism (165). Within this context, dietary intake is an essential factor for resilience of patients' gut microbiota and its impact on upper respiratory tract infections (145).

The use of early enteral nutrition has been associated with improved immunologic function, decreased bacterial translocation, and better mucosal integrity (111). Moreover, the composition of enteral nutrition has a great impact on intestinal homeostasis. The gut microbiota is normally preserved be feeding with various dietary components in different concentrations. With that in mind, an inadequate dietary composition may alter the composition of the intestinal microbiota, thus increasing the growth of opportunistic pathogens over commensals (111).

General nutritional consideration for ICU patients should be applied to COVID-19 patients (166). As COVID-19 is frequently associated with gastrointestinal symptoms, patients can be at high risk of refeeding syndrome. If this risk is present, SCCM/ASPEN guidelines recommend starting at ∼25% of the target energy intake (whether enteral or parenteral) (166). The ESPEN guideline estimates around 27 kcal/kg body weight/day, based on total energy expenditure, for patients aged >65 years with multiple comorbidities, or 30 kcal/kg body weight/day, based on total energy expenditure, for severely underweight patients with multiple comorbidities and older adults (individually adjusted on the basis of nutritional status, physical activity, and disease status) (167). An energy goal of 15–20 kcal/kg actual body weight should be reached within the first week of nutritional support even in COVID-19 (166). Recently, in a prospective observational study Cereda et al. in mechanically ventilated COVID-19 patients who have been fed with a low caloric intake in the early phase of ICU admission, found a higher risk of death. Additionally, patients with mild obesity were associated with higher mortality, while those with moderate-severe obesity were more difficult to wean from the ventilator (168). Early overfeeding should be avoided, because aggressive caloric intake can cause hyperglycemia or the need for insulin therapy (169). In case of contraindications to oral and enteral nutrition, parenteral nutrition should be implemented and increased within 3–7 days (170, 171). In critically ill patients intolerant to enteral feeding, intravenous erythromycin should be considered as the first-line prokinetic therapy, followed by intravenous metoclopramide or a combination of both (170). Prone positioning is being used with increasing frequency to treat both typical ARDS and respiratory distress in severe COVID-19 pneumonia. Traditionally, this leads to forced periods of rest from enteral nutrition (172), although enteral nutrition has recently been demonstrated to be feasible and safe in the prone position as well (173). In patients at high risk of aspiration, post-pyloric enteral nutrition can be provided instead (170) to reduce the possible risks related to prone positioning and development of pneumonia.

The specific recommendations for nutritional management in COVID-19 (167) suggest that a high-energy, low-to-normal carbohydrate (based on diabetic status and glycemic control), normal-to-high protein diet should be considered. Contrasting findings are available concerning the optimal protein intake for critically ill patients (174). Protein intake can influence the catabolic response. During the catabolic phase, within the first 10 days of ICU admission, a reduction in muscle mass of up to 1 kg/day in patients with multiorgan dysfunction can occur (175). A recent RCT compared enteral feeding with high-intact-protein formula (VHPF) with a standard high-protein formula (SHPF). The VHPF facilitated feeding without increasing energy intake, which is consistent with previous ESPEN guidelines (176). However, early high protein intake is associated with a lower mortality rate only in patients with a low skeletal muscle area at hospital admission, not in those with a normal skeletal muscle area (177). Another study found that improvement in daily protein intake could reduce 3-month mortality after hospital discharge (178). A standard high-protein (>20%) isosmotic enteral formula may be used in the early phase of critical illness, with possible addition of fibers (if tolerated) for maintenance of gut microbiota function (166). Consider 1 g protein/kg body weight/day in older persons (individually adjusted on the basis of nutritional status, physical activity, disease status, and tolerance), and 1.2–2.0 g protein/kg body weight/day (166) in patients with multiple comorbidities (167). An isocaloric, high-protein diet is recommended for obese patients, especially guided by urinary nitrogen losses (170); if this measurement is not available, a protein intake of 1.3 g/kg should be considered. The latest ESPEN guidelines recommend a daily protein intake of 1.3 g/kg, delivered progressively (170). However, a great number of COVID-19 patients require continuous renal replacement therapy as part of the systemic multiorgan dysfunction that they manifest. Thus, specific consideration of protein intake during the use of such filters for renal depurations should have been counted by novel guidelines (179).

The amount of glucose, whether parenteral or via carbohydrates by enteral feeding, should not exceed 5 mg/kg/min (170). However, current guidelines in COVID-19 did not account that hypertension, obesity, and diabetes mellitus are the most prevalent comorbidities that may alter patients' metabolic profile (180). Similar consideration may be done for lipids administration in a population composed by a large number of obese patients, as COVID-19 population is (180). Indeed, guidelines recommend that intravenous lipids for parenteral nutrition should not exceed 1.5 g/kg/day (170). The intake of carbohydrates and fat should be adapted according to energy ratio of 50:50 from fat and carbohydrates for ventilated patients (167). Additionally, a ketogenic diet for obese or diabetic patients should be considered (181). Since COVID-19 often leads to liver and renal failure, parenteral Gln dipeptide should not be administered (170). Blood glucose should be measured at ICU admission and at least every 4 h for the first 2 days. Insulin therapy should begin when glucose levels exceed 180 mg/dL (170). Triglyceride levels should be considered in cases of prolonged sedation with propofol or prolonged administration of intravenous lipid emulsion for parenteral nutrition (166). Adequate intake of vitamins and minerals is paramount for the prevention of viral infections. Particularly, vitamins A, E, B6, B12, C, and D; zinc; selenium; iron; and omega-3 polyunsaturated fatty acids should be administered with a view to ameliorating clinical outcomes, as advised for other viral illnesses (167, 182). A recent RCT demonstrated that no mortality advantages were found in critically ill patients who received early implementation of vitamin D (183). In COVID-19, a serum 25-hydroxyvitamin-D level of around 30 mg/mL reduced the risk for adverse clinical

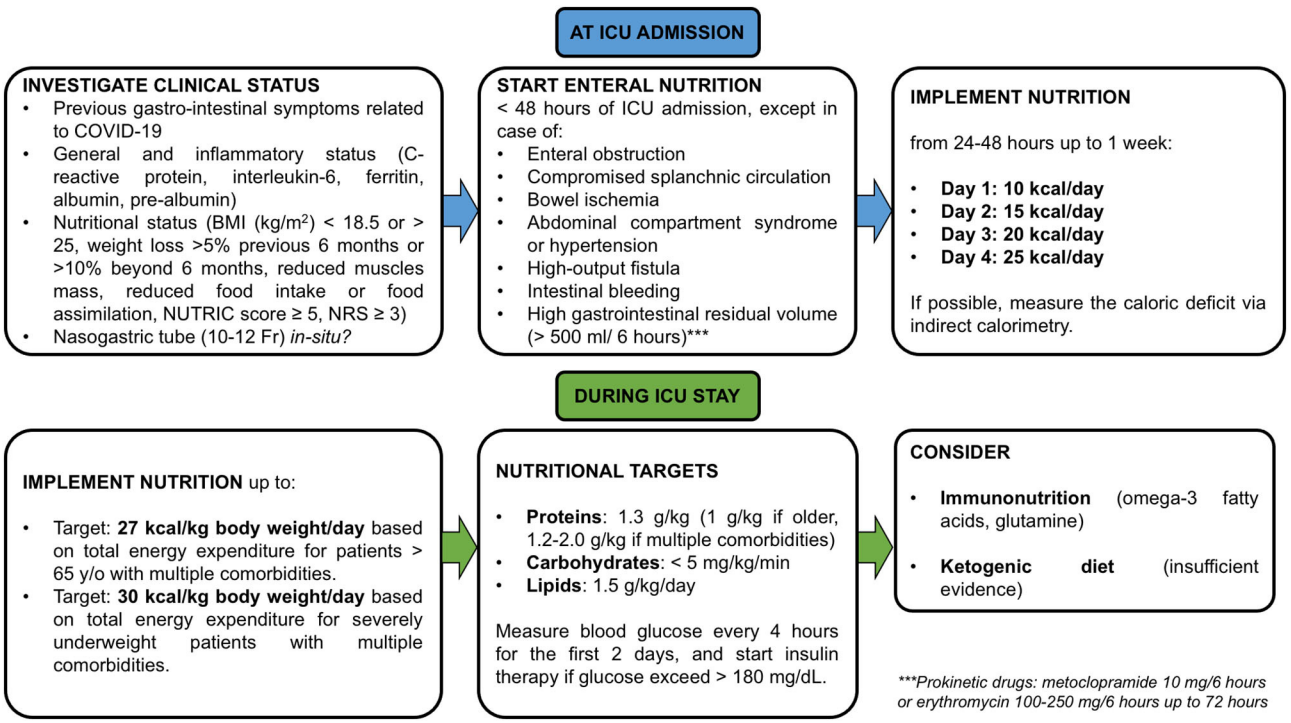

FIGURE 3 | Dietetic recommendations in cases of COVID-19 with ARDS. Nutritional recommendations for critically ill patients with COVID-19 and ARDS from ICU admission to ICU stay. NRS, nutritional risk screening. Each nutritional support is suggested to be calculated on Ideal body weight.

outcomes (184), but further studies are needed to confirm these findings. General dietetic recommendations for critically ill patients with COVID-19-ARDS are depicted in **Figure 3**.

Other Nutritional Interventions to Modulate Dysbiosis in COVID-19

Other nutritional interventions have been proposed to modulate the cytokine storm in ARDS and COVID-19, but studies are lacking. Therefore, the following sentences represent an overview of nutritional treatments for immune and inflammatory dysfunctions in COVID-19 patients. ARDS is considered an overwhelming systemic inflammatory process. Patients with COVID-19 frequently present with hypoalbuminemia and lymphopenia, which may reflect malnutrition and hyperinflammation and have been associated with a negative prognosis (1). Although the albumin level should not be considered a nutritional marker in patients with active inflammation, prealbumin levels are associated with progression to ARDS (185). Patients who survived severe COVID-19 pneumonia often present significant functional limitations, and experience higher morbidity and mortality (186).

Immunonutrition

Immunonutrition has been proposed for patients with severe COVID-19 pneumonia (187, 188) because supplementary immunonutrients and antioxidants have been shown to promote favorable outcomes in the general critically ill population (186, 189, 190). The severity of disease influences the efficacy of immunonutrition (190). In one meta-analysis, immunonutrition reduced mortality and improved oxygenation in patients with ARDS (191); however, more recent studies failed to replicate these findings (186, 192–194). Several products are available to provide immunonutrition. Broadly, these consist of antioxidant vitamins (e.g., vitamin E, vitamin C, carotene), trace elements (e.g., selenium, zinc), essential amino acids (e.g., glutamine, arginine), and essential fatty acids (e.g., omega-3 fatty acids, eicosapentaenoic acid, docosahexaenoic acid, linolenic acid) (186).

Monounsaturated and polyunsaturated fatty acids are involved in cytokine production (190). When immunonutritional enrichment of fatty acids is administered, many components of the immune response are modulated and suppressed (190) by modification of the lipid bilayer of multiple cell types. Omega-3 fatty acids are essential lipids that are able to suppress pro-inflammatory eicosanoid biosynthesis, reduce lung permeability, inhibit inflammation by enhancing T cell function, and decrease pulmonary edema (189, 195). On the other hand, the administration of omega-6 fatty acids may have opposite effects. Thus, the intravenous administration of lipid-enriched solutions may be detrimental, increasing mortality and complications in critically ill patients, because of the infusion of high amounts of omega-6 fatty acids (196).

Glutamine and arginine are sulfur-containing amino acids that have been proposed as components of immunonutrition for their immunomodulatory properties. Particularly, the properties of glutamine include improvement of gut barrier function and

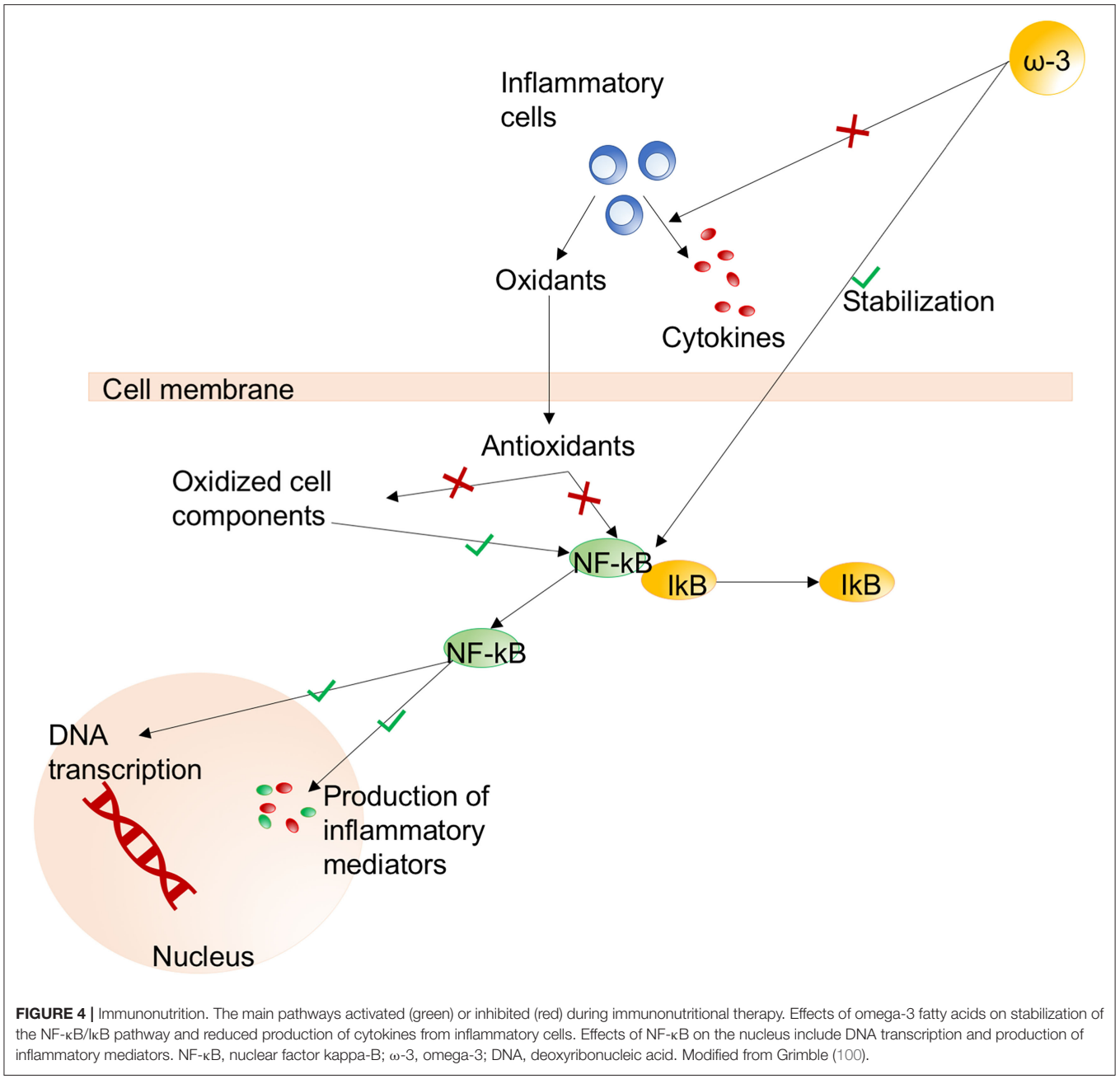

FIGURE 4 | Immunonutrition. The main pathways activated (green) or inhibited (red) during immunonutritional therapy. Effects of omega-3 fatty acids on stabilization of the NF-κB/IκB pathway and reduced production of cytokines from inflammatory cells. Effects of NF-κB on the nucleus include DNA transcription and production of inflammatory mediators. NF-κB, nuclear factor kappa-B; ω-3, omega-3; DNA, deoxyribonucleic acid. Modified from Grimble (100).

immunomodulation of lymphocyte, neutrophil, and macrophage function (186). Glutamine also enhances glutathione synthesis and cell proliferation, thus enhancing antioxidant mechanisms. Likewise, arginine enhances nitric oxide synthesis, lymphocyte function, growth hormone production, and anabolism (189). Arginine is synthesized from proline and participates in the synthesis of ornithine, which is essential for immune function. Arginine deficiency has been found to correlate with suppression of T cell proliferation and cluster of differentiation (CD)3 (190). An RCT of a specific anti-inflammatory and antioxidant nutritional therapy regimen for patients with COVID-19 is ongoing (197). Precursors of cysteine may be administered exogenously in the form of N-acetylcysteine or procysteine, although cysteine and methionine are not easily captured into cells (190). The putative mechanisms of immunonutrition are summarized in **Figure 4**. Although glutamine and antioxidants could be considered in patients with oxidative stress, benefits to outcomes have not been reported. On the contrary, an increase in mortality was found in critically ill patients with multiorgan failure (198). Therefore, caution is needed since conclusive evidences are not available yet.

Ketogenic Diet

Ketogenic diet is a nutritional alternative to mitigate inflammation in COVID-19 patients. The ketogenic diet is a low-carbohydrate, high-fat nutritional support strategy

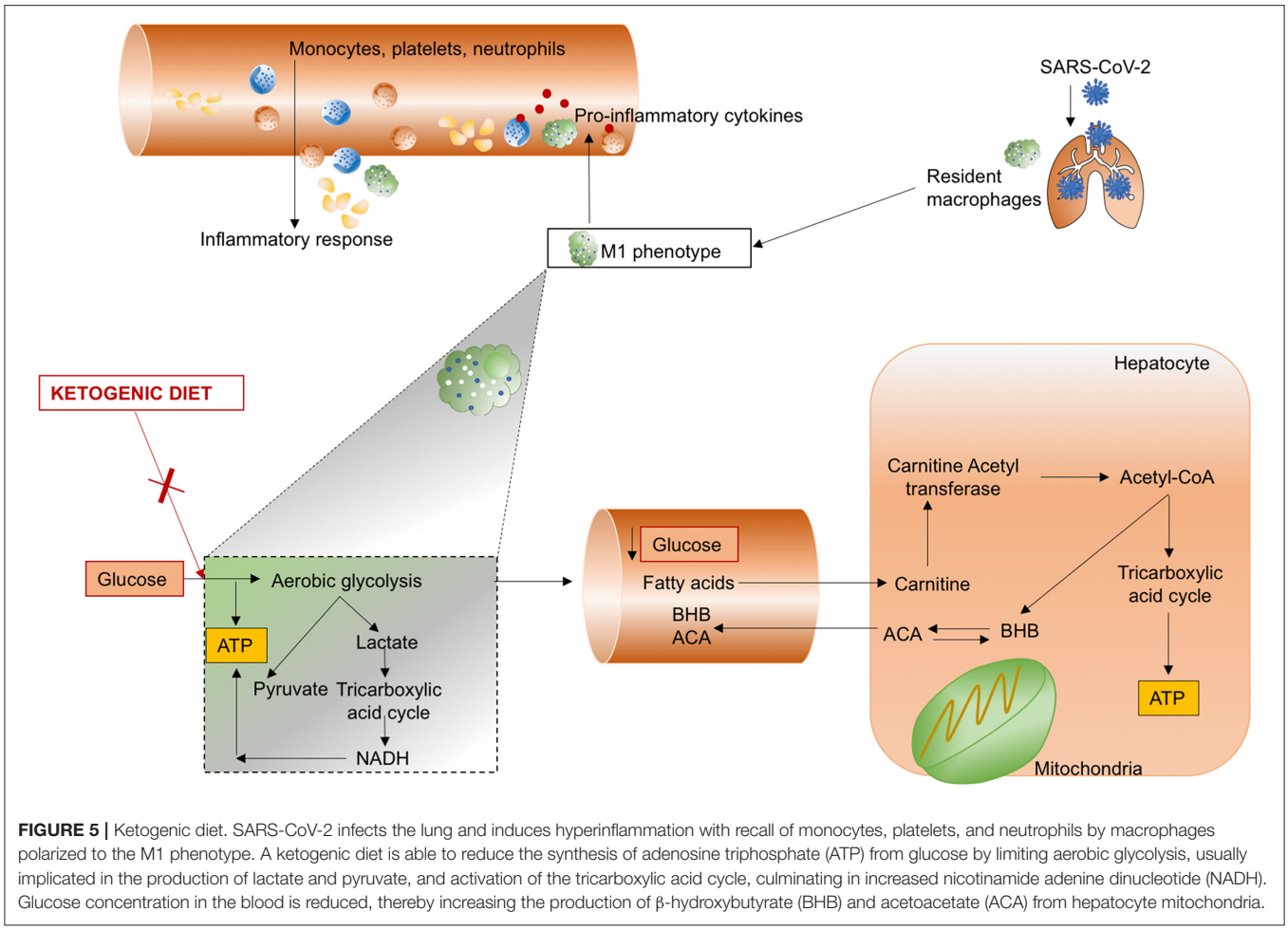

FIGURE 5 | Ketogenic diet. SARS-CoV-2 infects the lung and induces hyperinflammation with recall of monocytes, platelets, and neutrophils by macrophages polarized to the M1 phenotype. A ketogenic diet is able to reduce the synthesis of adenosine triphosphate (ATP) from glucose by limiting aerobic glycolysis, usually implicated in the production of lactate and pyruvate, and activation of the tricarboxylic acid cycle, culminating in increased nicotinamide adenine dinucleotide (NADH). Glucose concentration in the blood is reduced, thereby increasing the production of β-hydroxybutyrate (BHB) and acetoacetate (ACA) from hepatocyte mitochondria.

that promotes metabolic ketosis. This has proved to be efficient in controlling glucose levels and body weight, and in promoting anti-inflammatory effects in obesity and type 2 diabetes (199, 200). Ketogenic diets were initially proposed to control refractory status epilepticus and protect the central nervous system (201, 202). Over time, evidence emerged that very low-carbohydrate diets decreased energy intake while improving lipid and glucose homeostasis (203), as well as decreasing levels of inflammatory markers (181). Preliminary results in a murine model of beta coronavirus infection demonstrated that ketones protect against systemic inflammatory response (204). The rationale for using ketogenic diet in COVID-19 is summarized in the following paragraphs. Furthermore, a trial investigating the use of ketogenic diet for patients with COVID-19 is ongoing (205).

The release of inflammatory cytokines and caspase-1, as occurs in SARS-CoV-2 infection following the activation of innate immunity in response to damage-associated molecular pattern (DAMPs) (7), can be modulated by the nod-like receptor protein-3 (NLRP3) inflammasome (206). Ablation of NLRP3 is able to attenuate type 2 diabetes and atherosclerosis (7), which have been identified in most patients with severe COVID-19. During a ketogenic diet, alternative sources of energy are produced by the liver, including the ketone bodies β-hydroxybutyrate (BHB) and acetoacetate (ACA), to maintain the metabolic functions of the brain, heart, and skeletal muscles. The increased consumption of liver glycogen stores that is characteristic of all ketogenic diets is also associated with altered immune cell function. Specifically, the use of lactate as a source of mitochondrial oxidative energy plays a key role in the production of innate immune type I cells and interferon type I, which are effective in the host defense against viral infections (207). In an experimental mouse model, caloric restriction implemented through a ketogenic diet was found to exert anti-inflammatory effects; ketone bodies attenuated caspase-1 activation and IL-1β secretion by modulating the NLRP3 inflammasome (208). Recent research has proposed that the inhibitor of glycolysis, deoxy-D-glucose, could be a reasonable therapeutic strategy for SARS-CoV-2 infection (209), because it has been found to reduce the duration of ventilator support and partial pressure of carbon dioxide in patients with acute respiratory failure (210). The mechanisms of action of a ketogenic diet are summarized in **Figure 5**.

CONCLUSIONS

Dysbiotic states of the microbiota may impact on the pathogenesis, as well as on the complexity, of immune and inflammatory diseases. Several mechanisms have been identified as potential targets to reduce inflammation and secondary infections. Particularly, novel nutritional interventions have been proposed to regulate the mechanisms underlying dysbiosis of the lung and intestinal microbiota. However, further studies on patients with severe COVID-19 are needed to confirm the effective benefit of such interventions.

AUTHOR CONTRIBUTIONS

DB: conceptualization, writing original draft, review, and editing. CR, AF, ST, SS, VD, DG, AV, MB, IB, NP, LB, and AT: review and editing. PR and PP: writing, review, and editing. All authors contributed to the article and approved the submitted version.

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Pneumatosis Intestinalis in the Setting of COVID-19: A Single Center Case Series From New York

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This case series reviews four critically ill patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [coronavirus disease 2019 (COVID-19)] suffering from pneumatosis intestinalis (PI) during their hospital admission. All patients received the biological agent tocilizumab (TCZ), an interleukin (IL)-6 antagonist, as an experimental treatment for COVID-19 before developing PI. COVID-19 and TCZ have been independently linked to PI risk, yet the cause of this relationship is unknown and under speculation. PI is a rare condition, defined as the presence of gas in the intestinal wall, and although its pathogenesis is poorly understood, intestinal ischemia is one of its causative agents. Based on COVID-19's association with vasculopathic and ischemic insults, and IL-6's protective role in intestinal epithelial ischemia–reperfusion injury, an adverse synergistic association of COVID-19 and TCZ can be proposed in the setting of PI. To our knowledge, this is the first published, single center, case series of pneumatosis intestinalis in COVID-19 patients who received tocilizumab therapy.

Keywords: pneumatosis intestinalis, COVID-19, SARS-CoV-2, mesenteric ischemia, ischemia-reperfusion injury, molecular targeted therapy, tocilizumab, IL-6 inhibitor

INTRODUCTION

Pneumatosis intestinalis (PI) is a rare condition (prevalence ∼0.03%) defined as the presence of gas in the wall of the small or large intestine (1–3). PI can represent an incidental, benign finding (primary or idiopathic PI, 15% of cases) or a potentially life-threatening gastrointestinal disease (secondary PI, 85% of cases) (4). Secondary PI is frequently associated with chronic obstructive pulmonary disease (COPD) as well as ischemic, necrotic, and obstructive gastrointestinal insults (5, 6). PI is a radiographic sign characterized by linear and/or curvilinear gas collections in the

intestinal wall and is often indicative of systemic or local pathological processes affecting the bowel wall (7, 8). Secondary PI is frequently associated with different clinical scenarios, such as premature newborns with necrotizing enterocolitis, adults with obstructive pulmonary diseases as well as ischemic, necrotic, infectious, and obstructive gastrointestinal insults, celiac disease, amyloidosis, AIDS, rheumatic diseases, and certain drugs, particularly steroids, chemotherapeutics, glucosidase inhibitors, laxatives (lactulose), and molecular targeted agents such as tocilizumab (TCZ) (5, 7, 9–13). The clinical manifestations of PI depend on the bowel segments involved. When PI affects the small intestine, vomiting, abdominal distension, weight loss, and abdominal discomfort/pain are the most common manifestations. Less frequently, diarrhea, anorexia, and constipation can be present. When PI involves the large intestine, diarrhea, hematochezia, abdominal discomfort/pain, and distension are the most common signs and symptoms. Less frequently, constipation, weight loss, and tenesmus may occur (1, 14, 15). The pathogenesis of PI is poorly understood; however, clinical and preclinical studies suggest that PI results from a complex combination of abnormal biochemical, microbiological, and mechanical aspects of intestinal functioning (16).

In December 2019, a novel coronavirus [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] was identified in Wuhan, China as the primary cause of a potentially fatal and multisystemic disease [coronavirus disease 2019 (COVID-19)] (17–19). Since then, three meta-analyses reported that ∼15% of COVID-19 patients had GI symptoms, most commonly diarrhea (20–22). GI manifestations in COVID-19 have been acknowledged as early signs of severe/critical disease, usually preceding respiratory symptoms (23, 24). How COVID-19 affects the GI tract is still an open question. Nonetheless, a growing body of evidence suggests that the interaction between SARS-CoV-2 and angiotensin-converting enzyme 2 (ACE2) receptors may result in impaired gut microbiome and immunity (24–26). Furthermore, hypoxia, which putatively has a physiological role in intestinal homeostasis, can be altered as a consequence of COVID-19-induced hypoxia (24, 27).

Systematic reviews and other large observational studies have discussed the association of GI complications in patients undergoing TCZ treatment; however, PI after TCZ use has been recognized by a small number of reports (9, 28, 29). Intestinal perforation is particularly an infrequent but feared complication during TCZ therapy. The exact mechanism of TCZ and GI insults is unknown, but interleukin (IL)-6 antagonism, the primary mechanism of action of TCZ, may impair intestinal homeostasis and recovery capacity after intestinal ischemia (9, 30–33). Remarkably, a history of diverticulitis, non-steroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids use has also been recognized as a risk factor for GI perforation during TCZ treatment (30, 34).

Only four independent case reports have described PI in COVID-19 patients (35–38). Importantly, although TCZ is being utilized as an experimental treatment for COVID-19, the two together may have adverse synergistic effects resulting in increased risk for PI and other related complications. This is the first case series presenting the detailed clinical course of four COVID-19 patients who all received TCZ and developed PI.

CASE PRESENTATION 1

A 65-year-old man with a past medical history (PMH) of asthma, hypertension (HTN), hyperlipidemia (HLD), insulin resistance, and obstructive sleep apnea (OSA) was admitted to the hospital due to dyspnea, tachypnea [respiratory rate (RR), 22/min], cough, fever (103°F), and hypoxia [blood oxygen saturation levels (SpO_2), 81%] after having a 2-week period of fever, chills, and body aches. Symptoms had worsened in the last 72 h before admission. On admission, the patient was placed on a non-rebreather mask (NRB) at 11 L/min (LPM) due to respiratory distress, which partially improved hypoxia from SpO_2 81 to 91%. Three days after admission, the respiratory status worsened revealing diffuse bilateral ground-glass opacification on chest CT scan, along with increased counts of neutrophils in plasma, lymphopenia, and transaminitis. Labs showed increased ferritin and C-reactive protein (CRP) levels (**Table 1**), features compatible with the cytokine release-like syndrome associated with COVID-19 (39, 40). Based on his clinical condition with pending COVID-19 testing results, the patient was started on albuterol, meropenem, hydroxychloroquine, ascorbic acid, thiamine, TCZ, and enoxaparin prophylaxis. One day later, due to decreased oxygen saturation, the patient was placed in pronation. Upon worsening hypoxia, severe dyspnea, positive polymerase chain reaction (PCR) COVID-19 swab testing, and meeting the criteria for acute respiratory distress syndrome (ARDS), the patient was intubated. Furthermore, prophylactic enoxaparin was switched to intravenous (IV) heparin 1,500 U/h, and an IL-1 inhibitor (anakinra) was started. Shortly, a vasoplegic shock refractory to adjustments in sedative medications prompted onset of vasopressors (norepinephrine). Since admission, the patient had no bowel movements despite the use of laxatives (lactulose), prokinetics (metoclopramide), and enemas (saline laxative). Progressive abdominal distension warranted a CT scan demonstrating extensive colon and small bowel pneumatosis with mesenteric and portal venous gas, raising suspicions of bowel ischemia (**Figures 1A–D**). Based on the patient's clinical and pathological characteristics, lactate levels of 2.0 mmol/L, and no increased vasopressor requirement, surgical resection was not considered the best course of action at the time. Laxative regimen was enhanced with polyethylene glycol and senna. Monitoring of intra-abdominal pressure ranged from 13 to 19 mmHg, which suggested a likely abdominal compartment syndrome (41). Six days after initiation of mechanical ventilation, the patient developed non-oliguric acute kidney injury (AKI) likely secondary to COVID-19 sepsis and acute tubular necrosis (ATN) from hemodynamic instability. The patient was approached in a conservative, non-surgical fashion including switching propofol to ketamine, adjusting IV fluids, using piperacillin–tazobactam for enteric bacteria, and holding potential nephrotoxic agents. A repeated CT scan 12 days after the initial scan showed changes consistent with bowel ischemia, as well as signs suggestive of peritonitis, complicated by bowel

TABLE 1 | Pneumatosis intestinalis in the setting of COVID-19: case series summary.

	Past medical history	Initial clinical features	Abdominal imaging	Laboratory results during admission	Experimental "COVID-19 drugs" received	TCZ administration to PI manifestation (days)
Case #1	HTN, HLD, ASTHMA, IR, OSA	Dyspnea Tachypnea Hypoxia (SpO_2, 81%) Cough (non-productive) Fever (103°F) Chills Body aches ARDS	Abd. CT scan: extensive colon and small bowel pneumatosis with mesenteric and portal venous gas (**Figures 1A–D**).	Neutrophilia (88.8%), lymphopenia (5.2%) Hypokalemia (3.3 mmol/L), transaminitis (AST 64 U/L, ALT 47 U/L) Increased anion gap (18 mmol/L), D-dimer (2,986 ng/mL), CRP (14.17 mg/dL), LDH (545 U/L), and ferritin (1,013 ng/mL) Hypoxia (ABG ∼ PaO_2, 73 mmHg)	Anakinra Ascorbic acid Enoxaparin HCQ TCZ Thiamine	3 days
Case #2	HTN, HLD, DM, OSA	Dyspnea Tachypnea (RR, 40/min) Hypoxia (SpO_2, 76%) Cough (productive) Fever (103.9°F) Chest pain Chills Myalgias Hyporexia ARDS	Abd. CT scan: air presence in the portal vein and superior mesenteric artery, as well as cecal and small bowel pneumatosis (**Figures 2A–D**).	Neutrophilia (83%), lymphopenia (11.4%) Increased D-dimer (453 ng/mL), fibrinogen (894 mg/dL), BNP (1,164 pg/mL), CRP (45.34 mg/dL), procalcitonin (0.20 ng/mL), ferritin (1,196 ng/mL), and creatinine (2.01 mg/dL) Hyperglycemia (210 mg/dL), transaminitis (AST; 57 U/L) Hyperlactemia (5.1 mmol/L), hypokalemia (3.2 mEq/L) Oliguria (200 mL/24 h), eGFR (32 mL/min) Hypoxia (ABG∼PaO_2, 51 mmHg) LDH (646 U/L) Metabolic alkalosis (pH 7.48, HCO_3^- 30 mEq/L, BE 6.2 mmol/L)	AZI CP Enoxaparin MP TCZ	11 days
Case #3	HTN	Dyspnea Cough (non-productive) Hypoxia (SpO_2, 85%) Fever (100.9°F) Fatigue Non-bloody diarrhea	Abd. CT scan: diffuse small and large bowel pneumatosis (**Figures 3A–D**).	Neutrophilia (83.9%), lymphopenia (10.5%) Respiratory alkalosis (pH 7.51, HCO_3^- 24 mEq/L, pCO_2 30 mmHg) Hypoxia (ABG ∼ PaO_2, 61 mmHg) Hypoalbuminemia (2.8 g/dL), transaminitis (AST; 161 U/L, ALT; 109 U/L). Increased D-dimer (394 ng/mL), CRP (21.15 mg/dL), LDH (639 U/L), and ferritin (7,378 ng/mL)	Anakinra Enoxaparin HCQ MP TCZ	3 days
Case #4	HTN, DM, Stroke	AMS Upper respiratory symptoms (N/A)	Abd. CT scan: presence of gas in the portal vein and mesenterium as well as extensive bowel pneumatosis (**Figures 4A–D**).	Leukocytosis (13.76 × 10^9/L) Increased D-dimer (3,136 ng/mL), procalcitonin (0.70 ng/mL), CRP (3.64 mg/dL), and LDH (982 U/L) Hyperlactemia (8.6 mmol/L), hyperkalemia (5.6 mEq/L) Hyperglycemia (478 mg/dL), hypertriglyceridemia (918 mg/dL) Hypoalbuminemia (3.1 g/dL) Uremia (serum creatinine, 3.85 mg/dL/BUN, 150 mg/dL) eGFR (16 mL/min), oliguria (155 mL/24 h) Mixed acidosis (pH 7.14, HCO_3^- 18 mEq/L, pCO_2 56 mmHg)	HCQ MP Remdesivir TCZ	10 days

HTN, arterial hypertension; HLD, hyperlipidemia; IR, insulin resistance; OSA, obstructive sleep apnea; DM, diabetes mellitus; CRP, C-reactive protein; HCQ, hydroxychloroquine; TCZ, Tocilizumab; AZI, azithromycin; MP, methylprednisolone; CP, convalescent plasma; AMS, altered mental status; AKI, acute kidney injury; N/A, not available; ARDS, acute respiratory distress syndrome; ABG, arterial blood gases; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BE, base excess; eGFR, estimated glomerular filtration rate.

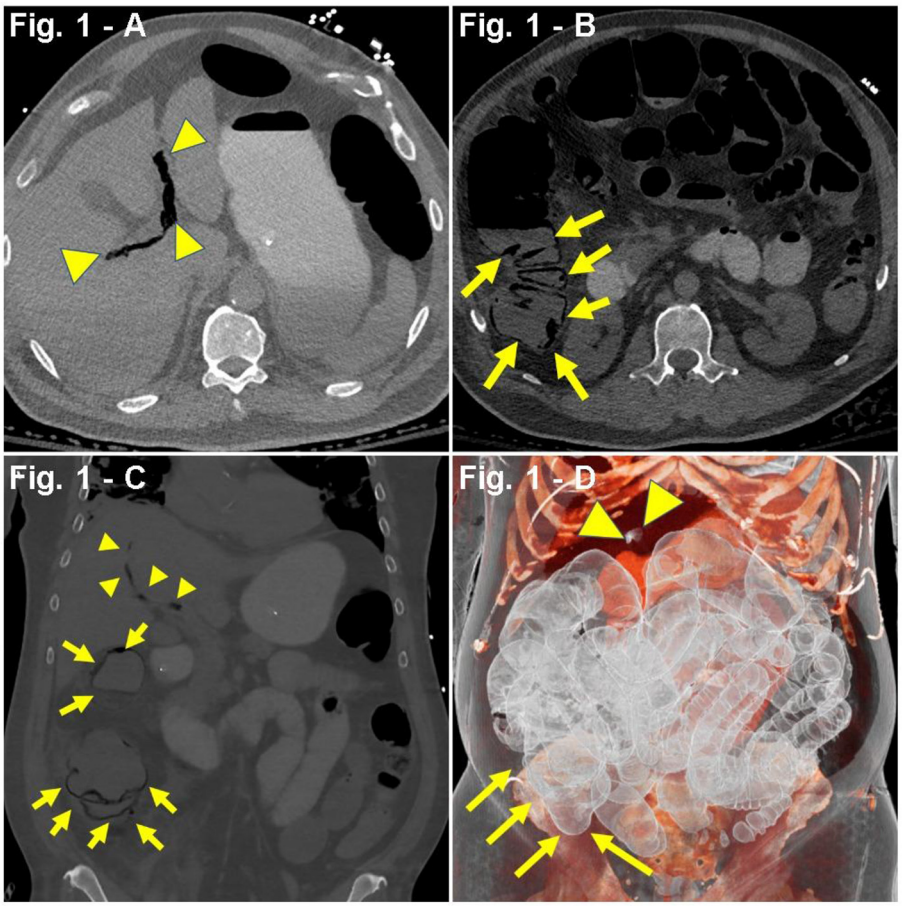

FIGURE 1 | (A–D) Case presentation of 65-year-old male patient with COVID-19, 5 days after tocilizumab (TCZ), non-contrast abdominal CT. **(A,B)** Axial, **(C)** coronal, and **(D)** 3D reconstruction, pneumatosis intestinalis (PI) involving ascending colon (yellow arrows), with dilated multiple right lower quadrant small bowel loops with mesenteric and portal venous gas (yellow arrowheads).

perforation, pneumoperitoneum, small bowel obstruction (SBO), enterocutaneous fistulas, and abscess formation. Additionally, the patient developed hematochezia and melena, requiring aggressive resuscitation, including multiple blood and frozen plasma transfusions, as well as repeated drainage procedures to address the intra-abdominal collections. Noteworthy, a CT angiogram ruled out active bleeding at the time of melena and hematochezia. The patient slowly and progressively recovered and was finally discharged for rehabilitation, 90 days after admission. In a delayed fashion, he underwent a right colectomy. Currently, he is alive and well.

CASE PRESENTATION 2

A 61-year-old man with a PMH of HTN, HLD, diabetes mellitus (DM), and OSA was admitted to the hospital after presenting with dyspnea, tachypnea (RR, 40/min), hypoxia (SpO_2, 76%), worsening cough (productive, non-bloody), fever (103.9°F), chills, myalgias, hyporexia, and chest pain. Symptoms began 4 weeks prior, and 2 weeks prior to admission, he received a course of azithromycin and oseltamivir. One week prior to admission, the patient visited the ED for myalgias, chills, and cough but was discharged with a normal chest X-ray (CXR). The physical examination during the second ED visit was remarkable for severe respiratory distress and bilateral basilar crackles. His hypoxia initially improved with 6 LPM nasal cannula (NC) from SpO_2 of 76–91%, albeit later requiring 6 L NRB (SpO_2, 76–95%). CXR revealed bilateral infiltrates, and a CT angiogram with contrast confirmed lung parenchyma compromise with extensive bilateral ground-glass opacities in both lungs. Pulmonary embolism (PE) could not be excluded due to motion associated with the hyperdynamic state. Lab workup revealed positive COVID-19 PCR test through nasal swabbing, lymphopenia, increased D-dimer (453 ng/mL), brain-derived natriuretic peptide (BNP) (1,164 pg/mL), and procalcitonin (0.20 ng/mL) (**Table 1**). During the first night of admission, the patient became severely hypoxic (PaO_2, 51%), with improvement in SpO_2 from 80 to 88% after aggressive resuscitation with steroids (IV methylprednisolone, 100 mg), diuretics (IV

furosemide, 40 mg), oxygen (15 LPM NRB), and pronation. On second day of admission, the patient was transferred to the ICU, received one dose of TCZ, and was started on IV methylprednisolone, 50 mg twice daily, IV furosemide, 40 mg daily, inhaled albuterol every 6 h, prophylactic enoxaparin, and non-invasive ventilation (BiLevel 18/14). On the second day of ICU admission, the patient received convalescent plasma (plasma from recovered COVID-19 patients). One week after admission, upon worsening hypoxia and hemodynamic instability, the patient underwent endotracheal intubation for mechanical ventilation and was started on a double regimen of vasopressors (vasopressin, 0.04 U/min and norepinephrine, 0.9 mcg/kg/min). The patient suffered two episodes of arterial thrombosis despite proper anticoagulation with argatroban. Five days after initiating mechanical ventilation, physical examination revealed a protuberant abdomen and dark output from the nasogastric tube (NGT). Further workup showed increased lactate and leukocytosis, hyperkalemia (5.8 mEq/L), increased creatinine (2.01 mg/dL), and oliguria. Abdominal CT scan reported gas in the portal vein and superior mesenteric artery, as well as cecal and small bowel pneumatosis (**Figures 2A–D**). The benefit of a surgical intervention was considered very low in the setting of an unstable patient with multiorgan failure; hence, it was approached conservatively, including antibiotics (metronidazole and vancomycin), proton-pump inhibitors (pantoprazole), renal replacement therapy [continuous veno-venous hemofiltration (CVVH)], fluid optimization, and metabolic support. On the 10th day of ICU admission, the patient developed refractory cardiopulmonary arrest associated with metabolic acidosis and lactate levels of 24 mmol/L.

CASE PRESENTATION 3

A 64-year-old man with a PMH of HTN was admitted for 1 week history of dyspnea, cough, fever (100.9°F), and fatigue. Pulse oximetry revealed hypoxia (SpO_2, 85%), which initially improved to SpO_2 of 90% with NC at 6 LPM, and later on to SpO_2 of 92–94% with 10 LPM NRB. A CXR showed bilateral ground-glass opacities. On the second day of admission, the patient developed non-bloody diarrhea. With pending results from PCR COVID-19 nasal swabbing, a presumptive diagnosis of COVID-19 pneumonia was established, and the patient was started on a regimen of PO hydroxychloroquine 200 mg twice daily, IV methylprednisolone 50 mg twice daily, SC prophylactic enoxaparin 40 mg daily, anakinra (IL-1 inhibitor, SC 100 mg every 6 h), and inhaled albuterol. Lab work revealed neutrophilia, lymphopenia, respiratory alkalosis, hypoalbuminemia, transaminitis, as well as increased d-dimer, CRP, lactate dehydrogenase (LDH), and ferritin (**Table 1**). Despite initial improvement, 5 days after admission, he presented with a nocturnal crisis of hypoxia (SpO_2, ∼60%), which improved after pronation. Four hours later, the patient (without any relevant psychiatric/neurological history) developed intermittent episodes of delirium, agitation, and altered mental status, which was treated with haloperidol. Subsequently, due to worsening hypoxia, the patient underwent sedation, endotracheal intubation, and mechanical ventilation. At this point, the patient was transferred to another ICU and, upon arrival, was found to have an unsecure airway, raising concern for potential aspiration. Based on this, the patient was started on a regimen of IV piperacillin–tazobactam and one dose of vancomycin. Nine days after initial hospital admission, the patient developed septic shock and prerenal acute kidney injury, which prompted hemodynamic support with a norepinephrine drip (0.02 mcg/kg/min). Enoxaparin was switched to IV sodium heparin due to a D-dimer of 987 ng/mL. Additionally, the patient received a single dose of TCZ. Three days after TCZ administration, routine physical examination showed abdominal distension and tympanism with digital percussion. An abdominal X-ray revealed features compatible with colonic ileus or pseudo-obstruction. Subsequent CT scan showed diffuse small and large bowel pneumatosis (**Figures 3A–D**). This was found in the setting of worsening kidney and liver function, increased ventilation requirements, acidosis (pH 7.17), and leukocytosis (35,000 WBC/mL). Due to broad multiorgan failure, the patient was not deemed a good surgical candidate for segmental resection. CXR showed additional bilateral consolidations in the lower lobes, along with worsening respiratory status, suggesting a superimposed pneumonia. At this point, with the diagnosis of septic shock and multiorgan failure, and considering the ominous prognosis, the family decided to prioritize comfort over other aggressive measures. The patient was withdrawn from mechanical ventilation and developed a cardiopulmonary arrest 4 min thereafter.

CASE PRESENTATION 4

A 64-year-old man with PMH of HTN, insulin-dependent type 2 DM, and stroke 3 years prior with no residual deficits was admitted to an out-of-network hospital due to altered mental status and acute kidney injury (serum creatinine, 2.2 mg/dL). The family reported upper respiratory symptoms 1 week before admission. No acute changes were observed in the patient's head CT scan. Due to concerns of a potential non-ST-segment elevation myocardial infarction (NSTEMI) in the setting of uncontrolled HTN, the patient was started on aspirin, clopidogrel, and a heparin drip. Based on a positive COVID-19 PCR nasal swabbing at admission and concerns for a potential bacterial pneumonia, hydroxychloroquine, remdesivir, ceftriaxone, and doxycycline were initiated. Worsening kidney function parameters (serum creatinine, 2.2–4.2 mg/dL) after antibiotic and antiviral treatment prompted suspension of these medications. One week after admission, the patient received a single dose of TCZ and was started on steroids (IV methylprednisolone, 40 mg every 8 h). By hospital day 10, despite non-invasive ventilation (BiPAP), the progressive worsening of the respiratory status required intubation and mechanical ventilation. One day later, the patient was transferred to our hospital upon family request. On initial assessment, the patient was found to be hypotensive, with oliguria (155 mL/24 h), mixed acidosis (pH 7.04, HCO_3^- 17 mEq/L, pCO_2 56 mmHg), hyperkalemia (5.6 mEq/L),

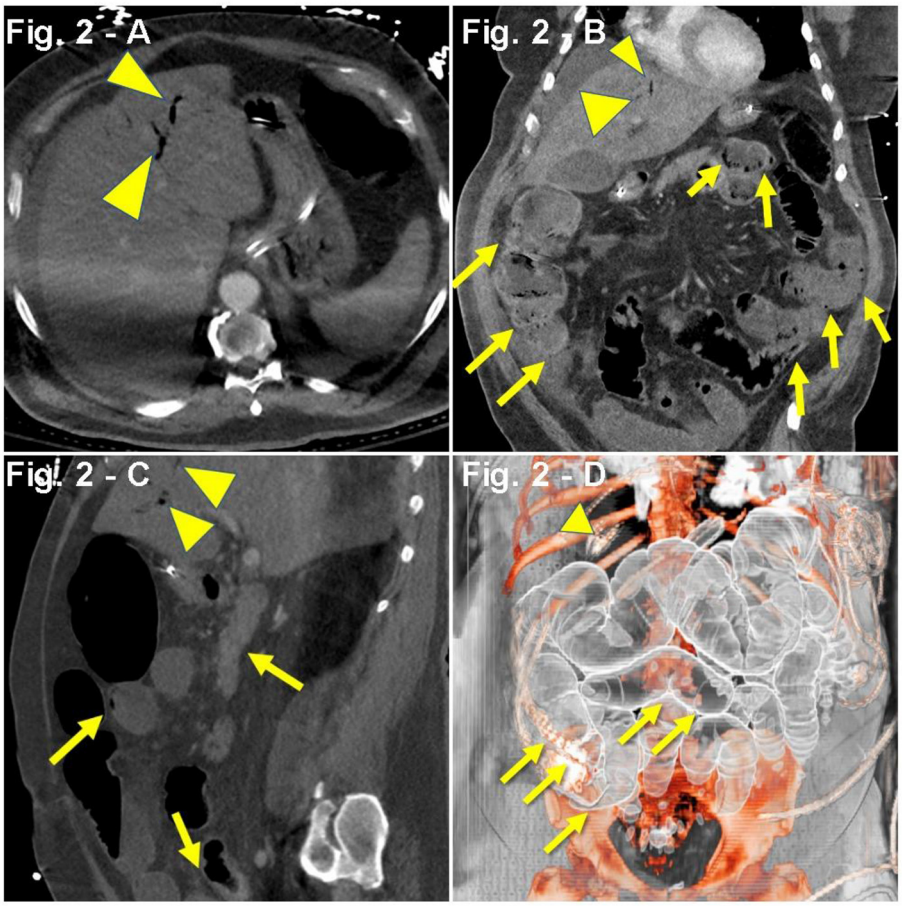

FIGURE 2 | (A–D) Case presentation of a 61-year-old male COVID-19 patient with respiratory failure on TCZ with rising lactate, abdominal ileus, abdominal CT with intravenous and oral contrast, **(A)** axial, **(B)** coronal, **(C)** sagittal, and **(D)** 3D reconstruction, with ileus and small and large bowel dilatation, with small bowel and cecal pneumatosis (yellow arrows) with portal gas (yellow arrowheads), and splenic and mesenteric vein gas.

hyperglycemia (478 mg/dL), hypertriglyceridemia (918 mg/dL), hypoalbuminemia (3.1 g/dL), and uremia [serum creatinine 3.85 mg/dL, blood urea nitrogen (BUN) 150 mg/dL], which prompted continuous renal replacement therapy (**Table 1**). Intensive resuscitation with albumin, bicarbonate, insulin, norepinephrine, and vancomycin was initiated. Propofol was discontinued and switched to dexmedetomidine. The patient also received IV pantoprazole 40 mg, polyethylene glycol, lactulose, senna, and methylnaltrexone. Subsequently, the patient developed fever (101.4°F), leukocytosis (33.16×10^9/L), and low platelets (85×10^9/L). Due to concerns of potential heparin-induced thrombocytopenia, heparin was suspended and replaced with argatroban. Despite intensive supportive care, vasopressor requirements increased prompting the addition of vasopressin at 0.04 U/min. Leukocytes count and lactate further increased (33.16×10^9/L to 40×10^9/L; 2.7–8.6 mmol/L, respectively). One week after the hospital transfer, abdominal distension on physical exam prompted a CT scan that revealed gas in the portal vein and mesentery as well as extensive intestinal pneumatosis (**Figures 4A–D**). Surgical assessment dismissed a potential bowel resection since the risks were considered greater than any potential benefit. The patient developed refractory septic shock and, 1 day later, a cardiopulmonary arrest.

DISCUSSION

Pneumatosis intestinalis is thought to result from a complex combination of biochemical, microbiological, and mechanical insults to the intestine (16). The biochemical hypothesis argues that PI originates from excessive hydrogen production by enteric bacteria through chyme fermentation. Support of this hypothesis includes observational studies demonstrating that patients with PI have elevated levels of hydrogen in their breath compared with control patients (42, 43). The microbiological or bacterial hypothesis suggests that gas forming bacteria, such as *Clostridium* species, infringe upon the mucosa through breaches, reaching the submucosa and subsequently forming intramural gas collections (44). Experimental models supporting this hypothesis include the improvement and resolution of the aforementioned intramural

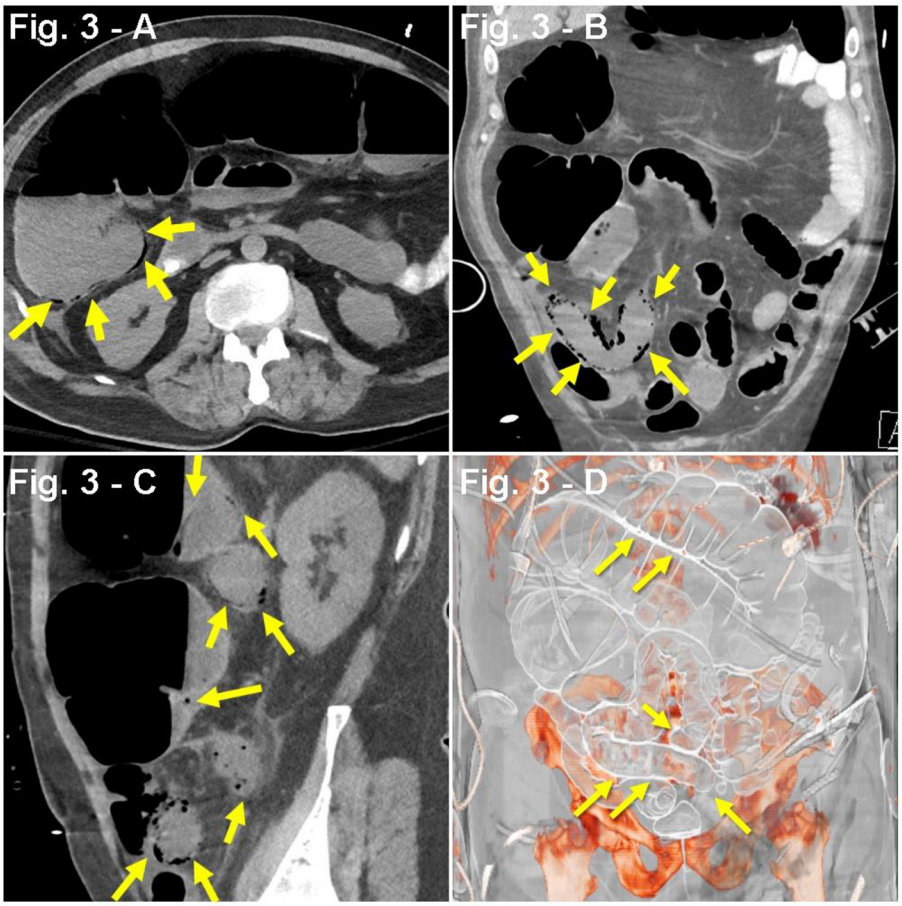

FIGURE 3 | (A–D) Case presentation of a 63-year-old male patient, with dyspnea, cough, fever from COVID-19, with bloody diarrhea, and abdominal distention 3 days after receiving TCZ, abdominal CT with oral contrast only, **(A)** axial, **(B)** coronal, **(C)** sagittal, and **(D)** 3D reconstruction with consolidation seen along lung bases, and pneumatosis of small bowel loops (yellow arrows) with dilated small and large bowel loops consistent with ileus.

gas collections by antibiotic treatment (45). An alternative mechanical hypothesis states that gas can reach the submucosal compartment of the intestinal wall either through breaks in the mucosa (intraluminal source) or the serosal surface (extraluminal source). Indeed, common conditions associated with mucosal disruption are consistently related with PI, such as necrotizing enterocolitis, inflammatory bowel disease, gastrointestinal (GI) tract infections, irritant ingestion, and intestinal ischemia (1). Gas originating extraluminally can be traced to conditions where air can diffuse through tissues, as occurs in COPD (46).

It should be acknowledged that PI is not a disease itself, but rather the imaging manifestation of an underlying pathology or combination of pathologies. As such, the underlying etiology (e.g., ischemia, drugs, infections) must always be addressed accordingly prior to specific treatments (47–49). When PI is accompanied with signs of peritonitis, pH <7.3, HCO_3^- <20 mEq/L, lactate >2.0 mmol/L, and/or portal venous gas, emergent exploratory laparotomy should be considered (50, 51). Treatment is usually based on the severity of symptoms and can range from repeated imaging in asymptomatic patients to elemental diet for mild symptoms, to antibiotics, oxygen therapy, and hospitalization for severe cases. Notably, clinical judgement is an instrumental component of the decision-making process (7, 45, 52–54).

Since March 11th of 2020, when the global COVID-19 pandemic was formally declared, a growing body of evidence has shown the systemic and extrapulmonary compromise that can potentially occur in the setting of COVID-19 (55). The involvement of neurological, cardiovascular, gastrointestinal, hematopoietic, endocrine, and immune systems have been described in many studies (56–59). Additionally, the ischemic damage seen during COVID-19 infection has also been described in several systematic reviews (60–63). Indeed, observational studies have shown the association of COVID-19 with abdominal ischemia; nonetheless, its pathophysiology remains unknown (64). Research has shown a clear association between high levels of proinflammatory cytokines and inflammatory markers with severe, critical, and fatal forms of COVID-19 (40). Under the logic of specifically targeting the COVID-19-associated "cytokine storm", trials with specific cytokine inhibitors, such as TCZ,

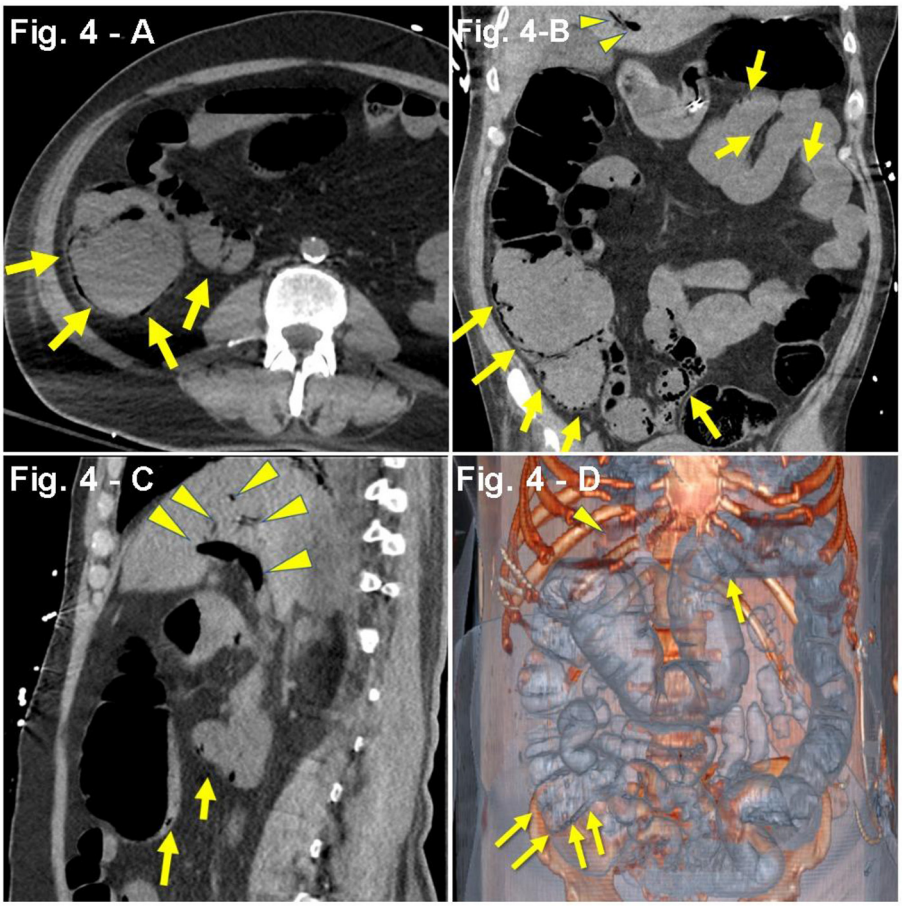

FIGURE 4 | (A–D) Case presentation of a 64-year-old male patient, with altered mental status, acute kidney injury, DM2, stroke, bacterial pneumonia with COVID-19, single-dose TCZ, hypotensive, oliguric, non-contrast abdominal CT only, **(A)** axial, **(B)** coronal, **(C)** sagittal, and **(D)** 3D reconstruction with pneumatosis of distal transverse colon, cecum, terminal ileum, and mesenteric venous gas adjacent to the terminal ileum (yellow arrows) concerning for bowel ischemia. There are foci of air in mesenteric vessels in the right lower quadrant, with portal venous gas (yellow arrowheads).

sarilumab, siltuximab (all anti-IL-6), and anakinra (anti-IL-1), have been conducted worldwide[1]. TCZ is an evidence-based treatment for rheumatoid arthritis; however, there are no clear benefits in the setting of COVID-19. At the time of writing, double-blind, randomized, clinical trials have failed to prove any benefit from these drugs in COVID-19 (65, 66). An observational study that included a cohort of 1,351 COVID-19 patients showed that patients receiving TCZ had a decreased risk of invasive mechanical ventilation and death compared to matched controls (67). Another study suggested that TCZ was associated with decreased vasopressor requirements (68). Although PI and gastrointestinal perforation have been recognized as potential adverse effects of TCZ, the mechanisms are completely unknown (9, 30).

Several hypotheses argue in favor of a prothrombotic, microangiopathic, and therefore ischemic effect of COVID-19: (1) SARS-CoV-2 virus can directly invade endothelial cells, resulting in endothelialitis, endothelial dysfunction, and thrombosis (69–72); (2) capillary viscometry showed hyperviscosity in critically ill COVID-19 patients (73); (3) platelet activation and platelet–monocyte aggregation formation in severe COVID-19 patients was documented (74); and (4) thromboelastography (TEG) parameters (decreased R and K values, increased K angle, and MA) consistent with a hypercoagulability state have been found in COVID-19 patients (75).

In short, this case series portrays four critically ill patients who, in the setting of ARDS due to severe COVID-19, received TCZ as an experimental treatment, and all developed complex clinical courses of PI, which subsequently resulted in perforation, sepsis, hemodynamic instability, multiorgan failure, and death in three out of four patients. Herein, we highlight a potential correlation between an infectious disease (COVID-19), an experimental drug in this setting (TCZ), and a rare GI complication (PI). COVID-19 and TCZ have been independently associated with PI (9, 36–38). Intestinal

[1]Available online at: https://clinicaltrials.gov/ct2/results?cond=&term=tocilizumab$+$covid-19&cntry=&state=&city=&dist=.

ischemia is a well-established cause of PI; however, the causative mechanism of PI during TCZ treatment is unknown. Preclinical studies suggested that IL-6 plays a critical role in intestinal epithelial proliferation and repair after ischemia–reperfusion, traumatic, and microbiological insults (30, 76). Clinical studies have shown IL-6's pivotal role in vascular endothelial growth factor production, as well as angiogenesis and wound healing (31–33).

Taken together, we venture to think that a possible negative and devastating synergy occurs between the microvascular insults from COVID-19, along with the lack of epithelial protection and vascular support from IL-6 blocking, ultimately resulting in intestinal wall damage, epithelium dysfunction, and intraluminal gas diffusion (Pneumatosis Intestinalis). However, it must be acknowledged that COVID-19 may affect intestinal homeostasis by other complex mechanisms involving gut microbiome and barrier functioning (24). To the best of our knowledge, this is the first case series of PI in COVID-19 patients, as well as the first reported from the same institution, and the first report of COVID-19 patients treated with TCZ who subsequently developed PI.

At the time of writing, COVID-19 is a novel entity with poorly understood pathology. Experimental, emergency, and compassionate use of drugs in COVID-19 has been the object of recent discussions. It should always be cautioned that deleterious interactions between drug-related adverse effects and intrinsic features of an infectious disease, in this case COVID-19, can lead to further complications (77, 78) "*Primum non nocere*".

LIMITATIONS

Discussions regarding the causal relationship between COVID-19 and TCZ with PI are beyond the scope of this publication. However, it is important to acknowledge that some medications that patients received (methylprednisolone and lactulose) may be linked to PI development (1, 13, 79–81). Furthermore, these four critically-ill patients received intensive care support, which inherently adds numerous variables, including known and unknown interactions between each other and the host, resulting in an uncertain number of potential confounders. Additionally, two patients (Cases 3 and 4) received initial care at an outside hospital, and although the hospital course summary was accessible, the variability of clinical setting may hide unknown confounders. Therefore, it is complex and not possible for the authors to establish any definite cause–effect connection between the described variables (COVID-19 and TCZ) with the highlighted clinical outcome (PI). Further preclinical and clinical research addressing interactions between COVID-19 and TCZ with PI is warranted.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Study approved by IRB #: 20-0884, Feinstein Institutes for Medical Research. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SM, LB, SG, CK, KH, and EM prepared the manuscript's first draft. SM, LB, and EM retrieved and corroborated the data. CK prepared the figures and edited the manuscript. LS-L, JA, TA, KS, EG, VN, NJ, CM, TY, RT, YC, MS, RC, SW, HH, MN, and SZaf collaborated in the discussion. AM-M, SZan, and CL collaborated in the review. All authors contributed to manuscript revision, read, and approved the submitted version.

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frontiers in Medicine

SYSTEMATIC REVIEW
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The Prognostic Value of Hyponatremia for Predicting Poor Outcome in Patients With COVID-19: A Systematic Review and Meta-Analysis

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Background: This meta-analysis aimed to assess the prognostic value of hyponatremia in patients with COVID-19.

Methods: We performed a systematic literature search on PubMed, Scopus, ScienceDirect, and Wiley up until January 26, 2021. The key exposure was hyponatremia, defined as sodium level below the reference level. The outcome of interest was poor outcome, which was a composite of mortality, severe COVID-19, and prolonged hospitalization. Severe COVID-19 was defined severe CAP or needing ICU care or IMV. The pooled effect estimate was odds ratio (OR). Sensitivity, specificity, positive and negative likelihood ratio (PLR and NLR), diagnostic OR (DOR), and area under curve (AUC) were generated.

Results: There were 11,493 patients from eight studies included in this systematic review and meta-analysis. The incidence of hyponatremia was 24%, and incidence of poor outcome was 20%. Hyponatremia was associated with poor outcome in COVID-19 (OR 2.65 [1.89, 3.72], $p < 0.001$; I^2: 67.2%). Meta-regression analysis showed that the association between hyponatremia and poor outcome was reduced by age (OR 0.94 [0.90, 0.98], $p = 0.006$) and hypertension (OR 0.96 [0.93, 0.94], $p < 0.001$). Hyponatremia has a sensitivity of 0.37 [0.27, 0.48], specificity of 0.82 [0.72, 0.88], PLR of 2.0 [1.5, 2.7], NLR of 0.77 [0.69, 0.87], DOR of 3 [2, 4], and AUC of 0.62 [0.58, 0.66] for predicting poor outcome. In this pooled analysis, hyponatremia has a 33% posttest probability for poor outcome, and absence of hyponatremia confers to a 16% posttest probability.

Conclusion: Hyponatremia was associated with poor outcome in patients with COVID-19.

Systematic Review Registration: PROSPERO, CRD42021233592.

Keywords: coronavirus–COVID-19, sodium, mortality, severe, critical, hyponatremia

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is now one of the most common diseases in the world (1). Although most of the patients have mild–moderate symptoms, a significant number of patients develop organ failure and require critical care (2). Identifying patients that require a more intense monitoring is of paramount importance due to limitation of human and medical resources, especially in the developing countries. Patients' characteristics and laboratory features proved to be helpful for this purpose (3–6).

COVID-19 may develop pneumonia and lead to sepsis that produces high levels of inflammatory cytokines (7, 8). Interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF) play a pivotal role in the development of sepsis. IL-6 has an inverse correlation with serum sodium which has a mechanism to stimulate hypothalamic arginine vasopressin (9–12). Several studies showed that pneumonia is associated with syndrome of inappropriate antidiuretic hormone (11, 13, 14); this mechanism may cause hyponatremia. Hyponatremia is related with prolonged time in the ICU and increased mortality rate in sepsis, cardiovascular disease, and chronic kidney disease (11, 15). Hyponatremia has been shown to increase mortality in patients with COVID-19. However, the prognostic value of this finding is still unclear. Several laboratory abnormalities have been shown to indicate poor prognosis; however, it does not directly translate to clinical value. This is the first systematic review and meta-analysis to address whether hyponatremia is a reliable biomarker. This meta-analysis aimed to assess the prognostic value of hyponatremia in patients with COVID-19.

MATERIALS AND METHODS

This is a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines compliant meta-analysis. This meta-analysis is registered in PROSPERO (CRD42021233592).

Eligibility Criteria

We included studies that fulfill all of these criteria: (1) observational retrospective and prospective studies, (2) COVID-19 patients, (3) hyponatremia and normonatremia, and (4) mortality/severe COVID-19/prolonged hospitalization/need for intensive unit care (ICU)/invasive mechanical ventilation (IMV).

We excluded the following studies: (1) preprints, (2) case reports, (3) conference abstracts, (4) review articles, and (5) abstract-only publication. Preprints were excluded to reduce bias. Conference abstracts or abstract-only publications were excluded because they often did not contain sufficient information and the analyses were only described in brief.

Abbreviations: AUC, area under curve; COVID-19, Coronavirus disease 2019; ICU, intensive care unit; IL, interleukin; IMV, invasive mechanical ventilation; NOS, Newcastle–Ottawa Scale; NLR, negative likelihood ratio; OR, odds ratio; PLR, positive likelihood ratio; REML, restricted-maximum likelihood; SIADH, syndrome inappropriate antidiuretic hormone; TNF, tumor necrosis factor.

Search Strategy and Study Selection

We performed a systematic literature search on PubMed, Scopus, ScienceDirect, and Wiley with keywords ("COVID-19" OR "Coronavirus Disease" OR "SARS-COV2") AND (Hyponatremia OR Hyponatremic OR "Low Sodium") up until January 26, 2021. We removed the duplicates and screened the title/abstract of the records. This process was performed by two independent authors, and discrepancies were resolved by discussion.

Data Extraction

Data extraction of the included studies was performed by two authors (R.P and I.I) independently. Both authors are medical doctors experienced in conducting systematic review and meta-analysis. The data of interest includes the author, design of the study, baseline characteristics, and outcome of interest. Discrepancies were resolved by discussion.

We made unsuccessful attempts to contact authors for studies that do not sufficiently report their data required for our analysis.

Exposure and Outcome

The key exposure was hyponatremia, defined as sodium level below the reference level for eunatremia. The outcome of interest was poor outcome, which was a composite of mortality, severe COVID-19, and prolonged hospitalization. Severe COVID-19 was defined severe pneumonia or needing ICU care or IMV. The pooled effect estimate was odds ratio (OR). Sensitivity, specificity, positive and negative likelihood ratio (PLR and NLR), diagnostic odds ratio (DOR), and area under the curve (AUC) were generated.

Risk of Bias Assessment

Risk of bias assessment was performed by two authors independently, using the Newcastle–Ottawa Scale (NOS) tool (16). There are three domains in NOS: (1) selection (representativeness, selection of comparator, and ascertainment of exposure), (2) comparability (outcome of interest was not present at the start and the two groups were comparable), and (3) outcome (independency of outcome, adequacy of follow-up, and lost to follow-up). Discrepancies were resolved by discussion.

Statistical Analysis

The incidence of hyponatremia and poor outcome was pooled using the meta-analysis of proportion. The random-effects DerSimonian–Laird method was used to generate the pooled effect estimate in form of OR and its 95% CI. *P*-values <0.05 were considered as statistically significant. To evaluate heterogeneity of the pooled analysis, we performed the I-squared (I^2) and Cochran Q tests, in which a value of $<50\%$ or $p < 0.10$ indicates significant heterogeneity. Sensitivity, specificity, PLR, NLR, DOR, and AUC were generated to evaluate the prognostic value of hyponatremia. To assess small-study effects and publication bias, funnel-plot analysis and Egger's were performed. Trim-and-fill analysis using the linear L0 estimator was performed due to asymmetrical funnel plot. Restricted-maximum likelihood (REML) meta-regression was performed for the association between hyponatremia and poor outcome, using age, male (gender), hypertension, diabetes, and chronic

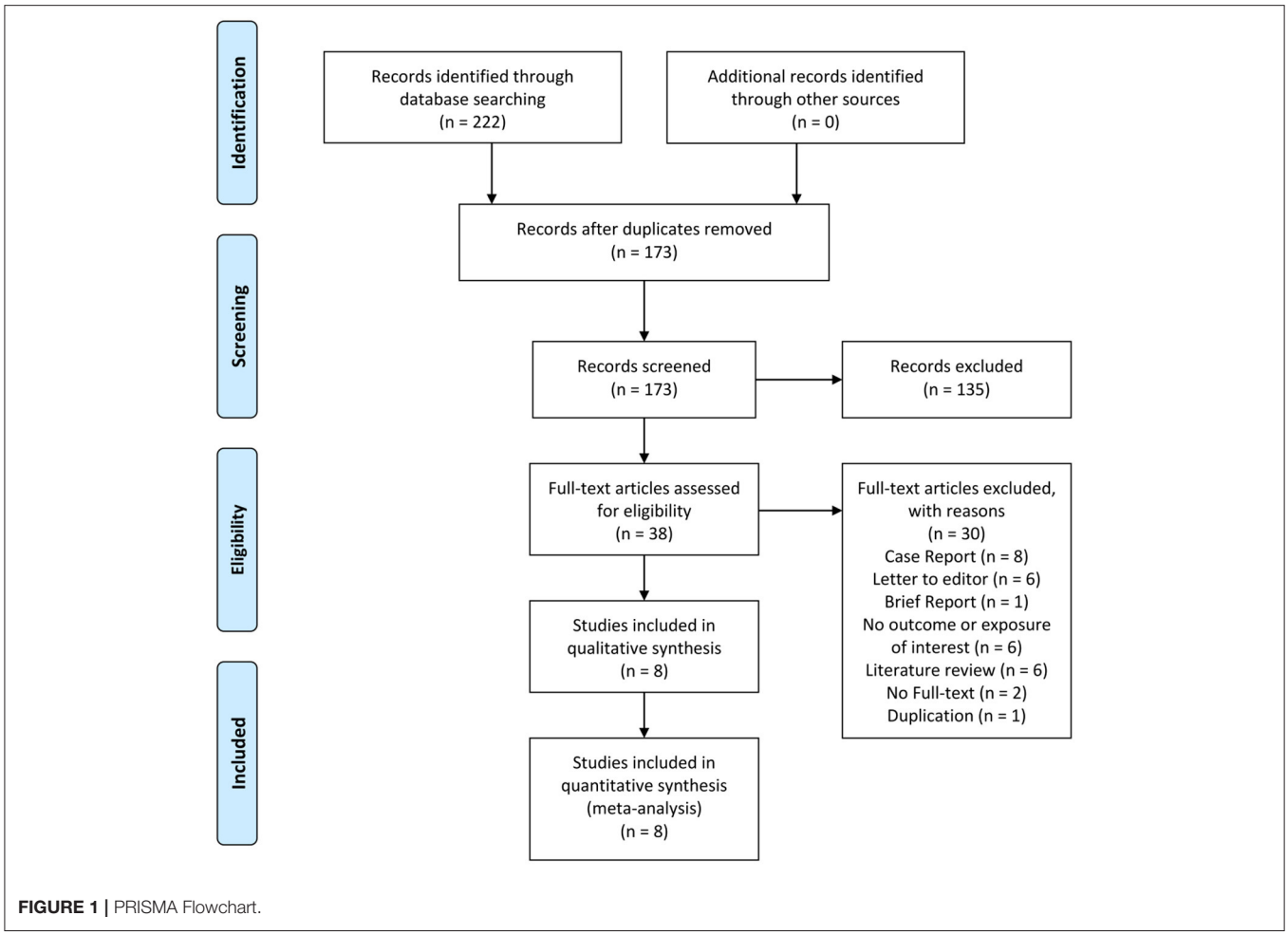

FIGURE 1 | PRISMA Flowchart.

TABLE 1 | Baseline characteristics of the included studies.

First author	Design	Sample	Cutoff point (meq/l)	Age (years)	Male (%)	Hypertension (%)	Diabetes (%)	CKD (%)	CVD (%)	Outcome	NOS
DeCarvalho, 2021	Case–control	594	≤135	65	55.8	39.6	18.7	9.3	14.1	ICU	6
Fendo, 2020	Retrospective	4490	<135	65.1	58	49.1	19	6.8	23.5	Mortality	8
Frontera, 2020	Retrospective	4452	≤120	64	65.6	43.2	30.3	13.2	8.5	Mortality	7
Hu, 2020	Retrospective	1254	<135	56.1	51.1	27.5	14.7	3.1	5.7	Mortality	6
Sarvazad, 2020	Cross-sectional	54	121–134	56	57	NR	NR	NR	NR	ICU	6
Tezcan, 2020	Retrospective	408	<135	54.3	46	31.9	23.5	3.2	10.5	Mortality	6
Wu, 2020	Retrospective	125	<136	55	52.8	28	20	NR	8.8	Prolonged hospitalization	7
Zeng, 2020	Retrospective	147	<135	42	61.1	16.1	7.4	0.7	5.4	ICU	5

CKD, chronic kidney disease; CVD, cardiovascular disease; ICU, intensive care unit; NOS, Newcastle–Ottawa scale; NR, not reported.

kidney disease as covariates. We performed sensitivity analysis by removing non-cohort studies. We used STATA 16 (StataCorp) to perform meta-analysis.

RESULTS

There were 11,493 patients from eight studies included in this systematic review and meta-analysis (**Figure 1**) (17–24). **Table 1** displays baseline characteristics of the included studies. The overall risk of bias as assessed with NOS was moderate. The incidence of hyponatremia was 24% [16%−31%]. The incidence of poor outcome was 20% [14%−35%].

Hyponatremia was associated with poor outcome in COVID-19 (OR 2.65 [1.89, 3.72], $p < 0.001$; I^2: 67.2%, $p = 0.003$) (**Figure 2**). The funnel plot was asymmetrical (**Figure 3A**), and trim-and-fill analysis resulted in an OR of 2.65 [1.89, 3.72]

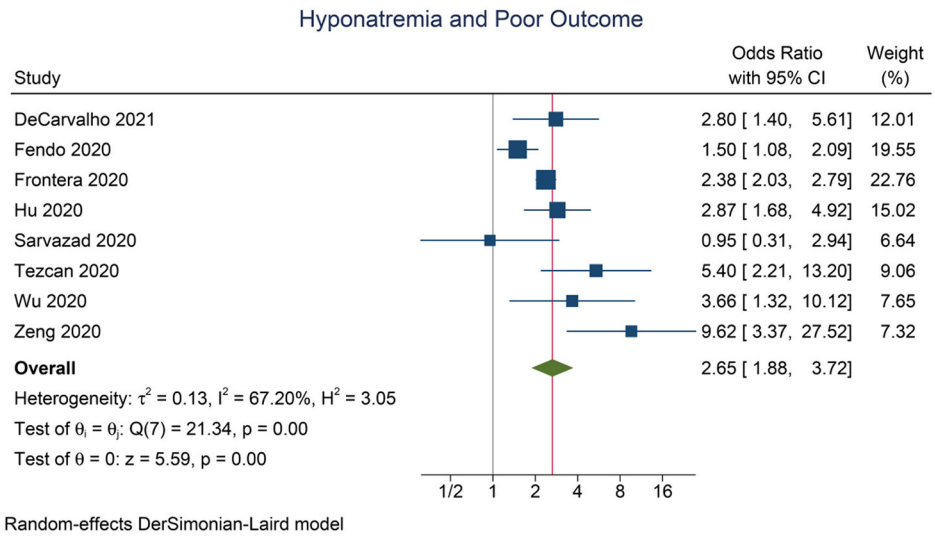

FIGURE 2 | Hyponatremia and poor outcome.

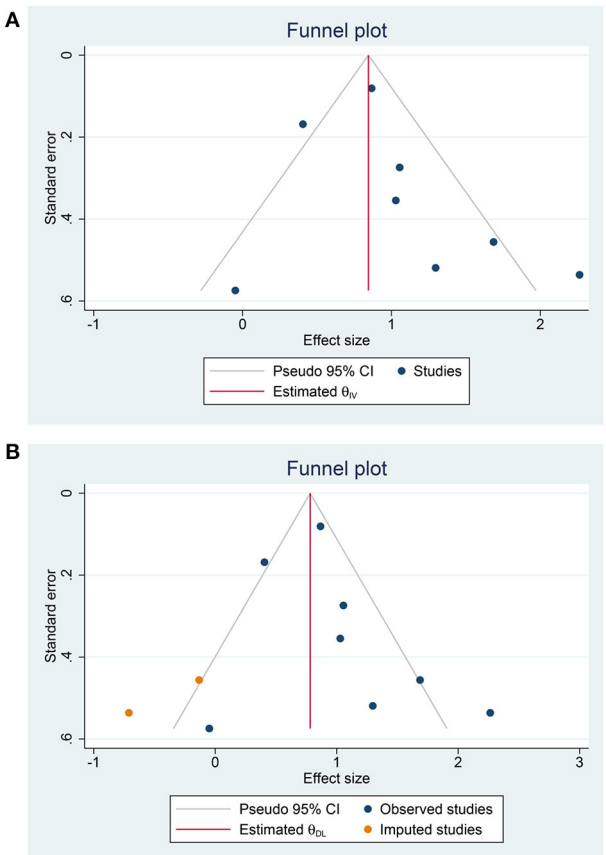

FIGURE 3 | Publication bias. Funnel-plot analysis **(A)** and trim-and-fill analysis **(B)**.

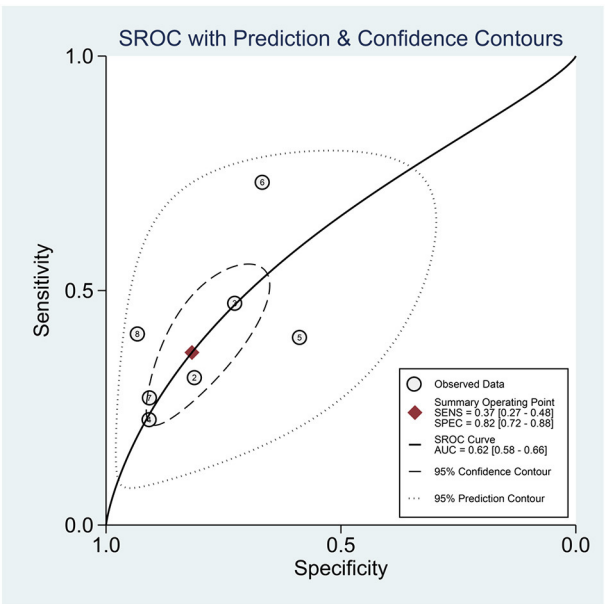

FIGURE 4 | SROC curve.

(**Figure 3B**). There is no indication for small-study effects ($p = 0.231$). Meta-regression analysis showed that the association between hyponatremia and poor outcome was reduced by age (OR 0.94 [0.90, 0.98], $p = 0.006$) and hypertension (OR 0.96 [0.93, 0.94], $p < 0.001$), but not male (gender) ($p = 0.532$), diabetes ($p = 0.308$), and chronic kidney disease ($p = 0.177$).

Hyponatremia has a sensitivity of 0.37 [0.27, 0.48], specificity of 0.82 [0.72, 0.88], PLR of 2.0 [1.5, 2.7], NLR of 0.77 [0.69, 0.87], DOR of 3 (2, 4), and AUC of 0.62 [0.58, 0.66] for predicting poor outcome (**Figure 4**). In this pooled analysis, hyponatremia has a 33% posttest probability for poor outcome, and absence of hyponatremia confers to a 16% posttest

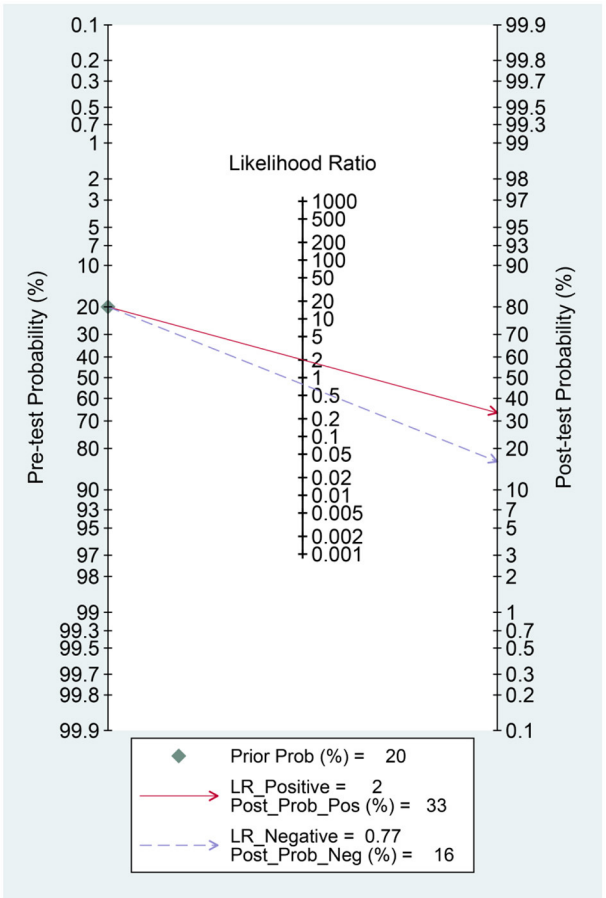

FIGURE 5 | Fagan's nomogram.

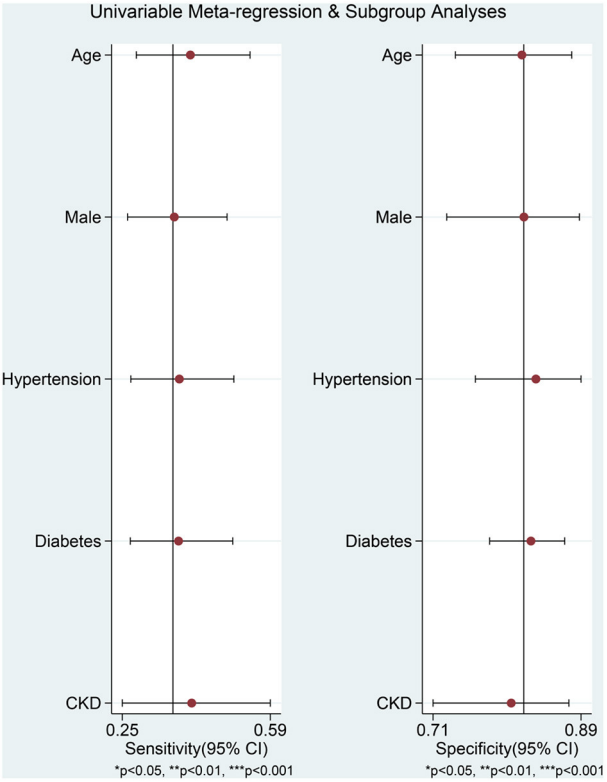

FIGURE 6 | Meta-regression analysis.

probability (**Figure 5**). Meta-regression and subgroup analysis showed that the sensitivity and specificity did not vary by age, male (gender), hypertension, diabetes, and chronic kidney disease (**Figure 6**).

Sensitivity analysis by removing non-cohort studies showed that hyponatremia was associated with poor outcome (OR 2.88 [1.95, 4.27], $p < 0.001$; I^2: 73.2%, $p = 0.002$), with sensitivity of 0.35 [0.24, 0.48], specificity of 0.84 [0.75, 0.90], PLR of 2.1 [1.5, 3.0], NLR of 0.77 [0.67, 0.87], DOR of 3 (2, 4), and AUC of 0.64 [0.60, 0.69].

DISCUSSION

Hyponatremia was associated with poor outcome in patients with COVID-19 with a 37% sensitivity and 82% specificity. There was an indication of publication bias as shown by the funnel-plot analysis; however, after trim-and-fill analysis, the result was still significant.

All of the studies except Sarvazad et al. demonstrate a significantly elevated risk of poor outcome in patients with hyponatremia. The study has a small sample size and contributes to the least weight in the pooled analysis. One of the possible explanations for the statistical insignificance is due to the inadequate sample size.

Meta-regression analysis showed that older age and hypertension modify the association, in terms of OR, between hyponatremia, and poor outcome. Both older age and hypertension have been shown to increase mortality in patients (25–27). The explanation for this modifying finding is currently unclear. However, neither variable significantly modifies the sensitivity and specificity.

In patients with COVID-19, volume depletion from gastrointestinal fluid losses causes ADH release that leads to hyponatremia (18). Additionally, SIADH is frequently encountered in patients with pneumonia and may contribute to hyponatremia (18, 28). IL-6 levels have been shown to be inversely correlated, and IL-6 itself has been associated with increased severity in patients with COVID-19; thus, hyponatremia may signify cytokine storm (29, 30). Additionally, hyponatremia may cause several neurological complications such as cerebral edema, seizures, and encephalopathy (22). An overly aggressive correction of hyponatremia may lead to central pontine myelinolysis; these factors may contribute to mortality and severity in patients with COVID-19.

Although this meta-analysis showed the association between hyponatremia and poor outcome in COVID-19, it did not necessarily equal to causality. Hyponatremia might be a bystander factor; for example, hyponatremia

might only indicate increased IL-6 or other parameters or condition that may actually increase the risk of poor outcome. Patients with hypertension may also experience hyponatremia through diuretics use, and meta-regression analysis indicates that the association between hyponatremia and poor outcome is slightly reduced in this population. This finding may imply that hyponatremia due to the natural history of COVID-19 is more significant than hyponatremia due to other causes, although further investigation is required.

Clinical Implications

Hyponatremia indicates a higher risk for poor outcome in patients with COVID-19; however, due to low sensitivity but high specificity, it can be used to rule in, but not rule out, poor prognosis. Moreover, hyponatremia alone has a poor AUC for predicting poor outcome in patients with COVID-19. Thus, combining hyponatremia with other variables in a prediction model will be more useful rather than using it as a standalone parameter.

Limitations

One limitation of this meta-analysis is publication bias in which there are more positive studies compared to negative studies being published. Most of the studies were retrospective in nature and highly prone to bias. This meta-analysis contained observational studies that either were descriptive or analyze cohorts with a prognostic objective. This meta-analysis established the association between hyponatremia and poor outcome in COVID-19, but did not prove causality. Finally, this meta-analysis provides the assumption that hyponatremia should be a risk factor to be taken into account in future prognostic models that may be constructed when exploring COVID-19 risk factors.

In conclusion, hyponatremia was associated with poor outcome in patients with COVID-19.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

MA: conceptualization, investigation, writing—review and editing, and supervision. RP: conceptualization, methodology, software, data curation, formal analysis meta-analysis, investigation, validation, writing—original draft, and writing—review and editing. AW: investigation and writing—original draft. I: data curation, investigation, and writing—original draft. TS and JM: investigation and writing—review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Medicine

BRIEF RESEARCH REPORT
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Use of Almitrine and Inhaled Nitric Oxide in ARDS Due to COVID-19

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Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is manifested by an acute respiratory distress syndrome (ARDS) with intense inflammation and endothelial dysfunction leading to particularly severe hypoxemia. We hypothesized that an impaired hypoxic pulmonary vasoconstriction aggravates hypoxemia. The objective of the study was to test the effect of two pulmonary vasoactive drugs on patient oxygenation.

Methods: Observational, single-center, open-label study in one intensive care unit (ICU) of the Paris area, realized in April 2020. Eligible patients had coronavirus disease 2019 (COVID-19) and moderate to severe ARDS [arterial partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) <200 mmHg] despite conventional protective ventilation. Exclusion criteria included pulmonary artery hypertension defined by a pulmonary artery systolic pressure (PAPs) >45 mmHg. The assessment of oxygenation was based on PaO_2/FiO_2 at (1) baseline, then after (2) 30 min of inhaled nitric oxide (iNO) 10 ppm alone, then (3) 30 min combination of iNO + almitrine infusion 8 μg/kg/min, then (4) 30 min of almitrine infusion alone.

Results: Among 20 patients requiring mechanical ventilation during the study period, 12 met the inclusion criteria. Baseline PaO_2/FiO_2 was 146 ± 48 mmHg. When iNO was combined with almitrine, PaO_2/FiO_2 rose to 255 ± 90 mmHg (+80 ± 49%, $p = 0.005$), also after almitrine alone: 238 ± 98 mmHg (+67 ± 75%, $p = 0.02$), but not after iNO alone: 185 ± 73 mmHg (+30 ± 5%, $p = 0.49$). No adverse events related to almitrine infusion or iNO was observed.

Conclusion: Combining iNO and infused almitrine improved the short-term oxygenation in patients with COVID-19-related ARDS. This combination may be of interest when first-line therapies fail to restore adequate oxygenation. These findings argue for an impaired pulmonary hypoxic vasoconstriction in these patients.

Keywords: acute respiratory distress syndrome, almitrine, nitric oxide, mechanical ventilation, COVID-19

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, identified as coronavirus disease 2019 (COVID-19), has affected millions of people worldwide since December 2019, with a mortality rate close to 1%. Severe SARS-CoV-2 is manifested by an acute respiratory distress syndrome (ARDS) defined according to the Berlin criteria (1), leading to particularly

prolonged mechanical ventilation. However, it has been advocated that the COVID-19 pneumonia is a specific disease with peculiar phenotypes: mainly that there is a dissociation between the severity of the hypoxemia and the respiratory mechanics (2). In addition, the vasculature is also particularly affected, including an endothelial dysfunction contributing to tissue damage (3).

Regardless of the etiology, the mortality of ARDS patients is improved when reducing the ventilator-induced lung injury (4), including protective ventilation at 6 mL/kg of predicted body weight (pbw) of tidal volume (VT) tolerating "permissive hypercapnia" (5, 6), residual functional capacity restoration by individual optimization of positive end-expiratory pressure (PEEP) (7), plateau pressure (Pplat) limitation $\leq$30 cmH_20, use of myorelaxants (8). Moreover, in cases of persisting severe hypoxemia [typically when the ratio of arterial partial pressure of oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) is >150 mmHg], prone position (PP) sessions for at least 16 consecutive hours have proven beneficial (9). In the most severe forms, when PaO_2/FiO_2 <80 mmHg despite these interventions, and/or when mechanical ventilation becomes harmful due to high Pplat, venovenous extracorporeal membrane oxygenation (ECMO) can be proposed (10).

The main mechanism of hypoxemia in ARDS is an inflammation-induced intrapulmonary shunt caused by alveolar flooding and alveolar collapse due to a loss of surfactant (11). Hypoxic pulmonary vasoconstriction (HPV) is a homeostatic mechanism that is intrinsic to the pulmonary vasculature in response to alveolar hypoxia, shunting the blood flow away from the hypoxic territories (12). Consequently, pulmonary pressure has been shown early to have a strong negative prognostic value in ADRS (13).

Nitric oxide (NO) is a selective pulmonary arterial vasodilator. When NO is inhaled (iNO), it improves ventilation–perfusion ratios by preferentially redistributing blood flow to the ventilated areas. In ARDS patients, iNO improves gas exchange and both pulmonary arterial hypertension and right ventricular failure, which both have negative prognoses in ARDS (13–15). Given a fairly favorable benefit–risk ratio, the physiological effects of iNO can therefore justify its use in severe ARDS when optimized mechanical ventilation does not correct hypoxemia (15, 16).

On the other hand, the inflammation may alter the intrinsic mechanism of HPV (12), leading to the consideration of testing selective pulmonary vasoconstrictors. Almitrine is a peripheral chemoreceptor stimulant that has been reported to improve the oxygenation in ARDS patients by increasing hypoxic pulmonary vasoconstriction (17). Therefore, its use has been proposed to improve gas exchange in ARDS, alone or in combination with iNO (18, 19). Although the effect of these drugs is often transient and their effect on mortality has not been established to date, the rationale for using a combination of perfused vasoconstrictors and inhaled vasodilators is to improve the ventilation/perfusion ratio (V/Q) through selective vasoconstriction of pulmonary vessels perfusing non-aerated areas and selective vasodilation of pulmonary vessels perfusing aerated areas.

Given the peculiar severity of hypoxemia in COVID-19 lung injury, we hypothesized that endothelium dysfunction may alter the HPV. Then, iNO and almitrine could be tested to improve the V/Q. The aim of our study was to assess the effect of these drugs, alone and in combination, on the oxygenation of patients with moderate to severe ARDS due to COVID-19.

Abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; HPV, hypoxic pulmonary vasoconstriction; iNO, inhaled nitric oxide; PP, prone position; PaO_2, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure; V/Q, ventilation/perfusion.

METHODS

This was an observational, single-center, open-label study in one intensive care unit (ICU) of the Paris area, realized in April 2020. The study was approved by the local ethics committee as a component of standard care. Patients and/or families were given information about the study. Following French regulations, all patients (or their relatives in case of death) were informed at discharge that the data collected during their stay could be anonymously used for scientific purpose and that they can ask to have their data erased.

Patients

Eligible patients had COVID-19 (confirmed by RT-PCR on a nasopharyngeal sample) and ARDS according to the definition of the Berlin criteria (1). All had CT scans. Patients were included if they had moderate to severe ARDS (PaO_2/FiO_2 <200 mmHg) despite conventional treatment: effective sedation and curarization, protective ventilation at 6 mL/kg with optimized PEEP level to maintain Pplat $\leq$30 cmH_2O, and had already at least one session of ventilation with PP; however, no patient was in PP at the time of the protocol. One patient was on venovenous ECMO at the time of the study. Exclusion criteria were known allergy to iNO and/or almitrine, pulmonary artery systolic pressure (PAPs) >45 mmHg, measured by a transthoracic echocardiography-Doppler standard examination.

Measurements

All the measurements concerning ventilatory and hemodynamic variables were carried out during the protocol by a single operator in charge of the patient. As part of the standard care of ARDS, a radial or femoral arterial catheter was placed in all patients, allowing monitoring of the systemic arterial pressure and sampling for blood gas analysis, including lactate. A transthoracic echocardiography was performed to evaluate the left and right ventricular function. The presence of right-to-left shunting was systematically evaluated before the initiation of the protocol. The PAPs was estimated from the flow of tricuspid regurgitation during echocardiography using $4\times Vmax + 10$ (representative of the mean right atrium pressure). Data of the mechanical ventilation were collected: VT, respiratory frequency, PEEP, PPlat, dynamic compliance, and driving pressure. The static compliance was calculated and according to the formula: VT/(Pplat-PEEP).

TABLE 1 | Baseline characteristics.

	Gender	Age (years)	Day	CRP (mg/L)	D-dimer (ng/mL)	Fibr (g/L)	VT (mL/kgpbw)	RR (per min)	PEEP (cmH_2O)	DP (cmH_2O)	Compliance (mL/CmH_2O)	VR	Lactate (mMol/L)	NAD (mg/h)
1	F	75	16	164	6,770	8.2	6	30	9	22	16	3.1	0.9	0
2	M	73	8	178	1,934	9.2	5.5	28	14	14	35	2.8	1.8	0.3
3	M	66	14	165	20,700	5.8	5	30	9	23	17	2.5	0.8	0
4	M	73	5	296	857	9.2	5.6	24	10	21	20	1.7	2	0
5	M	71	26	101	4,280	3.7	5.3	28	8	18	23	2.1	1.3	1
6*	F	76	15	298	671	6.5	3.6*	16	12	10	29	1.3	0.8	0
7	M	84	13	299	647	10	5.2	28	10	19	23	3.0	1.3	0
8	M	80	7	271	28,096	5.1	5.6	30	10	16	26	2.3	1.3	3
9	M	60	24	178	989	6.0	6	18	10	19	24	1.7	0.6	0
10	M	81	2	292	5,994	8.5	5.7	24	10	18	33	1.5	2.5	0.3
11	F	54	4	407	1,434	9.5	5.6	18	14	10	32	1.5	1.6	0
12	M	68	2	63	1,481	5.2	5.8	22	14	15	30	1.9	4	3.2
Mean		71.8	11.3	226	1,708	7.2	5.6	24.7	10	17.1	25.7	2.1	1.3	0
SD		8.7	8.1	99.5	(890–6,576)	2.1	(5.2–5.8)	5.1	(9.3–10.5)	4.3	6.2	0.6	(0.83–2)	(0–0.8)

*CRP, C-reactive protein; Day, days from intubation; DP, driving pressure; F, female; Fibr, fibrinogen; M, male; Mean, mean or median; NAD, norepinephrine; PEEP, positive end-expiratory pressure; RR, respiratory rate; SD, standard deviation or interquartile range; VR, ventilatory ratio; VT, tidal volume in kg per predicted body weight; *ECMO VV blood flow rate 4.5 L/min, sweep gas flow rate 4 L/min; $FiO_2 = 60\%$.*

Protocol

All patients were sedated, curarised, under assist-control ventilation with pure oxygen ($FiO_2 = 100\%$) throughout the complete protocol. The depth of sedation and curarization was controlled and unchanged. The ventilation parameters, vasopressors/inotropic posology, and fluid perfusion were planned to remain constant throughout the protocol.

A blood gas sample [including arterial pH, PaO_2, partial pressure of carbon dioxide ($PaCO_2$), lactate level] and an echocardiography examination with PAPs measurement were performed for each patient at (1) baseline, (2) after 30 min of iNO administration alone, (3) after 30 min of a combination of iNO + almitrine administration, and (4) after 30 min of almitrine alone. The iNO (KINOX®) was delivered continuously from a specific dispositive (Air Liquide, Paris, France) at a concentration of 10 ppm into the inspiratory limb of the ventilator. Almitrine (Vectarion®, Servier, Suresnes, France) was delivered intravenously *via* a central venous catheter at a concentration of 8 μg/kg/min. We did not plan any washout since the sequence of the protocol avoided any unexpected mix. Also, since we were interested in studying the combination of drugs, we did not plan a return to baseline between the changes of the regimen.

Statistical Analysis

Categorical variables are reported as numbers and proportions (%). Continuous data are reported as the mean ± standard deviation when normally distributed or median with interquartile ranges (25–75th) when not. Normal distribution was controlled by Shapiro tests. We used the $\chi 2$ test or Fisher exact test to compare categorical variables, the Mann–Whitney *U*-test to compare medians, and ANOVA to compare means. For all tests, $p < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS 25.0.

RESULTS

Population Characteristics

Fifty-four patients required mechanical ventilation for pneumonia due to COVID-19 from the beginning of the pandemic and 20 during the study period; 12 of them met the inclusion criteria (five had PAPs >45 mmHg, and three had PaO_2/FiO_2 >200 mmHg). Among these 12 patients (**Table 1**), nine were men (75%), mean age was 71.8 ± 8.7 years old, and seven patients had diabetes mellitus (58%) and hypertension (58%). Only one patient was a smoker (8%) with a documented chronic obstructive pulmonary disease (COPD). Most patients (11/12, 92%) had left ventricular ejection fraction (LVEF) >50%; two patients had segmental pulmonary embolism without right ventricular failure (17%). The mean duration of the mechanical ventilation at the time of inclusion was 11.0 ± 8.3 days. All patients received norepinephrine during their hospitalization, but only five (42%) still received it during the protocol.

The percentage of lung involvement on CT scan was 50% (40–70%). There was no correlation between CT score and the response to any of the treatments: for iNO ($r = 0.039$; −0.55–0.60; $p = 0.90$), iNO + almitrine ($r = -0.51$; −0.84–0.092; $p = 0.09$), almitrine ($r = -0.56$; −0.86–0.02; $p = 0.06$).

The median transthoracic echocardiographic measurements at baseline were: tricuspid annular plane systolic excursion (TAPSE) = 19.5 (16–21) mm, velocity time integral left ventricular outflow tract (VTI LVOT) = 17 (15.8–18.5) cm, right/left ventricular ratio = 0.48 (0.42–0.6), PAPs = 38 (33–42.3) mmHg, LVEF = 55% (52–60%).

TABLE 2 | Ventilatory Pattern During the Protocol.

	Baseline					*iNO*						*iNO + almitrine*						*Almitrine*					
	P/F	*PaCo₂*	*PAPs*	*ΔP*	*Cp*	*P/F*	*%*	*PaCo₂*	*PAPs*	*ΔP*	*Cp*	*P/F*	*%*	*PaCo₂*	*PAPs*	*ΔP*	*Cp*	*P/F*	*%*	*PaCo₂*	*PAPs*	*ΔP*	*Cp*
1	131	66	43	22	16	103	0.8	57	39	23	16	233	1.8	54	46	21	17	302	2.3	62	46	20	18
2	178	54	38	14	35	291	1.6	55	33	14	35	341	1.9	51	38	14	35	375	2.1	52	38	14	35
3	57	59	38	23	17	97	1.7	53	35	21	19	104	1.8	53	46	23	17	53	0.9	59	48	23	17
4	189	43	37	21	20	170	0.9	46	35	20	21	261	1.4	46	46	19	22	214	1.1	53	48	18	23
5	137	50	45	18	23	237	1.7	47	43	21	20	327	2.4	48	42	19	22	289	2.1	48	47	18	23
6*	71	56	43	10	29	76	1.1	53	41	10	29	196	2.8	48	47	12	24	248	3.5	47	42	12	24
7	162	65	33	19	23	165	1.0	67	30	20	22	221	1.4	61	35	21	21	216	1.3	64	39	21	21
8	194	42	42	16	26	206	1.1	39	40	15	28	251	1.3	41	43	15	28	241	1.2	42	45	16	26
9	195	56	40	19	24	305	1.6	61	37	18	25	342	1.8	59	40	19	25	305	1.6	64	42	19	25
10	134	39	27	18	33	224	1.7	37	26	17	31	265	2.0	36	28	18	31	148	1.1	39	29	18	31
11	197	44	32	10	32	199	1.0	42	30	10	32	398	2.0	42	31	10	32	357	1.8	40	33	10	32
12	111	52	28	15	30	150	1.4	57	26	14	30	115	1.0	55	33	14	30	106	1.0	58	38	14	30
12*	93	50	30	15	21	104	1.1	51	31	14	23	194	2.1	48	31	14	23	96	1.03	51	30	13	25
M	146	52	37	17	25	185	1.30	51	35	17	25	255	1.80	50	39	17	25	238	1.67	52	41	17	25
SD	48	8.9	5.7	4.3	6.2	76	0.35	9.1	5.2	4.3	5.9	90	0.49	7.8	6.7	4.0	5.7	98	0.75	9.2	6.9	3.9	5.4

*P/F, arterial partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2); ΔP, driving pressure; $PaCO_2$, partial pressure of carbon dioxide; PAPs, pulmonary artery systolic pressure; Cp, compliance; M, mean or median; SD, standard deviation or interquartile range; *ECMO, 12*, same patient but after norepinephrine removal and ECMO VV implantation; %, percentage of PaO_2/FiO_2 changes after each step.*

Ventilatory pattern at baseline was: VT = 5.6 (5.2–5.8) mL/kg, respiratory frequency = 24.6 ± 5.1/min, PEEP = 10 (9.3–10.5) cmH_2O, Pplat = 27.9 ± 3.0 cmH_2O, driving pressure = 17.1 ± 4.3 cmH_2O, compliance = 25.6 ± 6.2 mL/cmH_2O, PaO_2/FiO_2 =146 ± 48 mmHg, PCO_2 = 52 ± 8.3 mmHg, ventilatory ratio = 2.1 ± 0.6.

Protocol Results

Details of the evolution of ventilatory and hemodynamic variables are shown in **Table 2**. Evolution of PaO_2/FiO_2 is presented in **Figure 1**. After iNO, PaO_2/FiO_2 increased from 146 ± 48 mmHg to 185 ± 73 mmHg (+30 ± 35%, $p = 0.49$). After iNO combined with almitrine, PaO_2/FiO_2 increased significantly from baseline: 255 ± 90 mmHg, (+80 ± 49%, $p = 0.005$). With almitrine alone, PaO_2/FiO_2 was maintained significantly higher than that at baseline: 146 ± 48 to 238 ± 98 mmHg (+67 ± 75%, $p = 0.02$). The change in PaO_2/FiO_2 when iNO was stopped was not significant (238 ± 98 vs. 255 ± 90, $p = 0.67$). The PaO_2/FiO_2 increased by at least 20% in 50%, 92% and 75% of the patients after iNO, iNO + almitrine, and almitrine alone, respectively (**Table 2**). Six patients were poor responders (PaO_2/FiO_2 increase <20%) with iNO alone and four with almitrine alone, but only one was a poor responder to the combination of both drugs (patient 12). This patient was the only one responding better to iNO than to almitrine. Furthermore, when norepinephrine was withdrawn and ECMO was initiated, the protocol was restarted in this patient and he became a responder to the combination of both drugs.

We found no relationship between the change in PaO_2/FiO_2 during the protocol and any of the ventilatory variables assessed at baseline. Pplat, driving pressure, compliance, arterial pH, and PCO_2 levels did not change significantly during the trial. We observed no adverse events related to almitrine infusion or iNO. Hemodynamic variables remained comparable before and after the trial: arterial pressure (76.6 ± 12.6 vs. 74.8 ± 9.1 mmHg, $p = 0.69$), heart rate (91 ± 25 vs. 95/min ± 23 beats/min, $p = 0.66$), lactates [1.3 (0.9–1.9) vs. 1.6 (1.2–1.9) mMol/L, $p = 0.60$]. No patient developed acute cor pulmonale during the protocol.

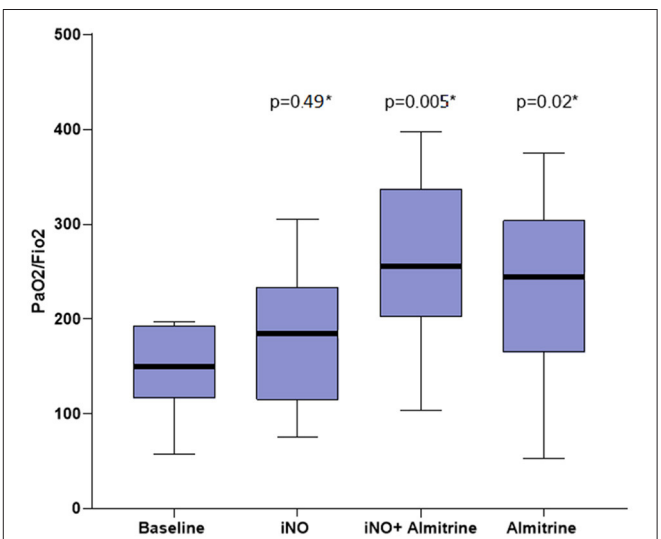

FIGURE 1 | Arterial partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) evolution, *comparison from baseline.

The serum inflammation marker levels at admission, peak, and day of trial were respectively: C-reactive protein (CRP): 213

± 105 mg/L, 333 ± 49 mg/L, 226 ± 99.5 mg/L; fibrinogen: 7.1 ± 2.1 g/L, 8.9 ± 1.3 g/L, 7.2 ± 2.1 g/L; D-dimer: 1,481 (989–5,994) ng/mL, 12,706 (3,522–22,948) ng/mL, 1,708 (890–6,576) ng/mL. We found no correlation between PaO_2/FiO_2 evolution after almitrine infusion and these marker serum levels. However, three patients had received interleukin (IL)-6 inhibitors that quickly decreased these markers' levels over time.

At the end of the protocol, the combination of iNO and almitrine was continued at the discretion of the physician in all patients. The median duration of mechanical ventilation was 36 (18–50) days. Five patients (42%) underwent a tracheostomy. The final mortality was 50% at 90 days (patients 3, 5, 7, 8, 10, and 12).

DISCUSSION

We found that the combination of iNO and intravenous almitrine infusion improved the short-term oxygenation of patients with ARDS due to COVID-19, even when they received moderate doses of norepinephrine. This immediate beneficial effect was obtained with moderate iNO concentrations (10 ppm) and almitrine (8 μg/kg/min). The use of higher doses of norepinephrine seems to alter the response to the combination of drugs. One patient (number 12) was not a responder when receiving more than 3 mg/h of norepinephrine and became a responder after norepinephrine withdrawal and ECMO initiation. No hemodynamic impairment occurred during our protocol study, with no significant modification in PAPs, heart rate, and plasma lactate level.

These results are consistent with past studies using invasive hemodynamic measurements in ARDS patients and confirmed the excellent tolerance of these drugs at these doses (19, 20). Some authors used higher doses of almitrine, up to 16 μg/kg/min, and they found that it could impair the loading condition of the right ventricle (21).

Almitrine improved the oxygenation of our patients alone or in combination. In contrast, the use of iNO alone did not allow a significant increase in PaO_2/FiO_2, and when the iNO was removed, the decrease in PaO_2/FiO_2 was again not significant. This argues for a moderate effect of iNO in our patients and, therefore, for an alteration of the expected HPV as a predominant mechanism of V/Q mismatch in COVID-19 ARDS. In order to further investigate this mechanism, larger studies with comparison of almitrine effects on COVID-19-related ARDS and other causes of ARDS could be interesting. Furthermore, we performed this protocol only on supine position. As almitrine and iNO are actually recommended in ARDS patients in cases of refractory hypoxemia despite PP (22), it should be interesting to investigate their effects in PP.

Recent meta-analysis on the application of iNO in ARDS has shown that iNO can improve short-term oxygenation, but it does not improve prognosis and has an increased risk of renal insufficiency (risk ratio between 1.55 and 1.59) (23–25). It needs to be kept in mind when the benefit–risk balance from the use of iNO arises.

These findings are in line with recently published studies. The same results were obtained at a lower dose of almitrine (2 μg/kg/min) associated or not with iNO in 19 COVID-19 patients with persistent refractory hypoxemia, with an increase of the median PaO_2/FiO_2 ratio from 79 (64–100) at baseline to 117 (81–167) after almitrine ($p = 0.001$) (26). Comparative results were found with infusion of 10 μg/kg/min of almitrine, associated in 75% of cases with iNO (10 ppm). Twenty-one patients (66%) were described as responders (increase of PaO_2/FiO_2 ratio ≥20% at the end of the infusion); the median PaO_2/FiO_2 ratio improvement was 39% (9–93%) and differed significantly between the responders and non-responders [67% (39–131%) vs. 6% (9–16%), respectively; $p < 0.0001$] (27). Some authors tested the dose effects of almitrine, and its infusion alone was associated with an improvement of PaO_2/FiO_2 ratio from 135 at baseline to 149 at 4 μg/kg/min and 215 at 12 μg/kg/min ($p = 0.06$) on 8/10 patients at the early phase of severe COVID-19 ARDS. In this study, three patients were on PP during the protocol and the amplitude of PaO_2 increase was different according to the patient's position (PP vs. supine position) supposing that the combination of gravitational and pharmacogical effects was synergistic to improve the VA/Q mismatch (28). The effects of iNO (10 ppm) alone and in association with 10 μg/kg/min almitrine was also tested just after a prone session. Authors founds that the median of PaO_2/FiO_2 ratio increased from 102 (89–134) mmHg at baseline to 124 (108–146) mmHg after iNO ($p = 0.13$) and 180 (132–206) mmHg after iNO and almitrine ($p < 0.01$) but showed no correlation between the increase in oxygenation caused by iNO–almitrine combination and that caused by proning (29). Another uncontrolled study showed conflicting results. The use of iNO, almitrine, or both did not improve the oxygenation in 20 severe COVID-19 ARDS; however, the patients of this study also had more serious lung injury than those in our study (median $PaO_2/FiO_2 = 106$) (30).

HPV, also known as the Euler–Liljestrand mechanism, is a homeostatic mechanism in which the small pulmonary arteries constrict in the presence of low alveolar oxygen tension. In that situation, a mitochondrial sensor dynamically changes reactive oxygen species and redox couples in pulmonary artery smooth muscle cells, leading to activate voltage-gated calcium channels and to increase cytosolic calcium, causing vasoconstriction. It improves V/Q matching by redirecting the blood flow from poorly ventilated lung regions to normally ventilated lung regions (31). Many factors inhibit HPV, including increased cardiac output, hypocapnia, hypothermia, acidosis/alkalosis, and PEEP. Different diseases are also known to alter the physiological mechanism of HPV such as liver cirrhosis, COPD, and sepsis. Lastly, different drugs may also alter the HPV mechanisms including anesthetic agents, isoproterenol, calcium blockers, and vasodilators. Chloroquine was found to decrease HPV through a combination of vasodilator, anti-proliferative, and anti-autophagic effects (32). None of these factors were present at the time of the protocol, but it is impossible to eliminate an effect of one or several of them, especially chloroquine that was given to all our patients in the pre-intubation phase. Nevertheless, the most probable cause of impaired HPV is inflammation, which is severe in COVID-19 patients, as it was in all our patients (33). The direct mechanism of impaired HPV and inflammation/endothelial dysfunction is unknown but may be part of the endothelium dysfunction, a silent component of inflammation (34) particularly found in COVID-19 and

predisposing patients to thrombosis and platelet activation (35). Indeed, endothelitis in lung vessels and others organs with the presence of viral elements within endothelial cells and an accumulation of inflammatory cells, with evidence of endothelial and inflammatory cell death, was found in COVID-19 patients (36).

Our study had several limitations. First, it was a monocentric study performed on a restricted number of patients. Then, the treatments were given in the same order, in the same dose for each patient, and not randomly. Furthermore, the design of the study did not allow us to assess whether this beneficial effect on oxygenation was sustained over time and/or may change the outcome. Despite these limitations, the homogeneous response to the protocol made it generalizable to all COVID-19 patients with moderate to severe V/Q mismatch, with few chances of being wrong.

CONCLUSION

Combining 10 ppm of iNO and 8 μg/kg/min of infused almitrine improved the short-term oxygenation in patients with ARDS due to COVID-19. Impaired hypoxic pulmonary vasoconstriction due to major inflammation and endothelial dysfunction may be a preponderant mechanism of hypoxia of this pathology. This combination may be of interest when first-line therapies of ARDS fail to restore the oxygenation sufficiently.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CMC Ambroise Paré local ethics commitee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.655763/full#supplementary-material

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$ECCO_2R$ in 12 COVID-19 ARDS Patients With Extremely Low Compliance and Refractory Hypercapnia

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Purpose: A phenotype of COVID-19 ARDS patients with extremely low compliance and refractory hypercapnia was found in our ICU. In the context of limited number of ECMO machines, feasibility of a low-flow extracorporeal carbon dioxide removal ($ECCO_2R$) based on the renal replacement therapy (RRT) platform in these patients was assessed.

Methods: Single-center, prospective study. Refractory hypercapnia patients with COVID-19-associated ARDS were included and divided into the adjusted group and unadjusted group according to the level of $PaCO_2$ after the application of the $ECCO_2R$ system. Ventilation parameters [tidal volume (VT), respiratory rate, and PEEP], platform pressure (Pplat) and driving pressure (DP), respiratory system compliance, arterial blood gases, and $ECCO_2R$ system characteristics were collected.

Results: Twelve patients with refractory hypercapnia were enrolled, and the $PaCO_2$ was 64.5 [56-88.75] mmHg. In the adjusted group, VT was significantly reduced from 5.90 ± 0.16 to 5.08 ± 0.43 ml/kg PBW; DP and Pplat were also significantly reduced from 23.5 ± 2.72 mmHg and 29.88 ± 3.04 mmHg to 18.5 ± 2.62 mmHg and 24.75 ± 3.41 mmHg, respectively. In the unadjusted group, $PaCO_2$ decreased from 94 [86.25, 100.3] mmHg to 80 [67.50, 85.25] mmHg but with no significant difference, and the DP and Pplat were not decreased after weighing the pros and cons.

Conclusions: A low-flow $ECCO_2R$ system based on the RRT platform enabled CO_2 removal and could also decrease the DP and Pplat significantly, which provided a new way to treat these COVID-19 ARDS patients with refractory hypercapnia and extremely low compliance.

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INTRODUCTION

Recently, COVID-19 disease caused by the novel coronavirus (SARS-CoV-2) has been a worldwide severe epidemic problem and resulted in thousands of deaths (1). Respiratory manifestation was one of the main clinical characteristics of this disease; about 15-20% of suspected and confirmed patients developed severe hypoxemia and required mechanical ventilation (2). Gattinoni et al. divided the COVID-19 pneumonia into two phenotypes: Type L and Type H (3), but in our clinical practice in Wuhan, we encountered a group of ARDS patients who presented a different phenotype from the two mentioned above, with refractory carbon dioxide (CO_2) retention, extremely low lung compliance, and low lung recruitability, which was also found in other centers (4, 5). Hypercapnia not only impairs innate immunity *via* evolutionarily conserved mechanisms (6), which reduce the ability to fight infection, but also has hemodynamic consequence, increasing pulmonary hypertension and worsening right ventricular function (7). A recent study showed that severe hypercapnia ($PaCO_2 \geq 50$ mmHg) appeared to be independently associated with higher ICU mortality in patients with ARDS (8). In order to correct the severe hypercapnia, minute ventilation and drive pressure were often forced to increase to far beyond the level of lung protective ventilation. This means higher mechanical energy and a higher risk of ventilator-related lung injury (9, 10). Therefore, extracorporeal carbon-dioxide removal ($ECCO_2R$) device came into our consideration. In this sudden outbreak of COVID-19, like all countries in the world (11), the number of ECMO machines has been in a state of serious shortage for quite a long time, and also the specific $ECCO_2R$ system. However, the RRT device is more feasible, and recent studies had improved that, $ECCO_2R$ based on a RRT platform enabled very low tidal volume ventilation with moderate increase in $PaCO_2$ in patients with ARDS patients (12, 13). Therefore, this prospective study was designed to assess whether the application of the $ECCO_2R$ system on RRT platform could decrease the DP and Pplat, thereby facilitated the protective ventilation in these patients.

METHODS

Patients

This single-center, prospective study was conducted during March 7 to April 15 in a newly constructed 32-bed ICU in Wuhan. All the medical staff were from Peking Union Medical College Hospital (PUMCH); 70% of them had experiences in the ICU ward. All the patients admitted were transferred from other hospitals and were all identified with COVID-19. This study was approved by the ethics review board of PUMCH (ZS-2332), and informed consent was obtained from legally authorized surrogates. The clinical trial protocol was registered with www.clinicaltrials.gov/ (Clinicaltrials.gov identifier: NCT04340414).

Refractory hypercapnia patients with COVID-19-associated ARDS were included, if the following inclusion criteria were met: (1) diagnosed with ARDS according to the Berlin definition and lung protective strategy was implemented after admission, which included low tidal volume (VT) ventilation (Vt 6 ml/kg of predicted body weight), low plateau pressure (Pplat < 30 cmH_2O), higher PEEP strategy, and prone positioning 16–20 h per day; (2) evolved into refractory hypercapnia ($PaCO_2 > 50$ mmHg), despite efforts of correcting CO_2 retention by increasing the respiratory rate and driving pressure. The exclusion criteria were patients with ICU stay < 24 h, decompensated heart failure, pregnancy, age < 18 years, acute brain injury, contradictions of systemic anticoagulation, catheter access to femoral vein or jugular vein impossible, and decision to limit therapeutic interventions.

$ECCO_2R$ System

The $ECCO_2R$ was provided by a low-flow gas-exchanger oxygenator (QUADROX-I pediatric HMO30000, MAQUET) integrated into the Primsaflex platform (Gambro-Baxter) with the slow continuous ultrafiltration (SCUF) mode, and the ultrafiltration was set at 0. The polymethyl pentene, hollow fiber, gas-exchanger membrane was connected to the extracorporeal circuit before the RRT filter (**Figure 1**). Two 12-Fr two-lumen hemodialysis catheters (arrow) were aseptically and percutaneously inserted under ultrasonography guidance into the right jugular vein and one of the femoral veins with a femoral-jugular pattern to prevent self-recirculation and improve the clearance efficiency. Systemic heparinization was used to maintain the activated partial thromboplastin time ratio (aPTTr) 1.5–2.0× that of the control. The continuous venous, arterial line and filter pressures were monitored in the Prismaflex device.

Protocol

After priming, the Prismaflex device was connected to the patient and the extracorporeal blood flow was progressively increased to 300-400 ml/min. In the beginning, a flow test was done to assess the efficiency of CO_2 clearance of the membranes. Pre- and post-oxygenator blood PCO_2 were compared when the sweep flow was adjusted to 0, 5, 10, and 15 L/min, and back to 0 L/min. Then, the sweep-gas flow through the $ECCO_2R$ was switched on the level with the best clearance efficiency. The changes of CO_2 clearance with time were also collected.

Half an hour later after, according to the arterial $PaCO_2$, the patients were divided into two groups. If the $PaCO_2$ decreased to lower than 50 mmHg, VT was gradually reduced from 6 to 5, 4.5 every 30 min until the $PaCO_2$ returned to the original level

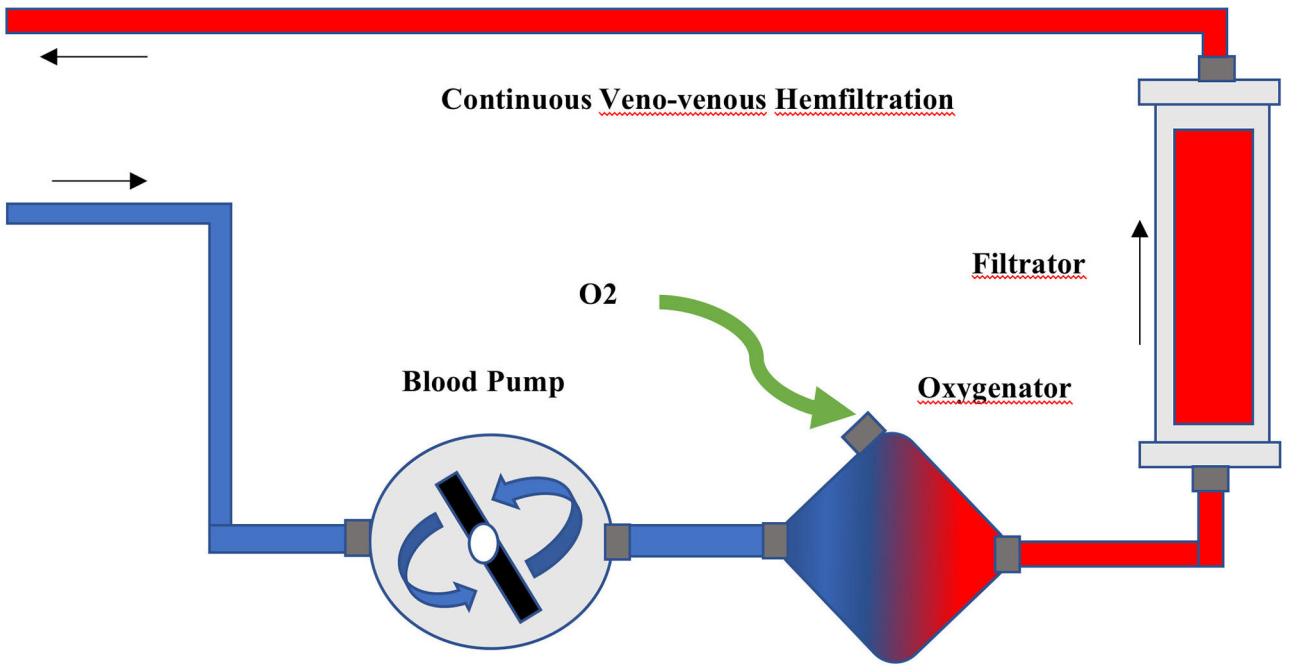

FIGURE 1 | The connection of hemofiltration and extracorporeal oxygenator.

and the pH > 7.2. If the $PaCO_2$ still remained above 50 mmHg, the VT would not be changed and the $ECCO_2R$ device was only used to reduce the hypercapnia. Refractory hypoxemia and/or hypercapnia could be managed at the attending physician's discretion, with recruitment maneuver, prone positioning, and so on. The flowchart is shown in **Figure 2**.

Data Collection

Ventilator settings (VT, PEEP, RR, Pplat, minutes ventilation, and FiO_2), hemodynamic parameters (MAP, HR, and vasopressor dose), arterial blood-gas values (pH, PaO_2, $PaCO_2$, HCO^{3-}, and lactate), heparin dose, and aPTTr were collected at baseline. After the run-in time, 30 min, 6 h, and 24 h after the connection, these values were also collected. Other variables such as complete blood count, liver function, and renal function were obtained daily. Respiratory-system compliance, driving pressure, and the mechanical power were calculated according to the standard formulas.

Statistical Analyses

Results are expressed as median (IQR) when abnormal distribution, and as mean ± SD when normal distribution, and both $p < 0.05$ defined statistical significance. Statistical analysis was performed using non-parameter analysis in chi-square test for comparison between different time intervals when distributed abnormally and using one-way analysis of variance (ANOVA) for repeated measures, followed by a *post-hoc* test, when distributed normally. Analyses were computed with IBM SPSS, version 23.0.1 (SPSS Inc., Chicago, IL, USA) software.

RESULTS

Thirty-two patients with ARDS were involved, and lung protective strategy worked in 17 patients with $PaCO_2$ < 50 mmHg, and three patients died within 24 h after admission. After the adjustment of ventilator parameters, $PaCO_2$ was still above 50 mmHg (64.5 [56–88.75] mmHg) in 12 patients and the $ECCO_2R$ devices were applied. At baseline, all these patients received protective ventilation with VT set at 5.94 ± 0.18 ml/kg PBW and PEEP at 6 [5.25, 8.0] cmH_2O, the respiratory rate was 32.58 ± 3.55 bpm, and the platform pressure and the driving pressure were 34.08 ± 6.91 mmHg and 27.17 ± 5.98 mmHg (**Table 1**).

The mean blood flow was 342.5 ± 49.20 ml/min, and in the flow test, when the sweep-gas flow was set at 10 L/min, the CO_2 clearance reached the best efficiency, 45.91 ± 7.70 ml/min. In all these patients, the flow was set at 10 L/min during the process. After the application of the $ECCO_2R$ device, the $PaCO_2$ in all the patients decreased, and during the 24 h, the CO_2 clearance nearly did not change little with time (**Figure 3**). There was no significant correlation between the CO_2 clearance and the start $PaCO_2$, the DP, and lung compliance.

In eight of these patients, the $PaCO_2$ could decrease below 50 mmHg, and the VT was reduced every 30 min until the $PaCO_2$ returned; in the other four patients, the $PaCO_2$ was still above 50 mmHg, and VT was not reduced. According to whether the VT was adjusted, we divided the 12 patients into two groups, adjusted group ($n = 8$) and unadjusted group ($n = 4$). In the adjusted group, 6 h after the flow test, VT was decreased from 5.9 ± 0.16 to 5.08 ± 0.43 ml/kg PBW ($p < 0.01$), and DP and Pplat were also decreased significantly from 23.5

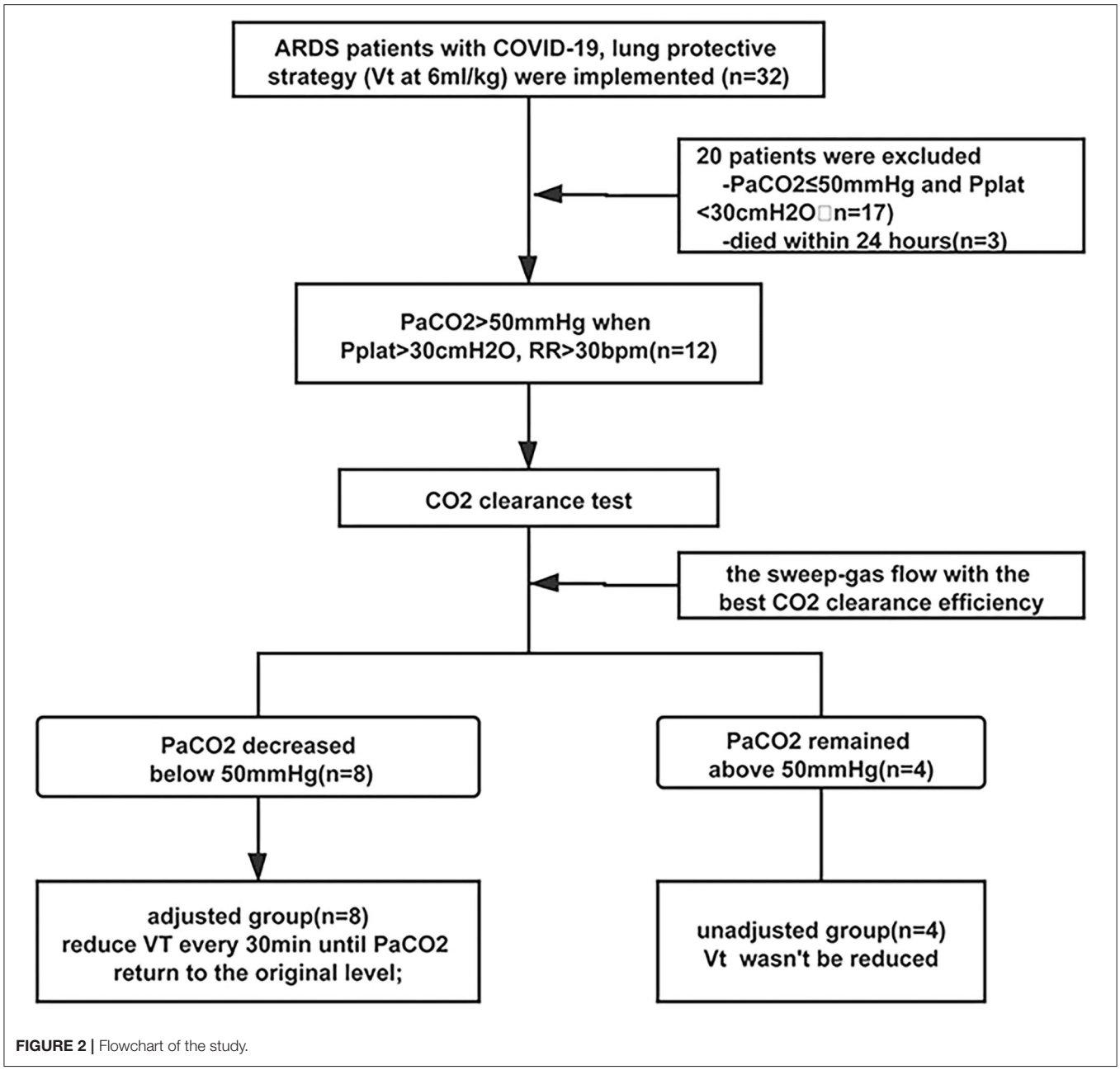

FIGURE 2 | Flowchart of the study.

± 2.72 mmHg and 29.88 ± 3.04 mmHg to 18.5 ± 2.62 mmHg ($p < 0.01$) and 24.75 ± 3.41 mmHg ($p < 0.01$). Furthermore, the mechanical power decreased from 21.25 ± 2.45 to 18.37 ± 2.76 mmHg, with no statistically significant difference ($p = 0.16$). Twenty-four hours later, the DP and Pplat slightly increased, but were still significantly reduced compared with the baseline (**Figure 4**).

In the unadjusted group, 6 h after the test, $PaCO_2$ decreased from 94 [86.25, 100.3] mmHg to 80 [67.50,85.25] mmHg, but with no statistical significant difference ($p = 0.0571$). Twenty-four hours later, the $PaCO_2$ increased slightly again.

DISCUSSION

The result of this single-center, prospective study showed that, in a group of COVID-19 ARDS patients with refractory hypercapnia and extremely low compliance, a low-flow $ECCO_2R$ system based on the RRT platform can easily and safely reduce the $PaCO_2$ level and significantly decrease the Pplat and driving pressure in moderate hypercapnia patients.

Hypercapnia was common with lung protective volume ventilation in COVID-19-related ARDS patients and could be corrected with an intermediate tidal volume (7–8 ml/kg

TABLE 1 | Baseline characteristics.

Characteristic	Total patients ($n = 12$)	Adjusted group ($n = 8$)	Unadjusted group ($n = 4$)
Sex (male/female)	6/6	4/4	2/2
Age (years) (IQR)	67.75 [62.25–71.00]	68.5 [63.75–71.5]	64 [58.25–76.5]
SOFA score, (IQR)	8 (7.0–10.0)	6.9 [6.25–11.0]	8.5 (7.25–9.75)
Pre-$ECCO_2R$ adjuvant therapy			
Neuromuscular blockade	12	8	4
Prone positioning	7	4	3
Recruitment maneuvers	9	6	3
ECMO	0	0	0
COVID-19 diagnosis			
Nucleic acid test (+)	12	8	4
Chest CT results(+)	12	8	4
IgM(+)	7	4	3
IgG(+)	6	3	3
Time from symptom onset to intubation (IQR)	27.1 [21.25–34.75]	21 [6.5–36.25]	31.5 [26.75–38.0]
Time from symptom onset to $ECCO_2R$ initiation (IQR)	43.5 [32.5–47]	39.0 [31.75–47.75]	46.0 [40.5–48]
Ventilation variable			
VT (ml/kg PBW)	5.94 ± 0.18	5.9 ± 0.16	5.93 ± 0.15
RR (bpm)	32.58 ± 3.55	31.25 ± 2.96	35.25 ± 3.4
PEEP(cmH_2O) (IQR)	6 [5.25–8.0]	6 [5.25–7.5]	7 [4.5–9.5]
Pplat (cmH_2O)	34.08 ± 6.91	29.88 ± 3.04	42.5 ± 3.42
Driving pressure (cmH2O)	27.17 ± 5.98	23.5 ± 2.72	34.5 ± 2.52
Compliance (ml/cmH2O)	13.29 ± 4.88	16.02 ± 3.42	7.83 ± 0.73
ABG			
pH (IQR)	7.33 (7.22–7.41)	7.34 (7.22–7.38)	7.30 (7.21–7.37)
PaO_2 (mmHg) (IQR)	81 (79.25–91.5)	80.5 (79.0–87.75)	87.0 (80.5–111.5)
$PaCO_2$ (mmHg) (IQR)	64.5 [56–88.75]	61 [53.5–64.75]	94 [86.25–100.3]
Outcome			
Mechanical ventilation durations (days)	12.5 (7.25–33.5)	21.5 (12.25–36.75)	8.2 (5.3–18.0)
ICU length of stay	21 (15.75–36.25)	20.6 (19.5–38.0)	13.5 (7.5–11)
28-day mortality	8/12	4/8	4/4

PBW) in some patients (4, 5). The conditions were more severe in our ICU, as 37.5% (12/32) of the ARDS patients had refractory hypercapnia despite ventilated with higher DP and higher respiratory rate than usual, and the lung compliance of our patients were relatively lower than reported in other centers. As in these patients, the hypercapnia occurred in the late stage of this disease in critical patients, which was 43.5 [32.5–47] days after the symptom onset, a reminder that the disease was still in progression at that time. Second, the bilateral diffuse ground-glass opacities and reticulation, compensatory emphysema, architectural distortion, and traction bronchiectasis were typical radiographic features on the CT in severe patients (14, 15), which indicated increased pulmonary dead space in these patients. Last, pathological findings such as exudation and mucous plug with fibrinous exudate in the alveoli could cause ventilatory disfunction.

Although, in the early 1990s, the concept of permissive hypercapnia was proposed for patients with acute lung injury, more studies have reported that hypercapnia has a lot of harmful effects, which include inhibition of cell membrane repair, impairment of alveolar fluid clearance, suppression of innate immunity and host defense (16–18), and significant hemodynamic consequences such as pulmonary hypertension and right ventricular dysfunction (19). Recent data suggest an association between values of $PaCO_2 > 50$ mmHg and increased mortality (8); therefore, CO_2 clearance is a necessary treatment in these patients. The present study showed that CO_2 clearance could be reached at 45.91 ± 7.70 ml/min, with the low-flow $ECCO_2R$ device with RRT platform. None of the severe adverse events occurred, although various AEs (e.g., cannulation-related accidents, hemorrhage, pump malfunction, and membrane clotting) were reported (12, 20, 21).

Apart from hypercapnia, the elevated driving pressure and the mechanical power were problems we were more worried about. Because of the low lung compliance of these patients, the driving pressure and the Pplat of these patients were still very high despite protective ventilation with 6 ml/kg. Actually, recent data have demonstrated that there is no safe upper limit for Pplat or DP, and the mortality rate with DP $\leq$ 14 cmH_2O is still as far as 20% (9, 22). As the ventilation variable with

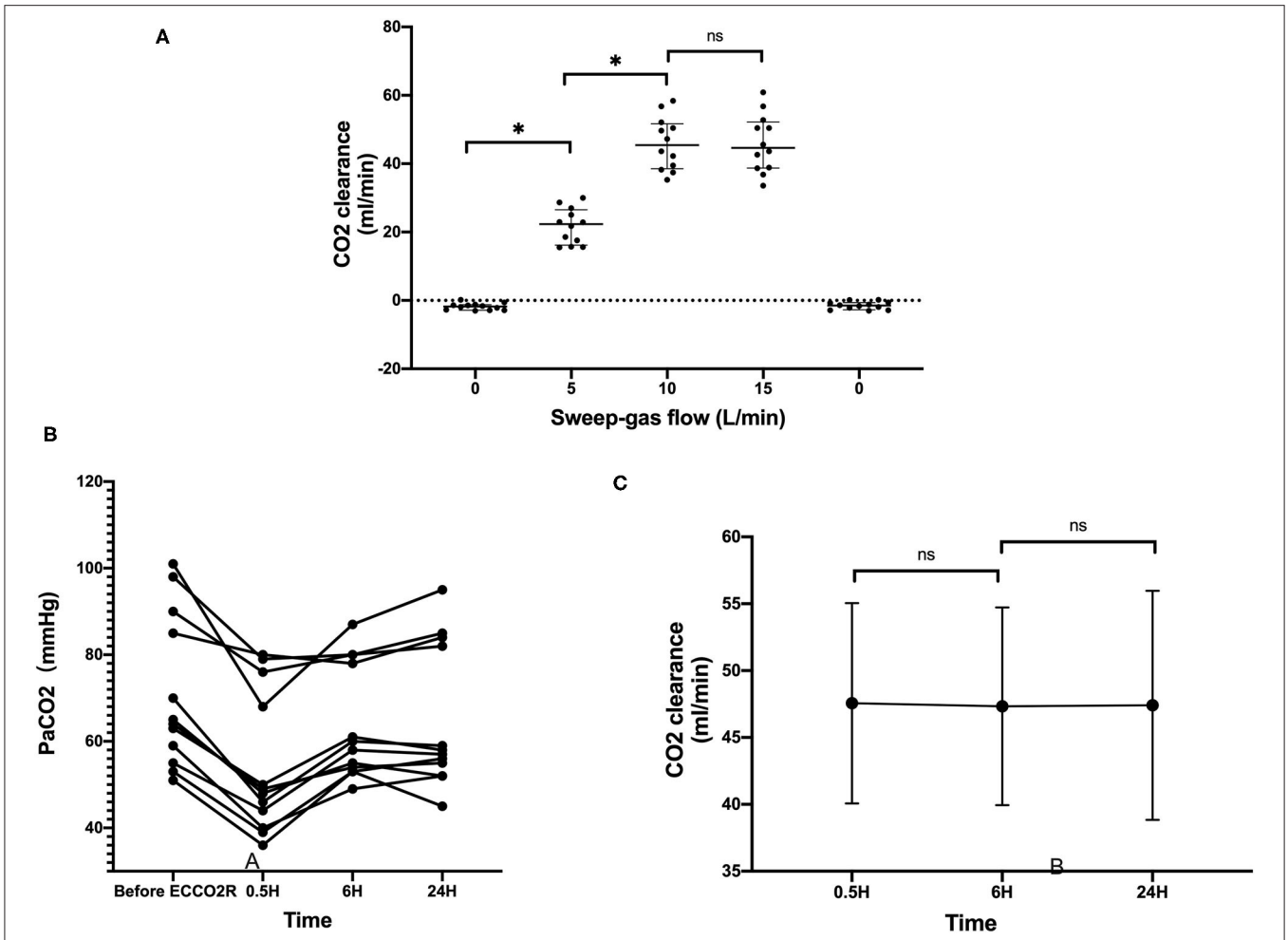

FIGURE 3 | The CO_2 clearance with the $ECCO_2R$. **(A)** The CO_2 clearance rate at different levels of sweep-gas flow. **(B)** The $PaCO_2$ levels of all the 12 patients before and after the $ECCO_2R$. **(C)** The CO_2 clearance rate with time $^*p < 0.05$; ns, no statistical significance.

the best stratified risk, patient outcomes may be improved with the decreasing of DP owing to changes in ventilator settings such as VT (9), and the mechanical power also showed a strong correlation with mortality risk (10). Therefore, in our study, when the $PaCO_2$ was reduced with the low-flow $ECCO_2R$ device, we preferred to decrease the DP and mechanical power first in the moderate hypercapnia group by reducing the VT gradually. In these patients, the DP was significantly reduced, and mechanical power was also reduced, although without statistical significance.

Our results demonstrated that, in these special group of COVID-19 ARDS patients, this low-flow $ECCO_2R$ system could be easily, safely, and efficiently applied, because the RRT platform is widely available, and it did not require specific venous access. As none of the medications had been proven to be effective in the critical patients with COVID-19, and the ECMO were not adequate in many ICUs (11), this low-flow $ECCO_2R$ system could provide a new way of correcting the respiratory acidosis and decreasing the DP, apart from the traditional methods such as prone positioning, recruitment maneuver, nitric oxide, and so on. It may help in the effort to reduce mortality in this global campaign against COVID-19.

Several limitations of our work should be addressed. First, only 12 critically ill patients were included. Although this system has been proven to be effective and safe in mild-to-moderate ARDS patients (12), because of the shortage of resources, only patients with the most needs were included, which were the refractory hypercapnia patients. Due to the exploratory nature of the study, which was not driven by formal hypotheses, the sample size calculation was waived. Instead, we hope that the findings present here will encourage a larger cohort study in these special patients. Second, the CO_2 removal rate of this system was lower than those reported in other studies (23), and the lower blood flows and catheters with faster flow rate could be considered to improve the CO_2 removal rate. Last, this study was mainly conducted to prove the feasibility of such an $ECCO_2R$ system applied to refractory hypercapnia patients with COVID-19-associated ARDS, and the system was limited

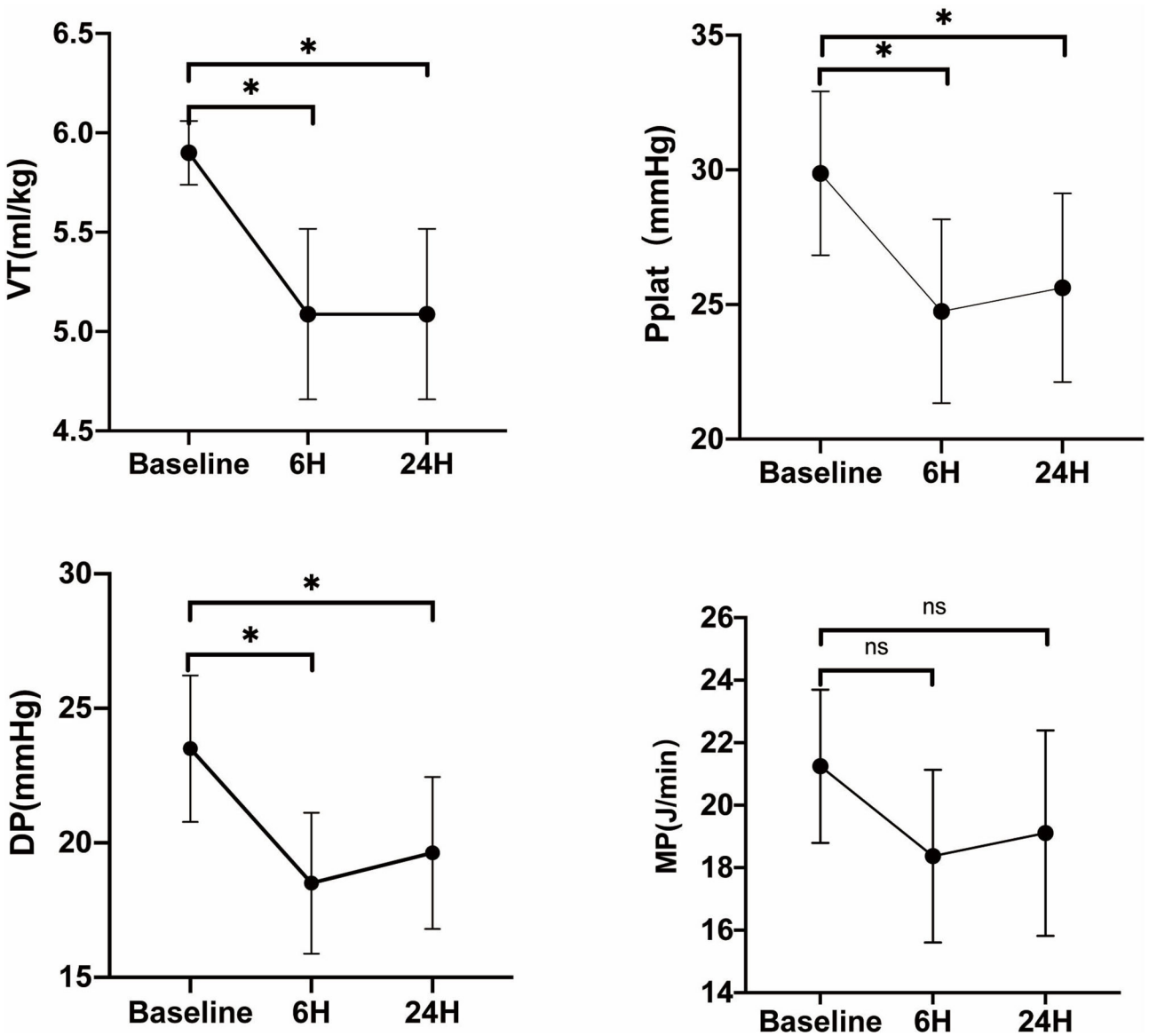

FIGURE 4 | Evaluation of VT, Pplat, DP, and mechanical power when tidal volume was reduced on ECCO$_2$R in the adjusted group. Vt, tidal volume; Pplat, end-inspiratory plateau pressure; DP, driving pressure; MP, mechanical power. *$p < 0.05$ vs. Baseline.

to a period of 24 h, as there was a theoretical risk of rupture of the circuit, and the influence of the outcome of these patients was limited.

CONCLUSION

We reported a group of COVID-19 ARDS patients with refractory hypercapnia and extremely low compliance and have demonstrated that a low-flow ECCO$_2$R system based on the RRT platform enabled CO_2 removal and could also decrease the DP and Pplat significantly. This less-invasive ECCO$_2$R technique was easily and safely implemented and provided a new way for intensivists in the global campaign against COVID-19.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XZ and YL: study conceptualization and writing—review and editing. XD, HC, HuZ, HoZ, and HH: study design. XD, HC, HuZ, HoZ, HH, WC, CW, WJ, YQ, ZL, JW, XY, TL, and SZ: methodology. XD, HC, HuZ, and HoZ: formal analysis and investigation. XD, HC, and HuZ: writing—original draft preparation. All authors commented on a previous version of the manuscript and all authors read and approved the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Evaluation of Positive End-Expiratory Pressure Strategies in Patients With Coronavirus Disease 2019–Induced Acute Respiratory Distress Syndrome

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Background: Different positive end-expiratory pressure (PEEP) strategies are available for subjects with coronavirus disease 2019 (COVID-19)–induced acute respiratory distress syndrome (ARDS) requiring invasive mechanical ventilation. We aimed to evaluate three conventional PEEP strategies on their effects on respiratory mechanics, gas exchanges, and hemodynamics.

Methods: This is a prospective, physiologic, multicenter study conducted in China. We recruited 20 intubated subjects with ARDS and confirmed COVID-19. We first set PEEP by the ARDSnet low PEEP–fraction of inspired oxygen (FIO_2) table. After a recruitment maneuver, PEEP was set at 15, 10, and 5 cm H_2O for 10 min, respectively. Among these three PEEP levels, best-compliance PEEP was the one providing the highest respiratory system compliance; best-oxygenation PEEP was the one providing the highest PaO_2 (partial pressure of arterial oxygen)/FIO_2.

Results: At each PEEP level, we assessed respiratory mechanics, arterial blood gas, and hemodynamics. Among three PEEP levels, plateau pressure, driving pressure, mechanical power, and blood pressure improved with lower PEEP. The ARDSnet low PEEP–FIO_2 table and the best-oxygenation strategies provided higher PEEP than the best-compliance strategy (11 ± 6 cm H_2O vs. 11 ± 3 cm H_2O vs. 6 ± 2 cm H_2O, $p = 0.001$), leading to higher plateau pressure, driving pressure, and mechanical power. The three PEEP strategies were not significantly different in gas exchange. The subgroup analysis showed that three PEEP strategies generated different effects in subjects with moderate or severe ARDS ($n = 12$) but not in subjects with mild ARDS ($n = 8$).

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Conclusions: In our cohort with COVID-19–induced ARDS, the ARDSnet low PEEP/FIO_2 table and the best-oxygenation strategies led to higher PEEP and potentially higher risk of ventilator-induced lung injury than the best-compliance strategy.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier: NCT04359251.

Keywords: acute respiratory distress syndrome, coronavirus disease 2019, positive end-expiratory pressure, mechanical ventilation, lung injury

INTRODUCTION

The World Health Organization announced the coronavirus disease 2019 (COVID-19) outbreak a pandemic on March 11, 2020. It has been reported that 67% of critically ill subjects with COVID-19 developed acute respiratory distress syndrome (ARDS) requiring invasive mechanical ventilation (1). Setting a sufficient positive end-expiratory pressure (PEEP) level is crucial for improving oxygenation, keeping alveoli open, and reducing cyclic reopening–closing ("atelectrauma") (2, 3). However, an unnecessarily high PEEP can increase the risk of overdistension, especially in subjects with low recruitability and severe lung inhomogeneity (4–8).

Determining the appropriate or "best" PEEP is, however, challenging (9). Several methods have been used in clinical trials and routine practice. ARDSnet low and high PEEP–fraction of inspired oxygen (FIO_2) tables are probably the most widely used methods in randomized controlled trials (10, 11). These tables, aiming at maintaining oxygenation while minimizing the use of high FIO_2, provided great feasibility for clinical practice. Alternatively, clinicians can perform a decremental PEEP trial (12), to find the PEEP providing the highest compliance ("best-compliance" strategy) or providing the highest ratio of partial pressure of arterial oxygen (PaO_2) to FIO_2 ("best-oxygenation" strategy) (13–15). The so-called best-oxygenation strategy has not been used in large clinical trials but might be widely embedded in clinical practice where the oxygen saturation by pulse oximetry is often used as a surrogate.

While the current guidelines suggest using higher PEEP (>10 cm H_2O) in subjects with COVID-19–induced ARDS (16), varied lung recruitability and responses to PEEP were reported from monocenter studies (17–19). Meanwhile, Marini and Gattinoni proposed that COVID-19–induced ARDS is probably different from conventional ARDS (20–22). It is unclear how those conventional PEEP strategies perform in this particular population. We thus want to evaluate three conventional PEEP strategies (ARDS low PEEP–FIO_2 table, best-compliance, and best-oxygenation strategies) in subjects with COVID-19–induced ARDS, to see whether they result in different PEEP settings, respiratory mechanics, gas exchange, hemodynamics, and potential risk of ventilator-induced lung injury (VILI).

MATERIALS AND METHODS

Study Population

This is a prospective physiologic study conducted in seven intensive care units (ICUs) of seven hospitals (Wuhan Jinyintan Hospital, The People's Hospital of Wuhan Xinzhou, Huangshi Hospital of Traditional Chinese Medicine, Wuhan Asia General Hospital, Wuhan Fifth Hospital, Wuhan Wuchang Hospital, and Wuhan Pulmonary Hospital, Wuhan, China) from March 5 to 16, 2020. Inclusion criteria were between 18 and 80 years old, laboratory-confirmed COVID-19, receiving invasive mechanical ventilation, and meeting the Berlin Definition of ARDS at clinical PEEP level. Exclusion criteria were pregnancy, hemodynamic instability (i.e., norepinephrine >0.05 μg/kg per minute or dopamine >5 μg/kg per minute), acute brain injury, pneumothorax, or pneumomediastinum.

The study was approved by the local Research Ethics Board. Written informed consent was obtained from substitute decision makers. The study was registered at ClinicalTrials.gov (NCT04359251).

Study Protocol

During the study, subjects were measured at a semirecumbent position under volume control ventilation with a square flow waveform. Tidal volume (V_T) was kept at 6 ml/kg per predicted body weight, and respiratory rate was kept the same at different PEEP levels. Subjects were administered a continuous infusion of analgesia and sedation. If spontaneous breathing effort was strong during sedation, neuromuscular-blocking agents were administered to suppress spontaneous breathing.

PEEP trial: (1) We first set PEEP by the ARDSnet low PEEP/FIO_2 table; goals of PEEP and FIO_2 settings were PaO_2 55-80 mm Hg, or SpO_2 88-95%. An arterial blood gas (ABG) was obtained at this PEEP level. (2) We then performed a recruitment maneuver by using continuous positive airway pressure at 30 cm H_2O for 30 s, to standardize lung volume history. (3) Thereafter, PEEP was set at 15, 10, and 5 cm H_2O for 10 min, respectively. At each PEEP level, an ABG was obtained. In addition, if a subject had extremely high plateau pressure (Pplat, e.g., >35 cm H_2O) or hemodynamic instable or refractory desaturation, the duration of that PEEP level was reduced for safety consideration (**Figure 1**).

"Best-compliance PEEP" was defined as the PEEP (among 15, 10, and 5 cm H_2O) providing the highest respiratory system compliance (C_{rs}).

"Best-oxygenation PEEP" was defined as the PEEP (among 15, 10, and 5 cm H_2O) providing the highest PaO_2/FIO_2 ratio.

Measurements

Airway pressure was measured using a ventilator (SV300, Mindray, China). Pplat was measured by performing end-inspiratory occlusion. Total PEEP ($PEEP_{tot}$) was measured by

performing end-expiratory occlusion. Static C_{rs} was calculated with the following formula: V_T/(Pplat – $PEEP_{tot}$) (23). Driving pressure was calculated with the following formula: Pplat – $PEEP_{tot}$. Mechanical power was calculated with the following formula: 0.098 × RR × V_T × (Ppeak – ½ × driving pressure) (24).

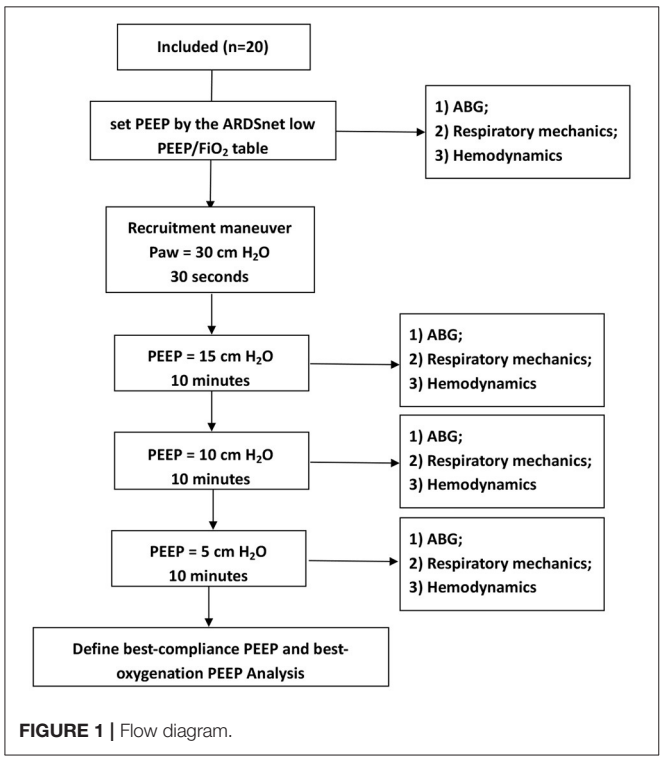

FIGURE 1 | Flow diagram.

Criteria of "High Risk of VILI"

To determine how many subjects were potentially exposed to high risk of VILI by three PEEP strategies, we defined the high risk of VILI by meeting one of the following criteria: (1) Pplat > 30 cm H_2O, (2) driving pressure > 15 cm H_2O, and (3) mechanical power > 25 J/min (11, 25, 26).

Data Collection

The general characteristics of subjects such as gender, age, height, Sequential Organ Failure Assessment (SOFA) score, and days of invasive mechanical ventilation were collected. Ventilator settings, mechanics parameters, ABG, blood pressure, and heart rate were also documented at study enrollment and during the PEEP trial.

Statistical Analysis

Data are presented as the mean ± standard deviation, unless specified otherwise. Comparisons between three PEEP levels were conducted by using analysis of variance with repeated measures or paired *t*-test, when appropriate. Comparisons between two groups (separated by PaO_2/FIO_2) were conducted by using independent *t*-test. $p < 0.05$ was considered statistically significant. SPSS 20.0 (Statistical Product and Service Solutions, Chicago, IL, USA) was used for statistical analysis.

TABLE 1 | Characteristics of COVID-19 patients with mechanical ventilation.

Characteristics	Overall (*n* = 20)	Mild ARDS (*n* = 8)	Moderate/severe ARDS (*n* = 12)	*P**
Males—*n* (%)	12 (60)	6 (75)	6 (50)	0.26
Age (years)	64 ± 7	63 ± 9	65 ± 6	0.38
Height (cm)	170 ± 9	174 ± 8	167 ± 8	0.07
SOFA	11 ± 2	11 ± 1	11 ± 3	0.59
IMV (days)	11 ± 6	10 ± 8	11 ± 4	0.77
V_T (ml/kg)	5.6 ± 0.8	5.6 ± 0.7	5.6 ± 0.9	0.88
FiO_2	0.66 ± 0.30	0.53 ± 0.22	0.74 ± 0.30	0.09
pH	7.36 ± 0.08	7.37 ± 0.05	7.35 ± 0.10	0.54
PaO_2 (mm Hg)	108 ± 53	138 ± 57	88 ± 41	0.03
PaO_2/FiO_2 (mm Hg)	180 ± 75	259 ± 25	126 ± 39	<0.001
$PaCO_2$ (mm Hg)	60 ± 18	62 ± 20	58 ± 17	0.67
P_{plat} (cm H_2O)	23 ± 6	22 ± 7	24 ± 5	0.50
PEEP (cm H_2O)	6 ± 2	6 ± 2	6 ± 2	0.97
ΔP (cm H_2O)	17 ± 5	16 ± 7	17 ± 4	0.50
Crs (ml/cm H_2O)	23 ± 8	27 ± 9	20 ± 6	0.05
MAP (mm Hg)	84 ± 12	88 ± 13	81 ± 10	0.22
HR (bpm)	95 ± 18	93 ± 15	97 ± 20	0.62

COVID-19, Coronavirus disease 2019; SOFA, sequential organ failure assessment; IMV, invasive mechanical ventilation; V_T, tidal volume; Pplat, plateau pressure; PEEP, positive end-expiratory pressure; ΔP, driving pressure; Crs, respiratory system compliance; MAP, mean arterial pressure; HR, heart rate.
**Patients with mild ARDS vs. patients with moderate or severe ARDS. Compared by t-test.*

RESULTS

Twenty subjects (12 men and eight women, aged 64 ± 7 years, SOFA score 11 ± 2) were enrolled. The subjects received various durations of invasive mechanical ventilation before measurement (11 ± 6 days). ICU mortality was 60% (12/20). The detailed characteristics including the baseline respiratory mechanics at clinical PEEP level are reported in **Table 1**.

Responses to 15, 10, and 5 cm H_2O of PEEP

As shown in **Figure 2**, Pplat, driving pressure, and mechanical power were significantly decreased when PEEP was reduced from 15 to 10 cm H_2O and from 10 to 5 cm H_2O. We failed to obtain ABG at PEEP 15 cm H_2O in three subjects because of extremely high Pplat (>50 cm H_2O) at high PEEP. After the recruitment maneuver, PaO_2/FIO_2 was similar at 15 and 10 cm H_2O of PEEP but dropped at 5 cm H_2O of PEEP ($p = 0.005$). $PaCO_2$ was significantly higher at 15 cm H_2O of PEEP than at 10 and 5 cm H_2O of PEEP ($p = 0.018$). Heart rate was similar at three PEEP levels, but mean arterial pressure (MAP) was lower at 15 cm H_2O of PEEP ($p = 0.012$).

Comparisons of Three PEEP Strategies

As shown in **Figure 2**, the PEEP guided by best compliance was lower than the PEEP guided by best oxygenation and the PEEP guided by ARDSnet low $PEEP/FIO_2$ table (6 ± 2 vs. 11 ± 4 and 11 ± 6 cm H_2O, $p = 0.001$). Pplat, driving pressure, and mechanical power by best-compliance strategy were lower than those by best-oxygenation strategy and ARDSnet low PEEP–FIO_2 table (Pplat: 21 ± 6 vs. 31 ± 11 and 32 ± 15 cm H_2O, $p < 0.001$; driving pressure: 15 ± 6 vs. 20 ± 9 and 21 ± 10 cm H_2O, $p < 0.001$; mechanical power: 15.9 ± 4.5 vs. 23.5 ± 9.6 and 22.9 ± 10.9 J/min, $p = 0.001$). C_{rs} by best-compliance strategy were higher than those by best-oxygenation strategy and ARDSnet low PEEP–FIO_2 table (26.8 ± 11.8 vs. 20.6 ± 8.0 and 20.3 ± 9.3 mL/cm H_2O, $p < 0.01$). PaO_2 by ARDSnet low PEEP–FIO_2 table was lower than those by best-compliance strategy and best-oxygenation strategy (93.3 ± 40.0 vs. 229.7 ± 159.8 and 187.4 ± 146.2 mm Hg, $p < 0.01$). Best-oxygenation PEEP provided highest PaO_2/FIO_2 (293 ± 137.8 mm Hg), whereas best-compliance PEEP provided higher PaO_2/FIO_2 than the ARDSnet low PEEP–FIO_2 table (252 ± 130 vs. 204 ± 103 mm Hg). $PaCO_2$ was similar among the three strategies ($p = 0.58$). MAP was significantly higher with the PEEP guided by best compliance than MAP with the

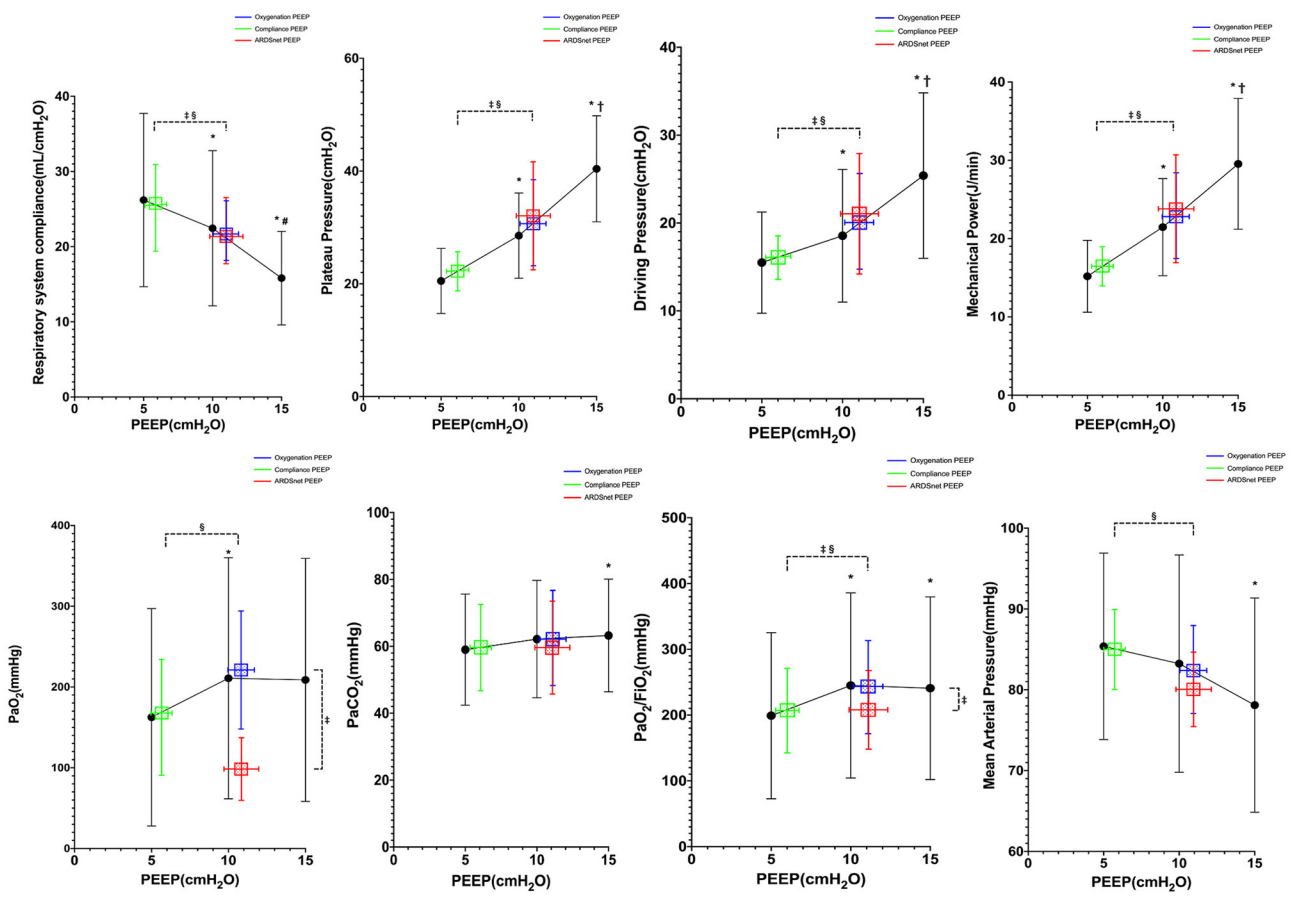

FIGURE 2 | Reponses to PEEP in all subjects ($n = 20$). *vs. PEEP 5 cm H_2O, $p < 0.05$; †vs. PEEP 10 cm H_2O, $p < 0.05$; ‡vs. oxygenation PEEP, $p < 0.05$; §vs. ARDSnet PEEP, $p < 0.05$.

other two strategies ($p < 0.001$), whereas heart rate was similar ($p = 0.96$).

Subgroup Analysis

We divided subjects into two subgroups (mild ARDS and moderate/severe ARDS) according to PaO_2/FIO_2 at study enrollment based on Berlin Definition (27). Characteristics of the subjects, including gender, age, SOFA score, and duration of mechanical ventilation were similar between two subgroups. PaO_2 and PaO_2/FIO_2 were higher in the mild ARDS group than those in the moderate/severe ARDS group. V_T, FIO_2, $PaCO_2$, Pplat, PEEP, driving pressure, C_{rs}, MAP, and heart rate at baseline (before initiation of the protocol) were not different between the two groups (**Table 1**).

There were eight subjects in the study with mild ARDS at study enrollment. Pplat, driving pressure, and mechanical power decreased significantly from PEEP 15 to 5 cm H_2O (**Figure 3**). PEEP levels were not significantly different among the three PEEP strategies. PaO_2, Pplat, C_{rs}, and mechanical power were not different among the three PEEP strategies (**Figure 3**). However, driving pressure at best-oxygenation PEEP and that at ARDSnet PEEP were higher than driving pressure at best-compliance PEEP (16 ± 8 and 18 ± 11 vs. 14 ± 7 cm H_2O, $p = 0.03$). There was one subject with missing ABG results. $PaCO_2$, MAP, and HR at PEEP guided by the three strategies were similar (**Figure 3**).

There were 12 subjects with moderate/severe ARDS at study enrollment. Pplat, driving pressure, and mechanical power decreased significantly from PEEP 15 to 5 cm H_2O (**Figure 4**), whereas MAP increased significantly at lower PEEP (**Figure 4**). ARDSnet PEEP and best-oxygenation PEEP were higher than the best-compliance PEEP (12 ± 7 and 12 ± 4 vs. 6 ± 2 cm H_2O, $p = 0.007$). Pplat, driving pressure, and mechanical power at best-oxygenation PEEP and ARDSnet PEEP were higher than at best-compliance PEEP (Pplat: 35 ± 12 and 36 ± 15 vs. 22 ± 14 cm H_2O, $p = 0.002$; driving pressure: 23 ± 10 and 24 ± 10 vs. 16 ± 5 cm H_2O, $p = 0.002$; mechanical power: 26 ± 11 and 25 ± 11 vs. 16 ± 5 J/min, $p = 0.004$) (**Figure 4**). C_{rs} at best-compliance PEEP was higher than those at best-oxygenation PEEP and ARDSnet PEEP (23.0 ± 7.8 vs. 16.6 ± 4.8 and 16.7 ± 7.5 ml/cm H_2O, $p < 0.01$). There were three subjects without ABG measurements at PEEP 15 cm H_2O as previously mentioned. PaO_2 and PaO_2/FIO_2 were lower with ARDSnet PEEP. pH, $PaCO_2$, MAP, and HR between the three strategies were similar.

Potential Risk of VILI

In mild ARDS subjects, the potential risks of lung injury induced by three PEEP strategies were similar and relatively

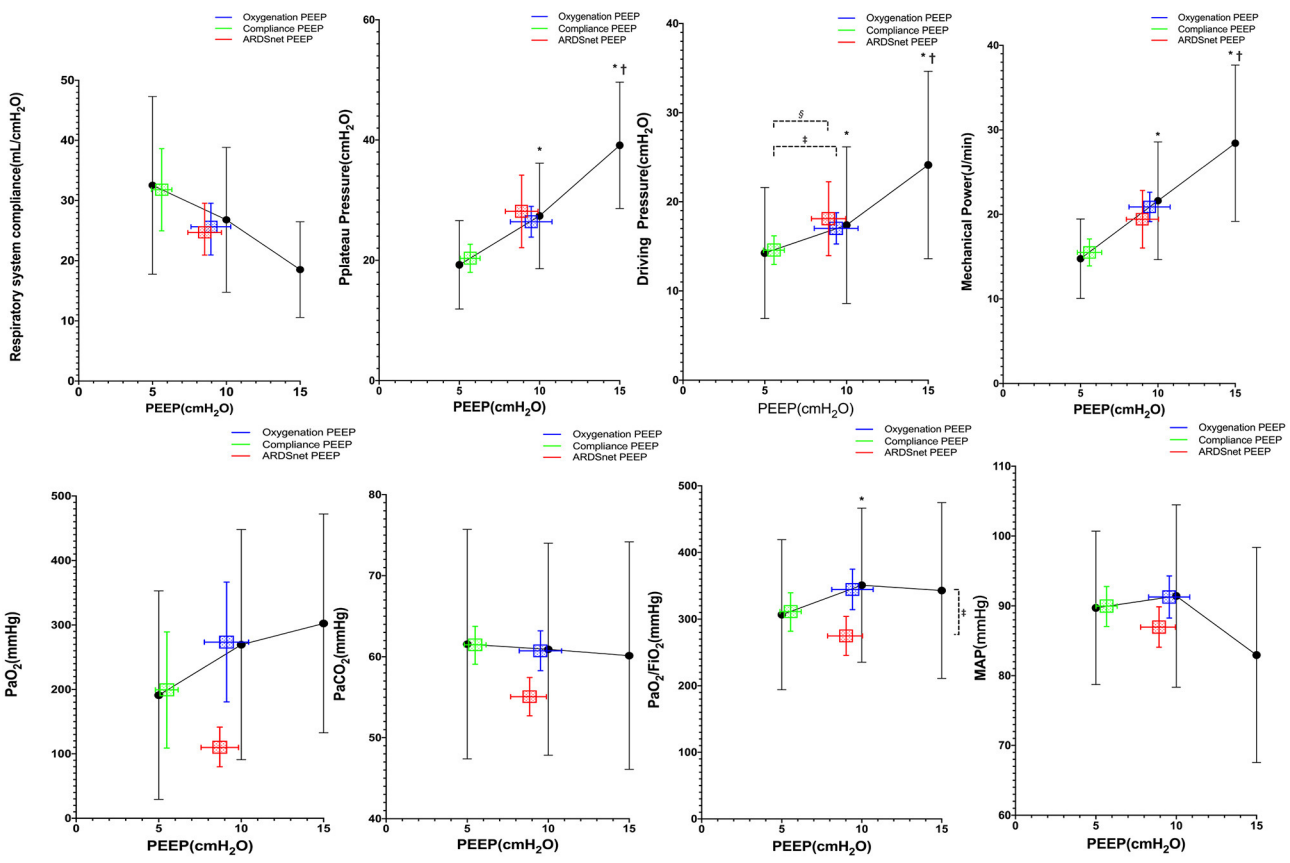

FIGURE 3 | Reponses to PEEP in subjects with mild ARDS ($n = 8$). *vs. PEEP 5 cm H_2O, $p < 0.05$; †vs. PEEP 10 cm H_2O, $p < 0.05$; ‡vs. oxygenation PEEP, $p < 0.05$; §vs. ARDSnet PEEP, $p < 0.05$.

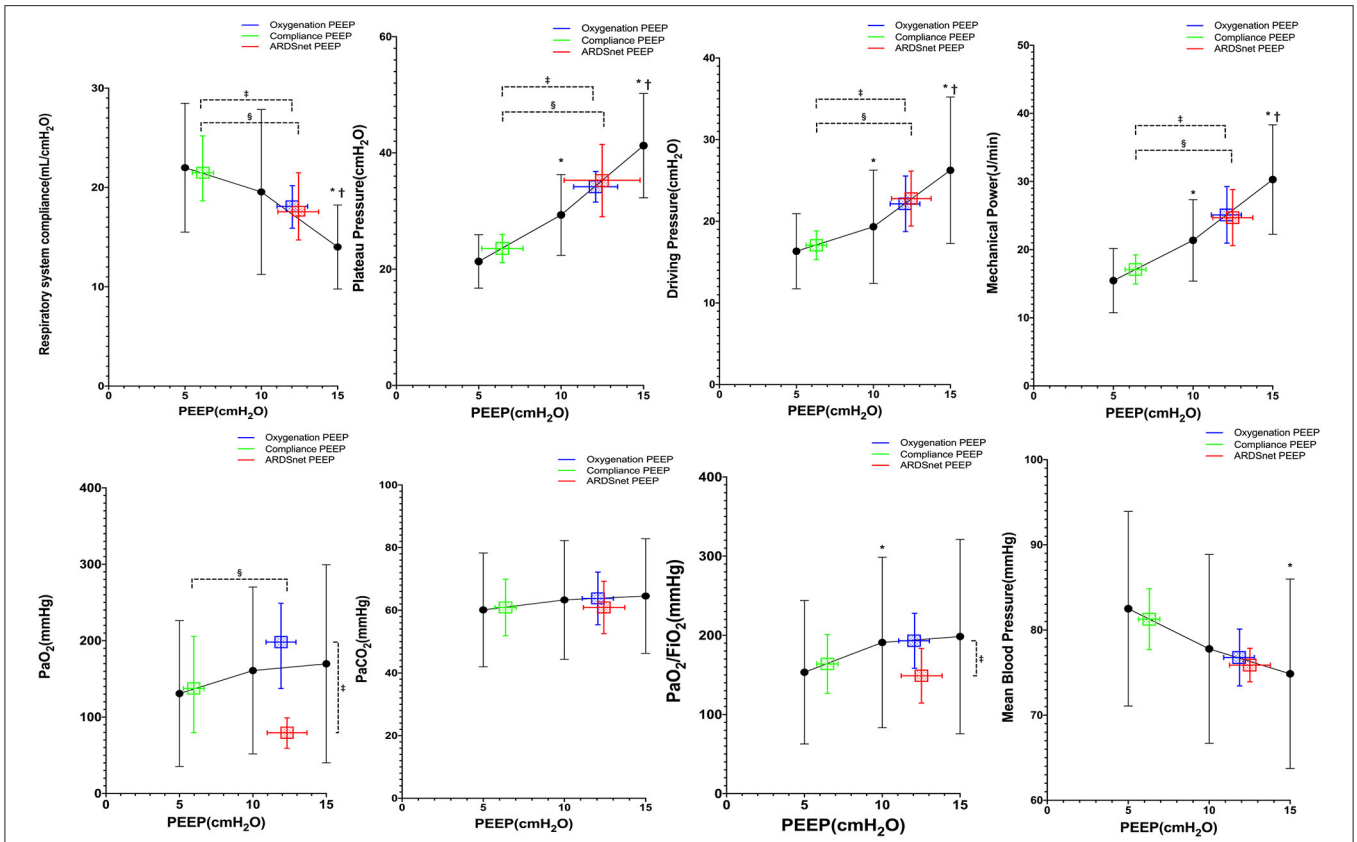

FIGURE 4 | Reponses to PEEP in subjects with moderate or severe ARDS ($n = 12$). *vs. PEEP 5 cm H_2O, $p < 0.05$; †vs. PEEP 10 cm H_2O, $p < 0.05$; ‡vs. oxygenation PEEP, $p < 0.05$; §vs. ARDSnet PEEP, $p < 0.05$.

TABLE 2 | Incidence of potentially high risk of ventilator-induced lung injury.

	Mild ARDS ($n = 8$)			Moderate or severe ARDS ($n = 12$)		
	Best-oxygenation	**Best-compliance**	**ARDSnet low PEEP table**	**Best-oxygenation**	**Best-compliance**	**ARDSnet low PEEP table**
$P_{plat} > 30$ cm H_2O *n* (%)	1 (12.5%)	1 (12.5%)	2 (25.0%)	8 (66.7%)*	1 (8.3%)	8 (66.7%)†
$\Delta P > 15$ cm H_2O *n* (%)	3 (27.5%)	2 (25.0%)	3 (27.5%)	10 (83.3%)	5 (41.7%)	8 (66.7%)
Mechanical Power > 25 J/min *n* (%)	2 (25.0%)	0	1 (12.5%)	6 (50.0%)*	0	7 (58.3%)†

Pplat, plateau pressure; ΔP, driving pressure.
**p < 0.05 by Fisher's exact tests in best-oxygenation PEEP vs. best-compliance PEEP.*
†p < 0.05 by Fisher's exact tests in ARDSnet low PEEP table vs. best-compliance PEEP.

low (**Table 2**). In moderate/severe ARDS subjects, however, both best-oxygenation PEEP and ARDSnet PEEP generated "injurious" Pplat (>30 cm H_2O) and mechanical power (>25 J/min) more frequently than best-compliance PEEP (**Table 2**).

DISCUSSION

The main findings of the present study are that in COVID-19–induced ARDS subjects mechanically ventilated in Wuhan, China, most of the subjects had a poor response to high PEEP. The PEEP/FIO_2 table and best-oxygenation PEEP had similar effects to best-compliance PEEP on gas exchanges and hemodynamics, but there was an increased risk of lung injury due to high PEEP levels particularly for the subjects with moderate/severe ARDS.

Lung recruitability of COVID-19–induced ARDS is highly variable. Our previous study assessed the potential for lung recruitment through the recruitment-to-inflation ratio (28),

showing that the majority of the cohort had poor recruitability to high PEEP in subjects with COVID-19–induced ARDS (19). In two recent studies by Beloncle et al. and Mauri et al., however, the potential for lung recruitment (assessed by the recruitment-to-inflation ratio) of subjects with COVID-19–induced ARDS in Italy and France was much higher than what we found in Wuhan, with larger intersubject variability (17, 18). Gattinoni and Marini proposed a hypothesis that COVID-19 pneumonia subjects should be divided into different phenotypes to offer different respiratory support (20–22, 29, 30). Subjects in the present study had poor response to high PEEP (dramatic increase in Pplat, driving pressure, mechanical power with reduction in MAP). These poor responses to high PEEP suggest poor lung recruitability in these subjects, which is consistent with our previous study in which lung recruitability was directly measured (19) and other studies (31–35). However, subjects in our study also presented with low baseline compliance, which were not the proposed "type H phenotype" patients and differ from other studies.

We suspect that the differences in lung recruitability and compliance among studies might be caused by different durations of invasive ventilation prior to study enrollment. The subjects in our study received relatively long durations of invasive mechanical ventilation before measurement (11 ± 6 days), which can generate progressive lung fibrosis and thus worsen the compliance and lower the lung recruitability. The time course of changes in mechanics has been well-illustrated by (29). Alternatively, these differences might be related to the different lineages of coronavirus (36–39).

Limiting the risk of hyperinflation of the "baby lung" when applying high PEEP to promote the recruitment of the collapsed lung is essential. The present study showed that the PEEP selected by ARDSnet low PEEP–FIO_2 table or the best-oxygenation methods was significantly higher than the PEEP selected by the best-compliance method. As a consequence, both ARDSnet low PEEP–FIO_2 table and the best-oxygenation strategies led to higher Pplat, driving pressure, and mechanical power. Although the thresholds of the limits of these parameters can be debatable, the present study showed that the incidences of "injurious" Pplat (>30 cm H_2O) and mechanical power (>25 J/min) were higher in ARDSnet low PEEP–FIO_2 table and the best-oxygenation strategy in subjects with moderate or severe ARDS. Although we did not test the ARDSnet high PEEP–FIO_2 table in our study, it obviously would have increased the risk of overdistension in our subjects. By contrast, the best-compliance strategy did not bring notable risk of overdistension in mild or moderate/severe ARDS subjects.

There are some limitations in our study. (1) Although it is a multicenter study, the sample size is less than expected because of a dramatic reduction in the number of newly admitted ICU subjects during the study. (2) Duration of mechanical ventilation of subjects involved after intubation was 11 ± 6 days in this study. Caution is required for comparing our results with other studies, which enrolled subjects in an earlier phase of mechanical ventilation. (3) We did not assess lung recruitability directly. Instead, we assessed the change in respiratory mechanics, gas exchange, and hemodynamic effects during the PEEP trial, which reflect the subjects' response to PEEP. (4) We simplified the PEEP trial compared to other studies, which used a decremental PEEP trial by 2 cm H_2O after a recruitment maneuver. (5) We did not measure biomarkers at different PEEP settings, which can help us better assess the risk of VILI.

In our cohort with COVID-19–induced ARDS from Wuhan, the ARDSnet low PEEP/FIO_2 table and the best-oxygenation strategies provide higher PEEP than the best-compliance strategy. Our subjects had poor responses to high PEEP as high PEEP often led to excessive Pplat, driving pressure mechanical power, and worse MAP. Further studies on the effects of PEEP on COVID-19–induced ARDS are needed to confirm our findings.

DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Wuhan Jinyintan Research Ethics Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

BD and HQ: conceptualization, methodology, project administration, visualization, funding acquisition, and supervision. CP and CL: formal analysis. CP, XS, HR, HW, LX, YH, and JX: investigation. CP, CL, and LC: writing—original draft. CP, CL, YY, and LC: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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OPINION
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Mechanical Thrombectomy for Stroke and COVID-19 Pandemic: A Critical Insight for Anesthesiologists

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INTRODUCTION

There is increasing evidence of a higher incidence of stroke in patients with coronavirus disease 2019 (COVID-19) infection (1, 2). This poses significant implications for anesthesiologists in the management of this complex patient population for emergency management of acute ischemic stroke (AIS). In this article, we would like to shed light on this topic by critically appraising the current literature specifically addressing anesthetic management during interventional treatment of ischemic stroke in patients with COVID-19.

COVID and Stroke

During the start of the pandemic, a brief report claimed a decreasing trend of mechanical thrombectomy in Shanghai by almost 50% (3). This trend was surprising as it was expected that AIS will be reported as a possible complication of COVID-19 (4, 5). Cohorts from three hospitals in China showed that up to 36% of patients with COVID-19 infection had a variety of neurological symptoms including headache, dizziness, encephalopathy, and anosmia (3–5). Similarly, during the initial pandemic phase in Italy, a study by Lodigiani et al. (388 consecutive patients with COVID-19) pointed out that the thromboembolic complications following COVID-19 represented an integral part of the clinical picture of the neurological manifestations of this viral infection; however, the exact incidence might have been still underreported due to the low number of specific imaging tests performed (6). Strikingly, another study (pooled analysis of four studies) also highlighted the similar notion that there was a higher chance (up to 2.5 times) of severe COVID-19 illness in patients with symptomatic cerebrovascular disease (7).

The incidence of overall stroke during the pandemic was reported (mainly retrospective data) to be between 2.5% and 6% from China and Europe, and it is more likely to occur within the first 14 days following the COVID-19 diagnosis (2, 3). During the COVID outbreak in Wuhan, the study by Huang et al. (221 patients with COVID-19) reported that 5% of the patients presented with AIS, 0.5% developed cerebral venous sinus thrombosis, and 0.5% with cerebral hemorrhage (8). This may be due to the raised serum concentrations of the inflammatory cytokines that caused endothelial damage and dysfunction, increasing the pro-coagulant activity of the blood, which essentially contributes to the formation of a thrombus over a damaged arterial plaque (8). In addition, they also noted that COVID-19 patients with new onset of stroke were significantly older (71.6 ± 15.7 vs. 52.1 ± 15.3 years, $p < 0{\cdot}05$) as compared to those not infected (8). Similarly, another study from Wuhan, China, reported 14 cases of stroke out of 219 patients with COVID-19 symptoms and further concluded that COVID-19 should be included in the

differential diagnosis for patients with symptomatic cerebrovascular diseases (9). Looking at the various associations, a recent study of 46,248 patients with COVID-19 by Yang et al. revealed the two most prevalent comorbidities: hypertension (17%) and diabetes (8%). Both are also risks factors for stroke. Interestingly, cardiovascular disease accounted for only 5% of the patients, supporting an association between COVID-19 and stroke in a population without the typical vascular risk factors (10). They further concluded that the COVID-19-induced hypercoagulability was probably the most important mechanism of thrombosis in patients presenting with cerebrovascular symptoms. Thus, the higher incidence of cerebrovascular events was more likely due to the pronouncement of the underlying stroke-related characteristics than a new finding in COVID-19 patients (10).

The recently concluded STAR and the ENG trials in COVID-19 patients from 28 stroke centers in five countries reported that the median age distribution in patients presenting with stroke was 58 years, and there were no significant differences in the distribution with either gender or race. They also reported a low number of confirmed COVID-19 infections among patients with AIS undergoing mechanical thrombectomy. They concluded that intubation prior to mechanical thrombectomy during the early stages of stroke was associated with a greater in-hospital mortality and lower functional independence at discharge (11).

Anesthesia and Mechanical Thrombectomy

Endovascular revascularization treatment remains the standard of care for AIS caused by large (cerebral) vessel occlusion in patients presenting within 6 h from the onset of symptoms of stroke. This is true even during the pandemic if patients meet specific neuroradiological criteria. There seems, however, to be an ongoing debate with regard to the ideal anesthetic technique for this procedure (1, 2). General anesthesia (GA) and conscious sedation (CS) have been described for patients undergoing endovascular thrombectomy (EVT) (**Table 1**). The advantages of GA included airway protection with lesser risks of pulmonary aspiration, patient immobility, and higher patient compliance. In contrast, local anesthesia or CS, with the patient spontaneously breathing, is associated with shorter procedure time and lower hemodynamic instability. However, the pandemic situation poses additional anesthesia risks.

Pooled data from multiple studies have shown that patients who underwent endovascular treatment under GA have worse outcomes compared to those with CS (12). Wan et al., in a recent meta-analysis of 6,703 patients, reported that patients in the GA arm had lower odds ratios (ORs) of favorable outcome when compared to those in the CS group (OR = 0.62, 95% CI = 0.49–0.77). Moreover, patients in the GA group were associated with a statistically significant higher risk of mortality (OR = 1.68, 95% CI = 1.49–1.90) (12). Brinjikji et al., in a meta-analysis, have suggested that the time delay associated with intubation could have led to worse outcomes for patients in the GA group (13). This meta-analysis, however, failed to prove non-significant or non-clinically relevant differences in most of the prespecified time intervals and procedure durations. Albeit the time intervals were shorter in the CS group, there were no significant differences in the groin puncture to reperfusion time or any differences in the total duration of the intervention found. Interestingly, they found that the mean time delay caused by the induction of GA compared to monitored anesthesia care (MAC) was only 6 min (13).

In contrast, a recent systematic review and meta-analysis of pooled data from four randomized control trials (RCTs) showed that patients who underwent EVT under GA had higher rates of successful recanalization and good functional outcomes at 3 months compared to patients treated with CS (14). The GA group also had non-significant trends toward a lower 3-month mortality. The proportions of patients with good functional outcomes at 3 months were 49.3% in the GA group and 36.6% in the CS group, an absolute difference of 12.7% (14). The value of these findings is not clear, as, in general, observational studies and meta-analyses have reported worse outcomes after GA when compared to those patients who have had CS. One explanation could be a selection bias in other studies compared to that in Campbell et al. (14). In summary, both GA and CS have been shown to be safe with good functional outcomes after mechanical thrombectomy. However, the choice of anesthetic technique still depends on the individual patient's condition and the institutional practice.

TABLE 1 | Pros and cons of general anesthesia and monitored anesthesia care in COVID-19 patient undergoing mechanical thrombectomy for ischemic stroke.

General anesthesia	Local anesthesia
Pros	**Pros**
1. Avoidance of patient movement	1. Better haemodynamic profile
2. Airway protection	2. Less chances of postoperative nause and vomiting
3. Avoidance of aerosol contamination during the case	3. Access to neurological evaluation
4. Proetction of team	
5. Delayed neurological examination	
Cons	**Cons**
1. Highere chances of hypotenisve episodes	1. Risk of airway compromise
2. Higher chances of postoperative nausea and vomiting	2. Risks of image distortation and procedure failure (patient's movement related)
3. Potential for the time delay for starting the procedure	3. Risks of aerosol contamination if converted to GA or during coughing
4. Risks of extubation induced aerosol contaimination	4. Risks to team
5. Increase wait time after the extubation (if in neuroangio suite)	

DISCUSSION

There are minimal data on the outcome differences in patients with COVID-19. One of the main challenges with EVT during

Abbreviations: GA, general anesthesia; COVID 19, corona virus disease 2019; CS, conscious sedation; OR, odds ratio; CI, confidence interval; AIS, acute ischemic stroke; RCT, randomized control trial; EVT, endovascular thrombectomy; PPE, personnel protective equipment; PAPRS, powered air purifier respirators; N95—This is a Respirator Rating Letter Class.It stands for "Non-Oil" meaning that no oil-based particulates are present.

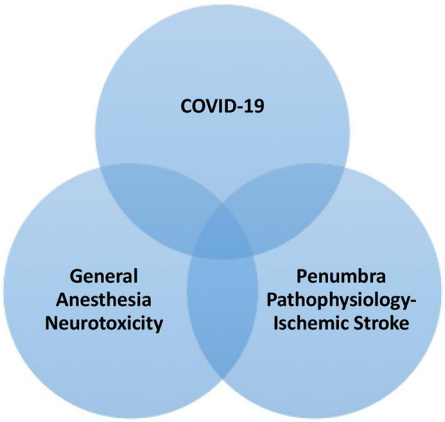

FIGURE 1 | The influence of COVID 19 on ischemic stroke during general anesthesia.

the pandemic was the risk associated with aerosol-generating medical procedures, such as airway management. Though avoiding GA may seem to be the choice in minimizing the risk of exposure, emergency airway management as a result of periprocedural complications increases the risk of exposure. The pathophysiology of stroke during anesthesia is not yet fully understood. However, they are cellular and molecular factors mediating GA-induced neurotoxicity and might be more prone during COVID-19 infection linked to reactive oxygen species (ROS) formation, mitochondrial permeability transition pore (mPTP) activation, increased Ca^{2+} influence, and increased tumor necrosis factor (TNF) and IL-1beta production (**Figure 1**).

Due to the increased chances of infectivity, and in order to minimize exposure and reduce the delay, it is recommended that patients presenting with a stroke during a pandemic should be directly referred to a tertiary care facility where EVT can be performed under MAC or GA in a negative pressure suite with ample availability of personnel protective equipment (PPE) kits without delay. Imaging and patient transport time should be kept to a bare minimum (14, 15).

Whether or not chest CT should be performed along with head CT in COVID-infected patients remains questionable. Li et al., in a recent study, revealed that 49 out of 51 COVID-infected patient's revealed COVID-19 findings on chest CT. The hallmark features were reported as ground glass opacities and consolidation with or without vascular enlargement, interlobular septal thickening, and air bronchogram signs. The chance of a missed diagnosis of COVID-19 in this study was found to be very low (3.9%) (16). The other argument can be made that, in such a subgroup of patients, performing chest CT for grading the severity of lung involvement can be helpful in the decision-making for choosing the type of anesthesia (GA *vs*. CS) for such procedures (16).

Hypoxia, which is common in patients with stroke, may have significant adverse effects on an already ischemic brain, especially after stroke. An ischemic brain does not compensate in cerebral circulation especially during hypoxia like a normal healthy brain does (17). The role of oxygen therapy in ischemic stroke remains controversial because of the failure of clinical trials to demonstrate its efficacy due to the oxygen-induced free radical injury. The role of therapeutic oxygen in stroke remains uncertain due to the lack of evidence regarding its benefits. Roffe et al., in a large single-blind randomized clinical trial of 8,003 adults from 136 participating centers in the United Kingdom, concluded that, among non-hypoxic patients with acute stroke, the prophylactic use of low-dose oxygen supplementation did not reduce death or disability at 3 months (17).

With regard to oxygen saturation in COVID-19 patients, Shenoy et al., in a recent meta-analysis, concluded that the revaluation of target oxygen saturation in COVID-19 patients is essential, both in the inpatient and outpatient settings. While conducting randomized control trials in the inpatient settings, a target SpO_2 >96% (upper target PaO_2 limit of 105 mm) *vs*. a target SpO_2 of 92–95% would be complex in terms of logistics. In reality, an SpO_2 in the upper end of 92–96% in both inpatients and outpatients with COVID-19 would be ideal (18).

Patients with signs and symptoms or with known exposure to COVID-19 should be meticulously assessed by an experienced airway specialist. The decision to intubate for an EVT must be justified to a patient's need for airway protection, the risk of exposure to the airway provider and the risk to other care providers, and the potential success of the EVT. If the patient requires an advanced airway post-EVT before leaving the interventional radiology (IR) suite, the endotracheal tube (ET) should be clamped before transferring onto an exhaust filtered transport ventilator or manual ventilation with two viral filters. Once admitted in the intensive care unit (ICU), as deemed essential, the patient should be extubated in a negative pressure environment with the airway providers sporting adequate PPE (19).

In a recent cross-sectional survey, Chowdhury et al. sent a questionnaire to 259 tertiary care stroke centers with neurointerventional facilities worldwide. They found that the number of stroke patients and EVT cases were reported to have decreased during the pandemic (19). Most participants reported conducting COVID-19 testing before (49%) or after (31%) the procedure; surprisingly, 20% of the centers did not test at all. Only 16% of the participating centers reported using a negative pressure room for the EVT (18). Strikingly, 50% of the participating centers reported no changes in the anesthetic management of AIS patients undergoing EVT during the pandemic (19). Most centers (71%) apparently reported that intubation of patients requiring GA for EVT during the pandemic was performed in the neurointerventional suite, followed by the emergency room (12%), a dedicated induction room outside the neurointerventional suite (11%), or in the ICU (6%) (20).

There are no current studies comparing the efficacy of GA vs. CS for mechanical thrombectomy in patients with diagnosed COVID-19. However, Sharma et al. published a consensus statement on behalf of the Society for Neuroscience in Anesthesiology and Critical Care (SNACC), and they recommended that, irrespective of the choice of anesthetic technique, airborne precautions have to be cautiously followed

for all patients (16). Diagnostic testing to rule out COVID-19 should be carried out, when deemed feasible, without a delay in EVT (16). The use of PPE, which includes N95 masks and powered air-purifying respirators (PAPRS), would be mandatory when performing airway manipulative procedures in patients with a known or suspected COVID-19 (16). They also recommended that the choice of anesthetic technique for EVT should be cautiously individualized for each patient, taking the patient's overall neurological and general status into account (16). In centers practicing CS for EVT, the threshold for the use of GA for EVT may be reduced during an active COVID-19 pandemic. Having stated this, not all patients presenting with a stroke would warrant a GA, as GA is associated with a risk of aerosol production. Airway interventions like intubation would require additional time taken to don and doff the PPE, and that might account for the delay in skin puncture time and revascularization (16). Sharma et al. also recommended that the most experienced anesthesiologist in the team should manage the airway. A closed-loop communication between the anesthesiologist and the interventional neuroradiologists with regard to the use of GA vs. MAC is of utmost importance. If the patient warrants a GA, then its induction should be carried out in an airborne isolation room equipped with negative pressure suites. The decision to proceed with induction and GA should be made early to avoid delays in puncture time and revascularization (15).

Smith et al. suggested that the decision to intubate a patient for EVT must be a delicate balance that would justify the patient's need for a definitive airway, the risks involved for the personnel, the ventilator capacity of the hospital system, and the success of the procedure, which would establish cerebral perfusion (19). They also recommended that the intubation should be carried out in a negative pressure induction room if the interventional radiology suite is not equipped with negative pressure air systems, backed by institutional protocols and the Centers for Disease Control and Prevention (CDC) guidelines (19). Once a definitive airway is established, they also recommended that the patient is transported to the IR suite with transport ventilators equipped with exhaust port filters, being cautious of circuit leaks and disconnections (19).

CONCLUSION

All in all, data supporting an association between COVID-19 and stroke in populations without typical vascular risk factors are increasing. It seems that these patients are older and COVID-19 might not influence stroke solely through a single mechanism that might have implications well-beyond the clinical condition of stroke or related interventions. For managing such patients, there are three critical points to be considered. Firstly, anesthetic management in such patients should be individualized. Secondly, the anesthetic technique that is standard practice at the institution should still be the first choice. Finally, for the safety of the team, proper simulation, standard donning and doffing of PPE, and effective communication should be employed. Ideally, larger prospective studies are necessary to discuss the anesthetic management challenges in these patients. An awareness and knowledge of the underlying factors of these issues are paramount for the entire stroke team, including anesthesiologists, caring for this growing patient population.

AUTHOR CONTRIBUTIONS

WR has contributed significantly in writing and preparing this manuscript. LV and BS have contributed in providing critical insight and writing and editing the manuscript. BS has also contributed in making table and figure. TC is the corresponding author and contributed significantly in designing, conceptualizing, writing, and editing and providing critical insight. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: TC serves as an Associate Editor for Frontiers in Medicine. TC and BS both have served as Guest Associate Editor for Autonomic Neuroscience, Frontiers in Neuroscience, Frontiers in Neurology, and Frontiers in Physiology.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW
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Mortality and Clinical Interventions in Critically ill Patient With Coronavirus Disease 2019: A Systematic Review and Meta-Analysis

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Objective: The aims of this systematic review and meta-analysis were to summarize the current existing evidence on the outcome of critically ill patients with COVID-19 as well as to evaluate the effectiveness of clinical interventions.

Data Sources: We searched MEDLINE, the Cochrane library, Web of Science, the China Biology Medicine disc, China National Knowledge Infrastructure, and Wanfang Data from their inception to May 15, 2021. The search strings consisted of various search terms related to the concepts of mortality of critically ill patients and clinical interventions.

Study Selection: After eliminating duplicates, two reviewers independently screened all titles and abstracts first, and then the full texts of potentially relevant articles were reviewed to identify cohort studies and case series that focus on the mortality of critically ill patients and clinical interventions.

Main Outcomes and Measures: The primary outcome was the mortality of critically ill patients with COVID-19. The secondary outcomes included all sorts of supportive care.

Results: There were 27 cohort studies and six case series involving 42,219 participants that met our inclusion criteria. All-cause mortality in the intensive care unit (ICU) was 35% and mortality in hospital was 32% in critically ill patients with COVID-19 for the year 2020, with very high between-study heterogeneity ($I^2 = 97\%$; $p < 0.01$). In a subgroup analysis, the mortality during ICU hospitalization in China was 39%, in Asia—except for China—it was 48%, in Europe it was 34%, in America it was 15%, and in the Middle East it was 39%. Non-surviving patients who had an older age [−8.10, 95% CI (−9.31 to −6.90)], a higher APACHE II score [−4.90, 95% CI (−6.54 to −3.27)], a higher SOFA score [−2.27, 95% CI (−2.95 to −1.59)], and a lower PaO_2/FiO_2 ratio [34.77, 95% CI (14.68 to 54.85)] than those who survived. Among clinical interventions, invasive mechanical ventilation

[risk ratio (RR) 0.49, 95% CI (0.39–0.61)], kidney replacement therapy [RR 0.34, 95% CI (0.26–0.43)], and vasopressor [RR 0.54, 95% CI (0.34–0.88)] were used more in surviving patients.

Conclusions: Mortality was high in critically ill patients with COVID-19 based on low-quality evidence and regional difference that existed. The early identification of critical characteristics and the use of support care help to indicate the outcome of critically ill patients.

Keywords: mortality, critically ill patients, COVID-19, clinical interventions, supportive care

INTRODUCTION

With the rapid spread of coronavirus disease 2019 (COVID-19) globally, as of June 2, 2021, a total of 171,222,477 confirmed cases had been reported in 215 countries, areas, or territories, and COVID-19 has been responsiblefor at least 3,686,142 deaths (1). Critically ill patients are always companied by a high risk of lives, which may be complicated by an uncontrolled systemic inflammatory response leading to acute respiratory distress syndrome (ARDS) and multiple organ dysfunction. Patients with ARDS and requirement for respiratory support need urgently to be transferred to the intensive care unit (ICU). It is reported that nasal cannula or mask, high-flow nasal cannula, non-invasive ventilation (NIV), invasive mechanical ventilation (IMV), and veno-venous extracorporeal membrane oxygenation (VV-ECMO) were widely used in COVID-19 according to the severity of respiratory dysfunction (2–4). Cardiac injury is common in COVID-19, with an incidence of 36% and closely related to a higher risk of mortality (5). It is reported that, in a systematic review and meta-analysis, the pooled incidence of acute kidney injury (AKI) was 28.6% among hospitalized COVID-19 patients from the USA and Europe and 5.5% among patients from China. Kidney replacement therapy (KRT) was used in 20.6% of patients admitted to the intensive care unit (6).

As is universally known, the mortality of critically ill patients is higher than that of ordinary patients. A systematic review reported that the summary estimate for all-cause mortality was 10% for adult patients with COVID-19 and 34% for critically ill patients within minor countries (7). In order to gain a clearer picture of the mortality of critically ill patients within major countries and clinical interventions or supportive care for organ dysfunction in the ICU, we meta-analyzed the relevant literature. The results may provide a narrative for the mortality of critically ill patients with COVID-19 as well as the effect of clinical characteristics and interventions between surviving and non-surviving patient groups.

METHODS

This systematic review was performed in compliance with the Centre of Reviews and Dissemination guidelines (8) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (9). In order to complete the systematic review and provide some references for clinical intervention during COVID-19 as soon as possible, this review was not registered.

Eligibility Criteria

We included studies that focused on the mortality of critically ill patients with laboratory-confirmed COVID-19, clinical characteristics, and interventions or supportive care of organ dysfunction.

We included original studies that fulfill the following criteria: (1) the type of study was cohort, case–control, or case–series designs, (2) the study topic was related to the mortality, clinical characteristics, and interventions or supportive care of critically ill patients with COVID-19, which is defined as a positive result of a real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs (10), and (3) the study was published or posted in English or Chinese. We excluded duplicates, conference abstracts, letters, and studies for which we could not access the full text and missing data of outcomes. In order to avoid a small size, only studies of more than 50 patients were included. If there were two or more studies that included the same population, only the study with the largest sample size was chosen.

In this review, the primary outcome was the mortality of critically ill patients with COVID-19. The secondary outcomes included all sorts of supportive care, including non-invasive respiratory support, IMV, KRT, and vasopressor. Critically or severely ill patients were defined as those patients who were admitted to the ICU or required respiratory support. Surviving patients were defined as those discharged from the ICU or hospital or who remained hospitalized. Non-surviving patients were defined as those who died in the ICU or hospital. Immunoregulation therapy includes corticosteroids, interferon, and intravenous immunoglobulin G.

Search of Studies

Two reviewers (ZQ and SL) carried out the search independently in the following six electronic databases from their inception to May 15, 2021: MEDLINE (*via* PubMed), the Cochrane library, Web of Science, China Biology Medicine disc, China National Knowledge Infrastructure, and Wanfang Data. The main terms were "mortality," "critically ill patient," "severely ill patient," "novel coronavirus," "2019-novel coronavirus," "Novel CoV," "SARS-CoV-2," "COVID-19," "2019-CoV," "invasive mechanical ventilation," "high flow nasal cannula," "non-invasive ventilation," "extracorporeal membrane oxygenation,"

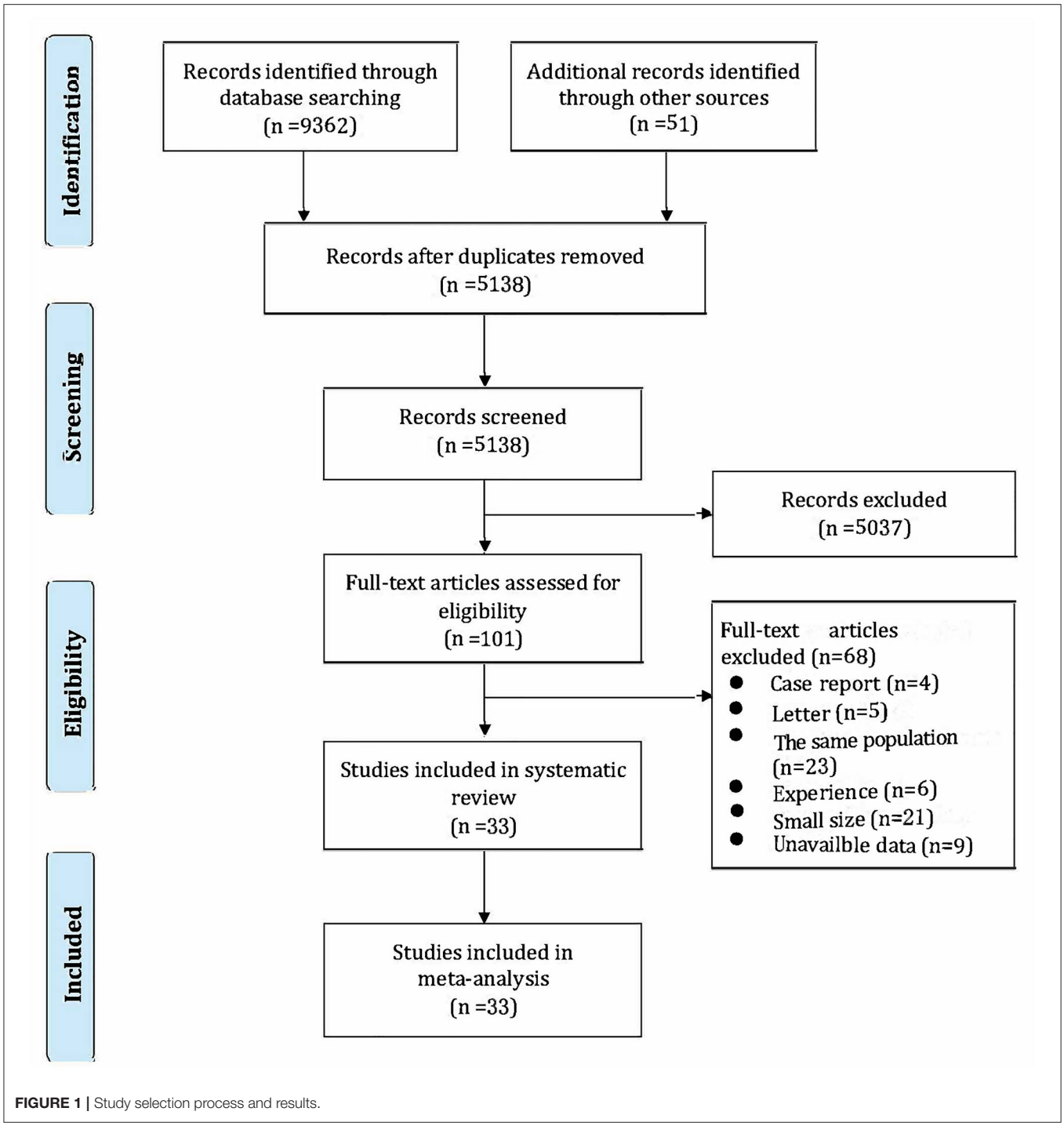

FIGURE 1 | Study selection process and results.

"renal replacement therapy," "kidney replacement therapy," "vasopressor," and so on (the details of the search strategy can be found in **Supplementary File 1**). Moreover, we also searched the clinical trial registry platforms, the Google Scholar, the reference lists of the identified reviews, and the preprint platforms [including SSRN (https://www.ssrn.com/index.cfm/en/), medRxiv (https://www.medrxiv.org/), and bioRxiv (https://www.biorxiv.org/)] for further potential studies.

Selection of Studies

After eliminating duplicates by using EndNote X9.3.2 software, two reviewers independently screened all titles and abstracts first, and then the full texts of potentially relevant articles were

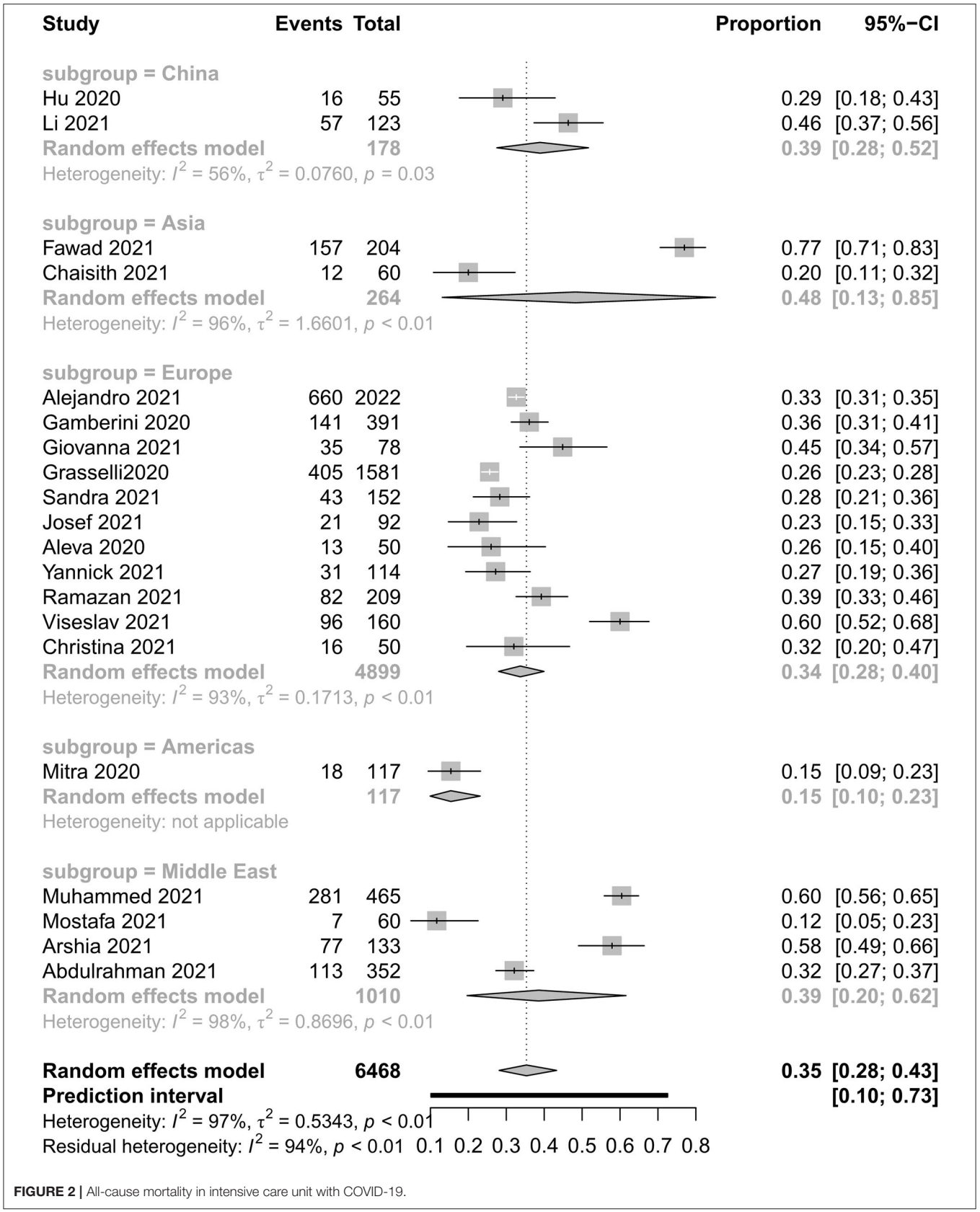

FIGURE 2 | All-cause mortality in intensive care unit with COVID-19.

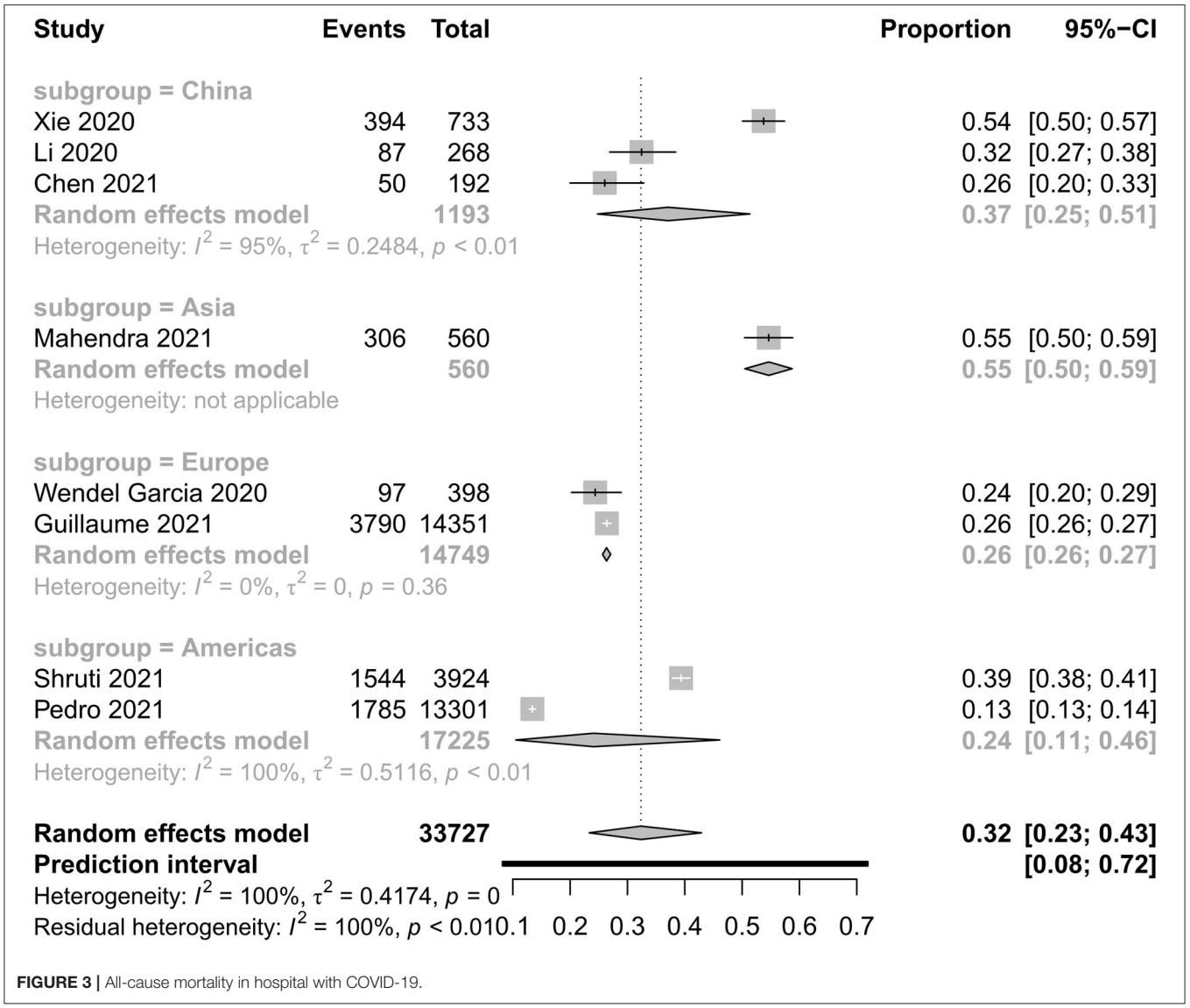

FIGURE 3 | All-cause mortality in hospital with COVID-19.

reviewed to identify the final inclusion. Discrepancies were settled by discussion or consultation with a third reviewer. All reasons for exclusion of ineligible studies were recorded, and the process of study selection was documented using a PRISMA flow diagram (11).

Data Extraction

Two reviewers (ZQ and SL) extracted data independently with a standard data collection form. Any disagreements were resolved by consensus, and a third reviewer (XL) checked the consistency and accuracy of all data. The following data and information were extracted for each included study: basic information (title, first author, publication year, funding, and study design), information on the participants (sample size, age, and inclusion/exclusion criteria of participants), details of the intervention and control conditions, outcome information [for dichotomous data, we abstracted the number of events and total participants per group; for continuous data, we abstracted the means, standard deviations (SD), and number of total participants per group].

Risk of Bias in Individual Studies

Two reviewers (ZQ and SL) assessed the potential risk of bias of each included study independently. Discrepancies were resolved by discussion and consensus with a third researcher (XL). We assessed the risk of bias in cohort studies using Newcastle–Ottawa Scale (12), which contains eight domains: representativeness of exposure cohorts, selection of non-exposure cohorts, determination of exposure, outcome events that did not occur before study initiation, comparability of cohort based on design or analysis, assessment of outcome events, adequacy of follow-up time, and completeness of follow-up. For case series, we used the Joanna Briggs Institute critical appraisal checklist for case series (13), which consists of 10 domains. Each domain was graded as one sore if reported.

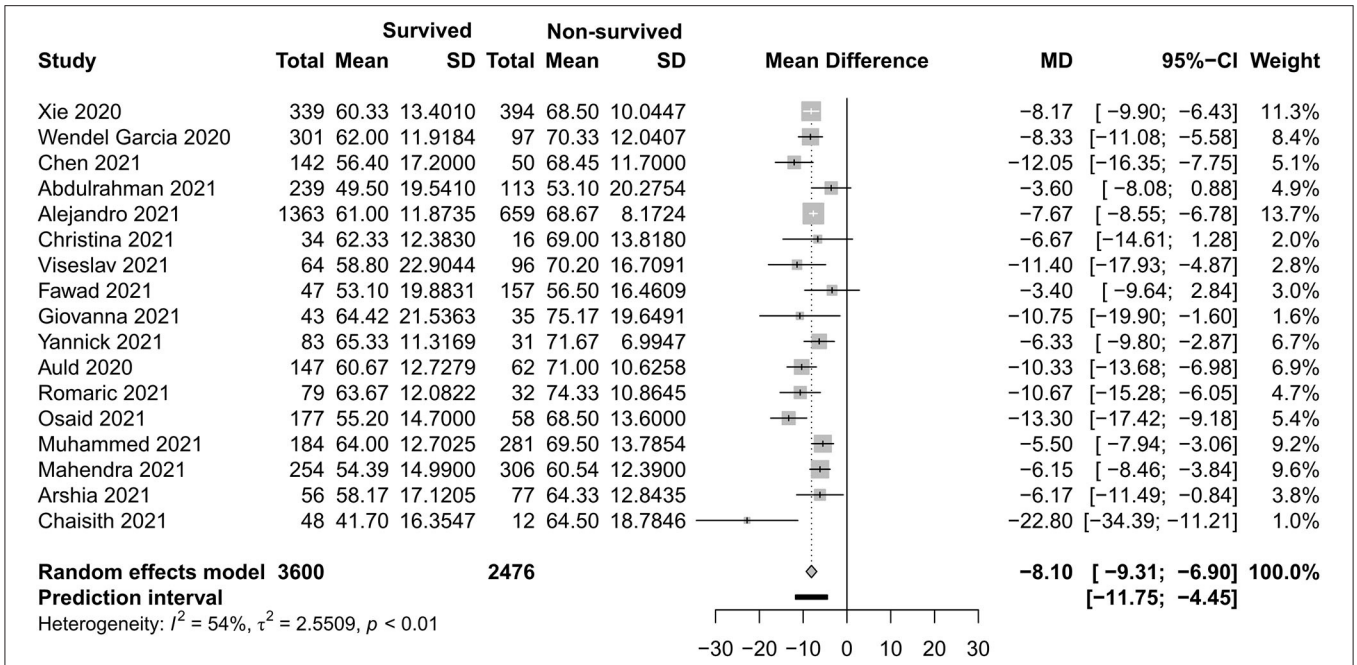

FIGURE 4 | Mean difference of age between survived and non-survived patients.

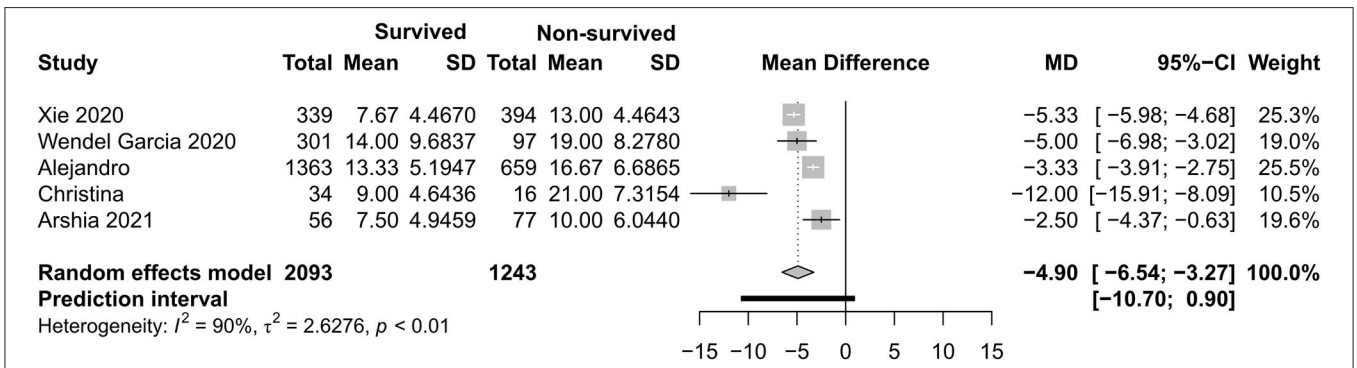

FIGURE 5 | Mean difference of Acute Physiological and Chronic Health Evaluation II score between survived and non-survived patients.

Statistical Analysis

All statistical analyses were performed using RStudio, version 1.3.1056. Comparable data from studies with one outcome were pooled using forest plots according to the Cochrane Handbook by using random-effects model separately (14). Mortality in the ICU and in hospital was used for a detailed description. A subgroup analysis was performed according to different regions. For dichotomous outcomes, we calculated the risk ratios (RR) and the corresponding 95% confidence intervals (CI) and *P*-values. For continuous outcomes, we calculated the standardized mean difference and its corresponding 95% CI if means and SD were reported. Furthermore, 95% prediction interval (PI) was used to evaluate the range that, we assert with 95% certainty, will fall into during a future validation test. We reported the effect size with 95% CI by using random-effects models. Two-sided $P < 0.05$ were considered statistically significant. Heterogeneity was defined as $P < 0.10$ and $I^2 > 50\%$.When effect sizes could not be pooled due to only one study for a comparison, we reported the study findings narratively. We used sensitivity analyses to evaluate the stability of mortality outcomes of the included studies. For a result that included more than 10 studies, publication bias was tested by visual funnel plots.

Quality of the Evidence

The quality of evidence for each outcome was assessed by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The

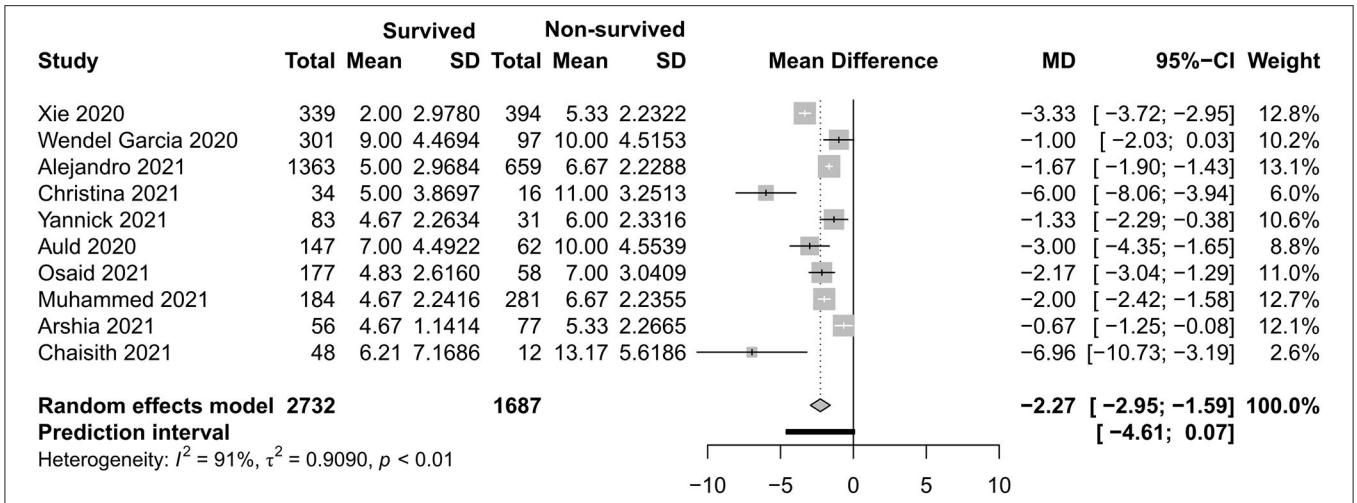

FIGURE 6 | Mean difference of Sequential Organ Failure Assessment score between survived and non-survived patients.

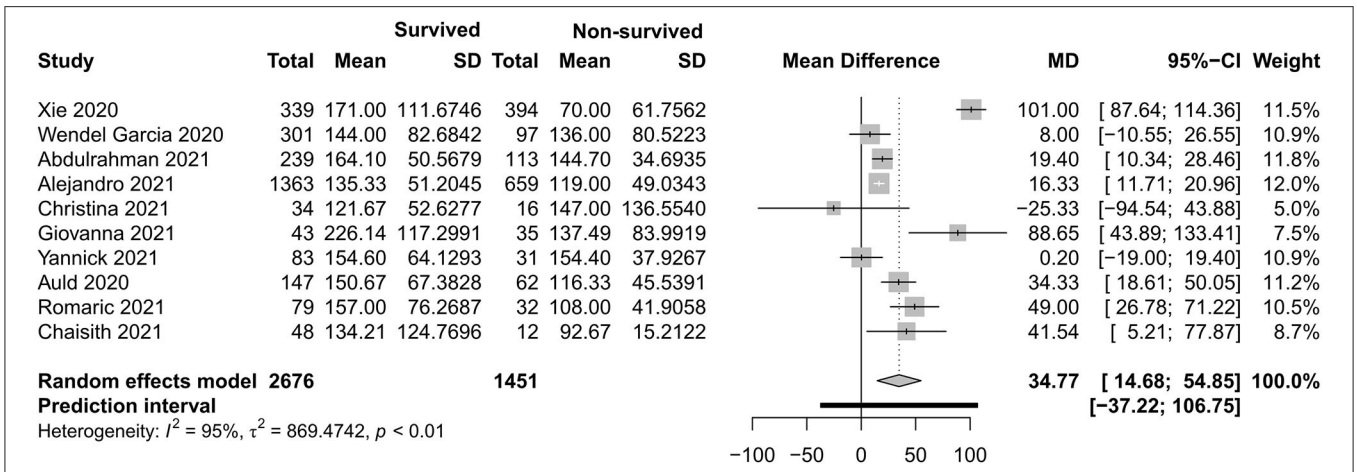

FIGURE 7 | Mean difference of the PaO_2/FiO_2 ratio between survived and non-survived patients.

judgments of quality for specific outcomes were based on five main factors: study design and execution limitations, inconsistency, indirectness, imprecision of results (random-effects model), and publication bias across all studies (15, 16). The quality of evidence for each outcome was graded as high, moderate, low, or very low (17) and presented in "GRADE Evidence Profiles" (18).

RESULTS

Search Results

The literature search retrieved 9,362 records through database searching and 51 additional records through other sources, which included 36 from the Google Scholar and 15 from preprint platforms. After removing duplicates, we screened the titles and abstracts of 5,138 records and reviewed the full text of 101 articles. Finally, we included 33 studies (cohort studies and case–series) (19–51) that reported either the mortality of critically ill patients or the clinical interventions between surviving and non-surviving patients with COVID-19 (**Figure 1**). All of them were published in English.

The Characteristics of the Included Studies

The basic characteristics of the included studies of the mortality of critically ill patients are summarized in **Table 1** (**Supplementary File 2**). These 28 studies involving 40,195 participants were admitted between January 1 and December 30, 2020, which covered Asia, Europe, and America. Of the 28 studies, 19 were single-center studies and nine were multi-center studies in design. Mortality was demonstrated and concluded with a follow-up of more than 7 days and expressed as mortality in the ICU or in hospital. Among 33 studies, 17 studies (22, 25, 50, 51) with 6,414 participants compared clinical interventions between surviving and non-surviving patients. All studies assessed the risk of bias with scores of 3–9, indicating low to high quality (**Supplementary File 3**). A visual analysis of the

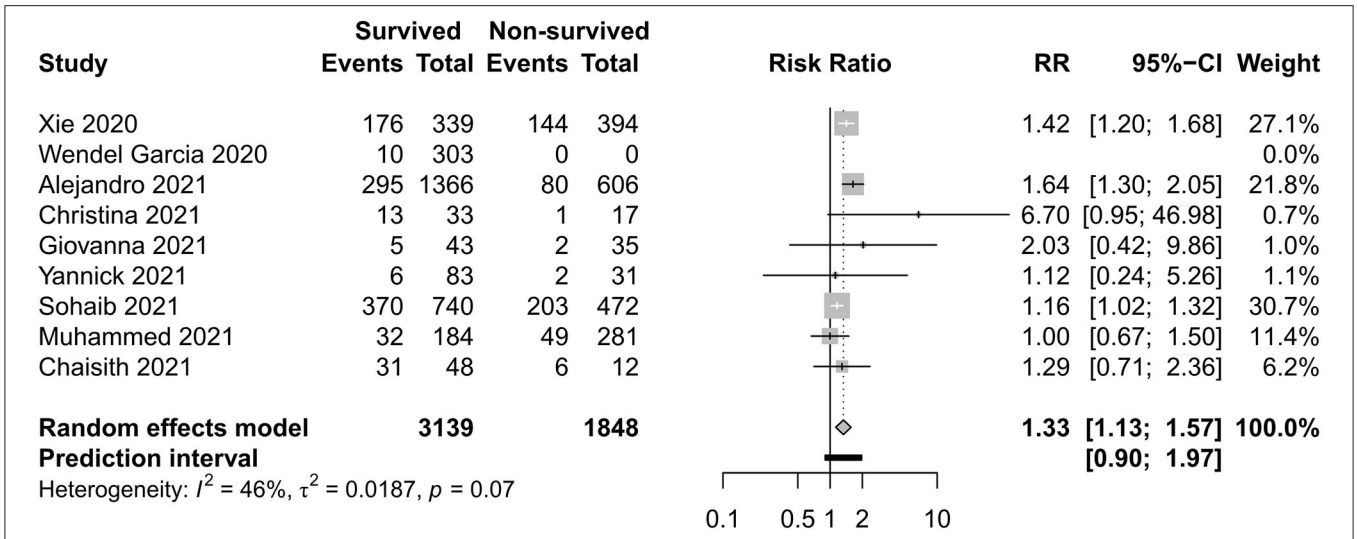

FIGURE 8 | Risk ratio of high-flow nasal oxygenation between survived and non-survived patients.

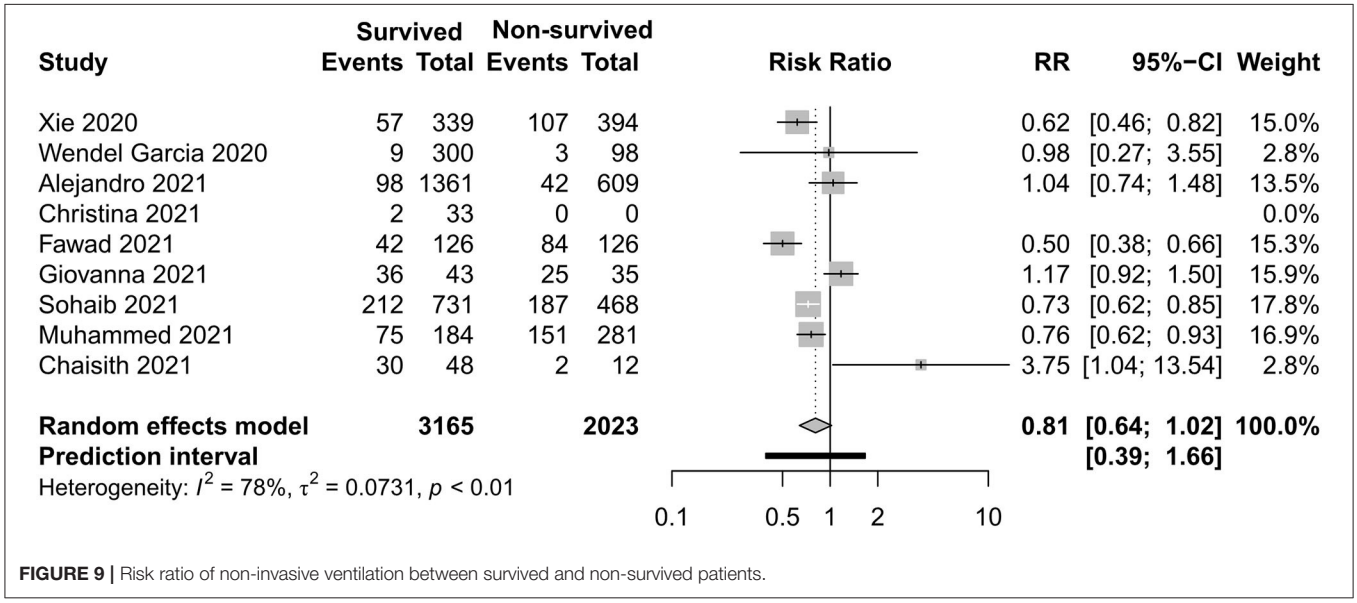

FIGURE 9 | Risk ratio of non-invasive ventilation between survived and non-survived patients.

funnel plot indicated that no publication bias was suspected in the results of age and mortality in the ICU. The results of IMV, PaO_2/FiO_2 ratio, and SOFA source were suggestive of publication bias (**Supplementary File 4**).

Clinical Outcome of Critically Ill Patients

Figures 2, **3** show all-cause mortality in the ICU and in hospital as per peer-reviewed studies from countries around the world. In the present study, all-cause mortality in the ICU was 35% in critically ill patients (95% PI, 10–73%) with very high between-study heterogeneity. In a subgroup analysis, the mortality in China was 39%, in Asia—except for China—it was 48%, in Europe it was 34%, in America it was 15%, and in the Middle East it was 39%. For mortality in hospital, all-cause mortality was 32% (95% PI, 8–72%) with very high between-study heterogeneity. In a subgroup analysis, the mortality in China was 37%, in Asia—except for China—it was 55%, in Europe it was 26%, and in America it was 24%.

Basic Clinical Characteristics Between Two Different Outcome Groups

Figures 4–**7** show the basic clinical characteristics including age, acute physiological and chronic health evaluation II (APACHE II) score, sequential organ failure assessment (SOFA) score, and PaO_2/FiO_2 ratio between surviving and non-surviving patients. Patients who did not survive had an older age [−8.10, 95% CI (−9.31 to −6.90)], a higher APACHE II score [−4.90, 95% CI (−6.54 to −3.27)], a higher SOFA score [−2.27, 95% CI (−2.95

TABLE 1 | Basic characteristics of included studies of mortality of critically ill patients.

Region	Nation	Study	No. patients	Study design	Single- or multi-center	Date	Follow-up	Outcome
Asia	China	Xie et al. (51)	733	Retrospective case series	Multi-center	Jan. 1 to Feb. 29	28-days	394 patients died
	China	Li et al. (38)	268	Retrospective, cohort study	Single-center	Jan. 26 to Feb. 5	32-days	87 patients died, 85 discharged from hospital
	China	Hu et al. (33)	55	Retrospective case series	Single-center	Jan. 8 to Mar. 12	28-days	16 patients died, 33 discharged home. Six transferred to isolation wards
	China	Chen et al. (24)	192	Retrospective case series	Single-center	Jan. 28 to Mar. 13	Until Mar. 13	50 died in the hospital and 142 were discharged
	China	Geng et al. (29)	123	Retrospective observational study	Single-center	Feb. 9 to Apr. 6	Until Apr. 6	57 died in ICU hospitalization and 66 were discharged
	Pakistan	Rahim et al. (44)	204	Cross-sectional study	Single-center	Apr. 1 to Aug. 31	Until Aug. 31	157 died in ICU hospitalization and 47 shifting from the ICU to a general isolation ward
	India	Mahendra et al. (39)	560	Retrospective observational study	Single-center	Jun. 1 to Oct. 30	30-days	306 died in hospital
	Thailand	Sivakorn et al. (52)	60	Prospective observational study	Single-center	Jan. 1 to 31	Until Jan. 31	12 died and 48 patients were alive at ICU discharge.
Middle East	Qatar	Najim et al. (41)	60	Prospective observational study	Single-center	Jun. 26 to Aug. 5	60-days or died or discharged from the ICU	Seven died
	Iran	Vahedi et al. (48)	133	Retrospective cohort study	Single-center	Feb. 1 to Jun. 30	Until Jun. 30	77 died in ICUs and other patients were recovered or discharged from ICUs.
	Saudi Arabia	Alharthy et al. (20)	352	Retrospective observational study	Single-center	Mar. 20 to May 31	28-days	113 died in ICU hospitalization
	Libya	Elhadi et al. (26)	465	Prospective cohort study	Multi-center	May 29 to Dec. 30	60-days	281 died in ICU and 184 discharged alive
Europe	Europe	Wendel Garcia et al. (50)	398	Prospective cohort study	Multi-center	Mar. 13 to Apr. 22	40-days	97 patients died and 301 discharged
	France	Fond et al. (27)	14,351	Retrospective cohort study	Multi-center	Feb. 1 to Jun. 9	until Jun. 9	3,790 died in hospital
	Spain	Rodríguez et al. (45)	2,022	Prospective observational	Multi-center	Feb. 22 to May 11	90-days	660 died in ICU and 1,362 discharged from ICU
	Italy	Gamberini et al. (28)	391	Retrospective observational study	Multi-center	Feb. 22 to May 4	Until May 15	141 died in ICU hospitalization, 39 still in ICU
	Italy	Carpagnano et al. (23)	78	Retrospective observational study	Single-center	Mar. 11.to Apr. 27	Until Apr. 27	35 patients died during hospitalization, 43 discharge from the ICU

(Continued)

TABLE 1 | Continued

Region	Nation	Study	No. patients	Study design	Single- or multi-center	Date	Follow-up	Outcome
	Italy	Grasselli et al. (30)	1,581	Retrospective case series	Multi-center	Feb. 20 to Mar. 18	7-days	405 patients died, 920 still in the ICU, 256 discharged
	Sweden	Jonmarker et al. (35)	152	Retrospective observational study	Single-center	Mar. 1 to Apr. 31	28-days	43 died in ICU
	Sweden	Järhult et al. (34)	92	Prospective observational	Single-center	Mar. 1 to Jun. 30	30-days	21 died in ICU
	Netherland	Aleva et al. (19)	50	Retrospective case series	Single-center	Mar. 9 to Apr. 7	86-days	13 patients died, 37 survived and discharged from ICU
	Netherland	Vogels et al. (49)	114	Retrospective observational study	Single-center	Mar. 1 to Jun. 4	28-days	31 died in ICU hospitalization
	Turkey	Gunduz et al. (31)	209	Retrospective observational study	Single-center	Mar. 24 to Jul. 6	Until their outcomes	82 died in ICU hospitalization
	Serbia	Popadic et al. (43)	160	Retrospective observational study	Single-center	Jun. 23 to Oct. 2	Until their outcomes	96 died in ICU hospitalization, 64 lived
	Greece	Routsi et al. (47)	50	Prospective observational study	Single-center	Mar. 11 to Apr. 27	Until Apr. 27	16 patients died, one still in the ICU, 33 discharged
America	US	Gupta et al. (32)	3,924	Retrospective cohort study	Multi-center	Mar. 4 to May 10	30-days	1,544 patients died, 2,058 discharged alive, 322 remained hospitalized.
	Canada	Mitra et al. (40)	117	Retrospective case series	Multi-center	Feb. 21 to Apr. 14	21-days	18 patients died, 12 remained in ICU, 16 discharged from ICU but remained in hospital, and 71 discharged home.
	Brazil	Kurtz et al. (36)	13,301	Retrospective cohort study	Multi-center	Feb. 27 to Oct. 28	60-days	1,785 patients died during hospitalization, 82 remained hospitalized

to −1.59)], and a lower PaO_2/FiO_2 ratio [34.77, 95% CI (14.68 to 54.85)] than those who survived.

Respiratory Support Care

Figures 8–**11** display different ways of respiratory support care during ICU hospitalization between surviving and non-surviving patients. High-flow nasal oxygenation (HFNO) was more commonly used in non-surviving patients [with RR 1.33, 95% CI (1.13–1.57)], and IMV was more commonly used in surviving patients [with RR 0.49, 95% CI (0.39–0.61)]. There was no statistically significant difference in NIV [RR 0.81, 95% CI (0.64–1.02)] and ECMO [RR 0.78, 95% CI (0.49–1.22)] between the two groups.

Renal and Cardiac Support Care

Figures 12, **13** exhibit the surviving patients who received more KRT [RR 0.34, 95% CI (0.26–0.43)] and vasopressor [RR 0.54, 95% CI (0.34–0.88)].

Quality of Evidence

We evaluated the quality of evidence for 11 outcomes. Among them, two outcomes (18%) were graded as of moderate quality, four outcomes (36%) were graded as of low quality, and five (45%) outcomes were graded as of very low quality. We produced "GRADE evidence profiles," and the details of GRADE can be found in **Supplementary File 5**.

Sensitivity Analysis

We conducted a sensitivity analysis on each result by omitting one study at a time. No study had a significant impact on the results of the meta-analysis (**Supplementary File 6**). A sensitivity analysis showed that all studies had little or acceptable effect on the total combined effect and that the results were stable.

DISCUSSION

The epidemic of COVID-19 is not stopping yet, especially in western countries. In previous reports, the incidence of

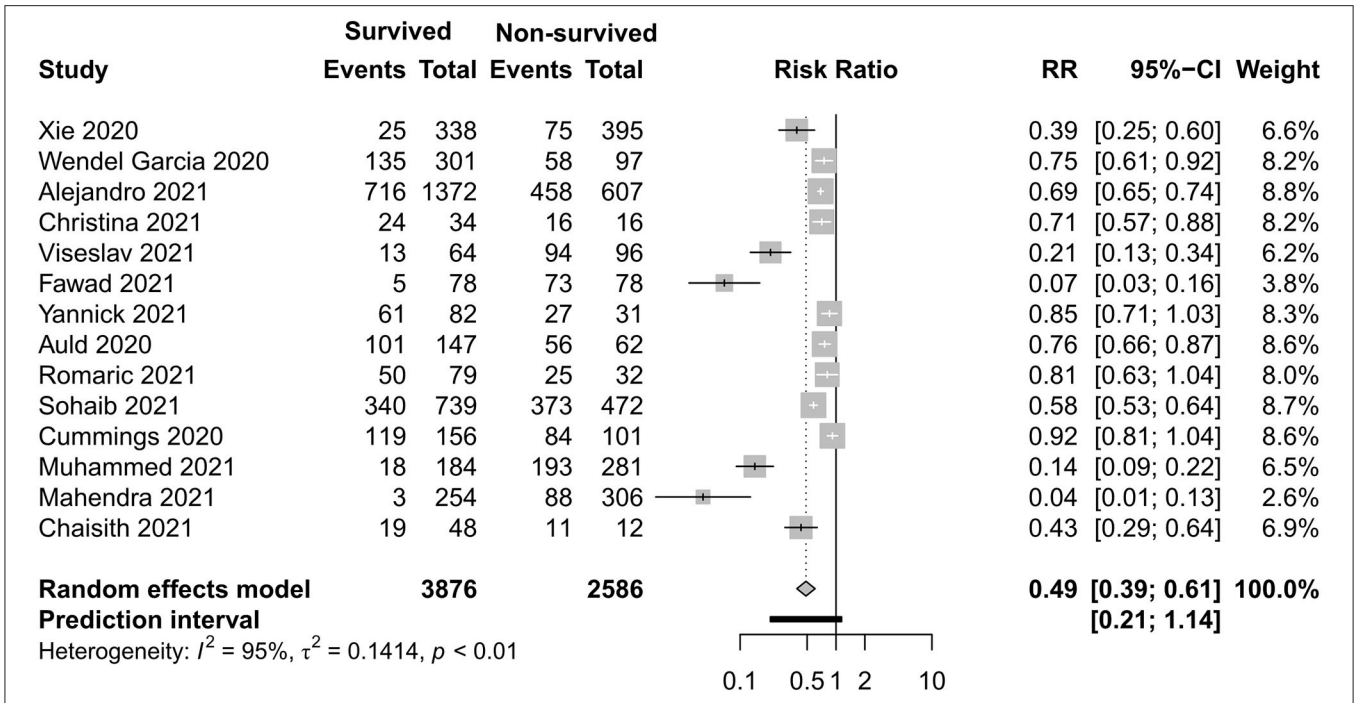

FIGURE 10 | Risk ratio of invasive mechanical ventilation between survived and non-survived patients.

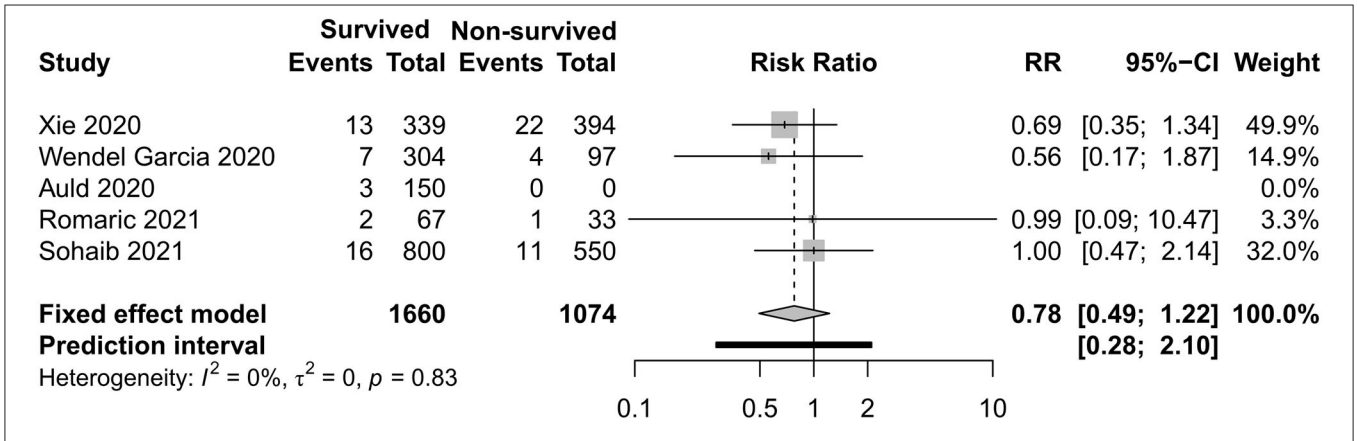

FIGURE 11 | Risk ratio of extracorporeal membrane oxygenation between survived and non-survived patients.

mortality associated with critically ill patients remains poorly characterized. The novel findings in this study include the mortality of critically ill patients with laboratory-confirmed COVID-19 worldwide and the clinical interventions between surviving and non-surviving patients. The results show that all-cause mortality in ICU was 35% and mortality in hospital was 32% around the world for the year 2020. Differences were distinct between regions. The incidence of mortality that occurred in Southeast Asia was as high as 48%, followed by 39% in China and the Middle East. The lowest incidence occurred in America, which is 15%. The plausible explanations for the high mortality in China and other Asia countries are that the arrival and peak of the COVID-19 pandemic in Asia were earlier than in any region, and there was a shortage of ICU resources and experience. Moreover, data may be subject to patient selection for ICU admission, and some nations adopted a stringent strategy (19). In addition, mortality also relates to the time of follow-up. Some of the participants remained in the hospital in mechanical ventilation even at the end of follow-up. A recent meta-analysis reported that all-cause mortality associated with COVID-19 was 10% overall and 34% in patients admitted to the ICU (7), but most of their participants were from China; in this part, we had a close result. This new meta-analysis included more participants and covered much wider regions.

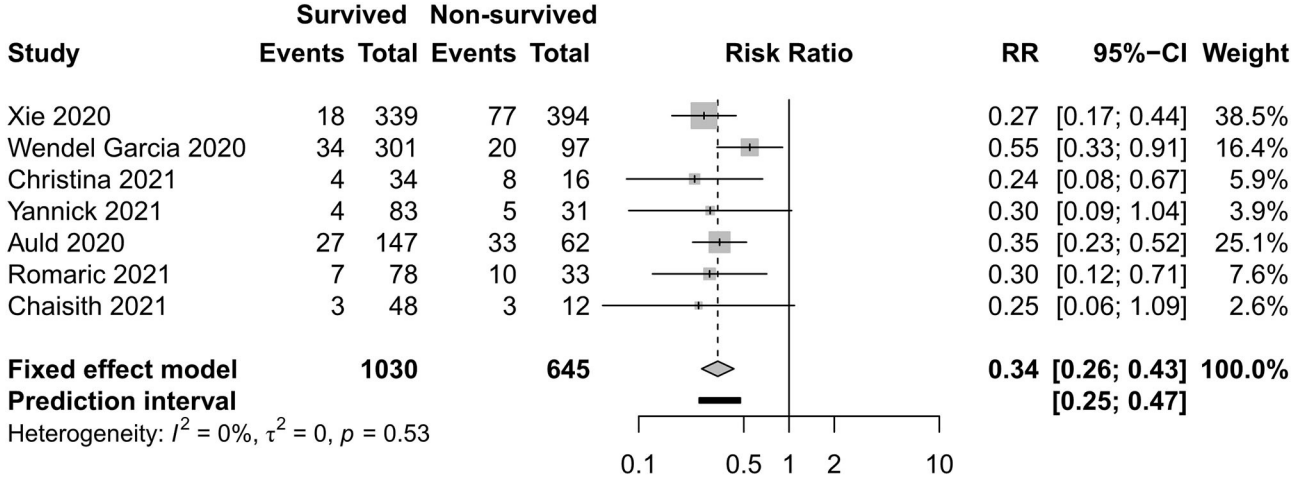

FIGURE 12 | Risk ratio of kidney replacement therapy between survived and non-survived patients.

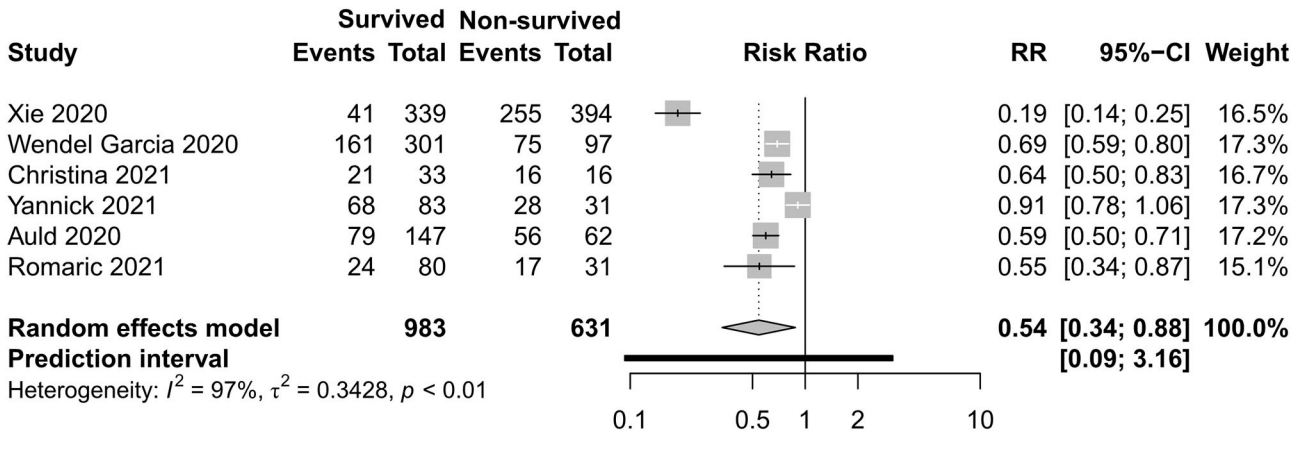

FIGURE 13 | Risk ratio of vasopressors between survived and non-survived patients.

Early identification and prompt organ function support care would provide relief in critical cases (53). Among the included studies, five identified independent risk factors were associated with ICU mortality from laboratory parameters to clinical intervention, but the results are not the same (22, 25, 38, 50, 51, 54). We compared the baseline clinical characteristics between surviving and non-surviving patients. What we found based on the univariate analysis was that old age, APACHEII score, and SOFA score displayed consistency with multivariate Cox regression analysis in these five studies. Besides these, the PaO_2/FiO_2 ratio is an important index to reflect the severity of respiratory failure. Our results also showed that the PaO_2/FiO_2 ratio is helpful to predict the outcome.

With regard to the outcome of the clinical interventions of this meta-analysis, respiratory support is the most important part of life sustaining treatments. According to this study, HFNO during ICU hospitalization was more often used in non-surviving patients, and IMV was more often used in surviving patients. In previous studies, Auld and Capone (22, 54) reported that receipt of IMV was associated with a decreased likelihood of survival. When we discuss the difference of respiratory support, respiratory support as rescue therapy and the different severity levels of the two groups should not be ignored. HFNO and NIV can be safely used in COVID-19-related mild–moderate ARDS. In the study of non-COVID-19, HFNO has been associated with lower mortality in hypoxemic respiratory failure (55), but in some moderate–severe ARDS patients, HFNO or NIV should be used cautiously due to rapid progression to severe type and a high risk of treatment failure. According to Mukhtar et al. (56), the use of NIV with a predefined algorithm in subjects with moderate–severe COVID-19 ARDS was successful in 77% of the subjects. IMV is the most widely used therapy of severe hypoxemia. The population with IMV was larger than with non-invasive support in this study. The need of endotracheal intubation and invasive mechanical ventilation was eight times that of non-invasive ventilation in a previous study (30). Although the timing

of IMV is disputed, as evidenced in a recent publication, a meta-analysis reported that early intubation was not associated with improved survival (57). A latest meta-analysis (42) reported that the timing of intubation may have not influenced the mortality of critically ill patients with COVID-19. ECMO can be taken into consideration if the respiratory dysfunction of patients develop into severe ARDS, which cannot sustain with IMV, but this salvage treatment did not have a statistically significant difference between the two groups. In a study with a small sample (3), two of five patients survived by the support of ECMO. The appropriate time and eligible patients need to be evaluated.

In a previous research, as high as 31% of patients in a cohort developed severe acute kidney injury requiring renal replacement therapy during hospitalization (25). High creatinine level, AKI, and receipt of RRT were independent risk factors for the in-hospital mortality of patients (22, 51, 58). Similarly, high high-sensitivity cardiac troponin I level, ischemic heart disease, cardiac injury, and vasopressor support were associated with death in patients (22, 38, 50, 51, 54). In the present study, the result shows that vasopressors and RRT were more often used in the surviving group.

There were some limitations in the current study that must be acknowledged. First is the high level of heterogeneity in the study. Plausible explanations for the heterogeneous risks of mortality include differences in age, nation and race, disease severity, and insufficient length of follow-up. It was difficult for us to control for the effects of these confounding factors. The heterogeneity in the component studies was addressed with random-effects models. Second, as for the secondary outcomes, is that this part of the clinical interventions was derived from an observational cohort, not a randomized controlled trial, so these results should be treated cautiously. The key purpose of this study is to describe the effect of the actual use of various clinical interventions in the surviving group and non-surviving group rather than the impact of individual measures on the prognosis. Third is that most studies were retrospective and recall bias might have occurred.

CONCLUSIONS

Mortality was high in critically ill patients with COVID-19 based on low-quality evidence, and intercontinental differences existed. The early identification of critical characteristics and the use of support care help to indicate the outcome of critically ill patients.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/ **Supplementary Material**.

AUTHOR CONTRIBUTIONS

LL, YC, and ZQ: concept and design. LL: administrative, technical, or material support. ZQ and SL: statistical analysis and drafting of the manuscript. LL and YC: supervision. All authors critical revision of the manuscript for important intellectual content, acquisition, analysis, or interpretation of data.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.635560/full#supplementary-material

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ATENA–A Novel Rapidly Manufactured Medical Invasive Ventilator Designed as a Response to the COVID-19 Pandemic: Testing Protocol, Safety, and Performance Validation

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Background: The urgent need for mechanical ventilators to support respiratory insufficiency due to SARS-CoV-2 led to a worldwide effort to develop low-cost, easily assembled, and locally manufactured ventilators. The ATENA ventilator project was developed in a community-based approach targeting the development, prototyping, testing, and decentralized manufacturing of a new mechanical ventilator.

Objective: This article aims to demonstrate ATENA's adequate performance and safety for clinical use.

Material: ATENA is a low-cost ventilator that can be rapidly manufactured, easily assembled, and locally produced anywhere in the world. It was developed following the guidelines and requirements provided by European and International Regulatory Authorities (MHRA, ISO 86201) and National Authorities (INFARMED). The device was thoroughly tested using laboratory lung simulators and animal models.

Results: The device meets all the regulatory requirements for pandemic ventilators. Additionally, the pre-clinical experiences demonstrated security and adequate ventilation and oxygenation, *in vivo*.

Conclusion: The ATENA ventilator had a good performance in required tests in laboratory scenarios and pre-clinical studies. In a pandemic context, ATENA is perfectly suited for safely treating patients in need of mechanical ventilation.

Keywords: COVID-19, ATENA, pandemic, ventilator, safety, performance

INTRODUCTION

The global pandemic Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2 created an urgent need for mechanical ventilators around the world (1). Even though the majority of patients develop mild (40%) or moderate (40%) symptoms, ∼15% develop a severe condition that requires oxygen support and 5% end up with respiratory failure and need intensive care admission (2–4).

The exponential pattern of viral transmission led to a rapid and overwhelming increase in hospitalizations and overflow to intensive care units for invasive ventilation. At the beginning of 2020, the number of available ventilators was scarce and contributed to a significant increase in morbimortality worldwide (5–7). The fight against the global COVID-19 pandemic required innovative actions. Globally, thousands of experts, companies, and volunteers worked to fill the global shortage of commercial ventilators, by developing open-source ventilators or finding strategies (8–12) for shared ventilation (13, 14). Likewise, in Portugal, CEiiA—an Engineering and Product Development Centre—led (15) the development of the ATENA ventilator in a community-based approach.

ATENA is a rapidly manufactured, low-cost, easily assembled, and locally produced mechanical invasive ventilator. It was developed in a short time, from design to prototype. The requirements for the ATENA ventilator were common to other proposals (11, 16): (i) easily sourced components available to the general public; (ii) "open-source" compatibility, namely, availability of design and easiness to replicate; and (iii) high accuracy in a range of ventilation strategies that allow high airway pressures for ARDS patients.

This paper aims to demonstrate the performance and safety of ATENA as a pandemic ventilator adequate for COVID-19 patients, following the requirements of different regulatory agencies.

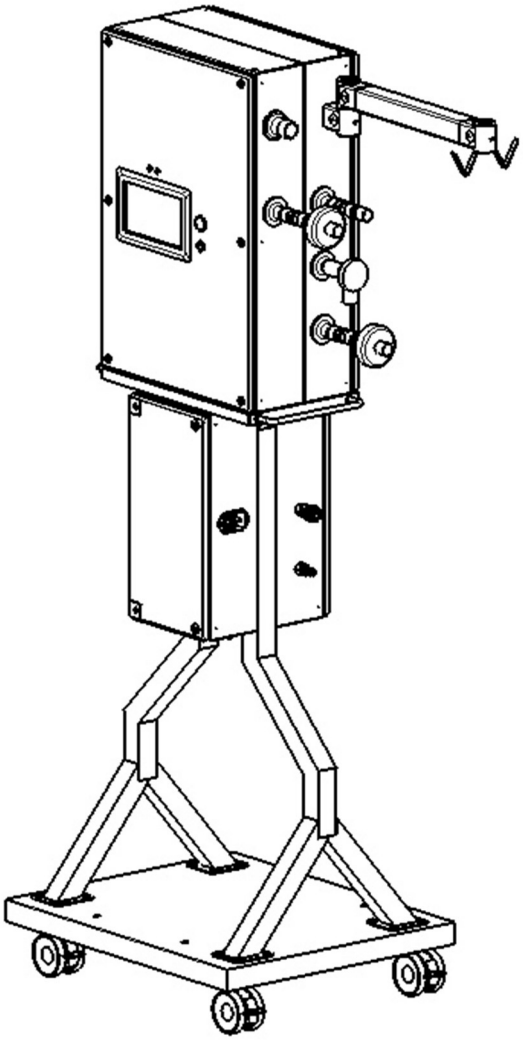

FIGURE 1 | Fully mature manufactured ATENA Ventilator unit.

MATERIALS AND METHODS

ATENA Design and Systems Breakdown

Overview

ATENA is a pneumatic ventilator, requiring high-pressure air and oxygen supplies to drive the respiratory cycles. Its control system hardware was locally designed, based on commercially available and inexpensive components. The software was developed in-house.

The main body is built using a stainless-steel wheeled structure and four sealed metal industrial boxes. These boxes are attached on each side of the structure (see **Figure 1**). They contain the pneumatic, electrical, and control modules. ATENA's overall specifications are described in **Table 1** (see also **Supplementary Table 1**).

The two upper boxes contain the respiratory circuit, with the required valves and sensors, and the control system. Gases in the respiratory circuit are at low pressure (<60 cmH_2O). One of the lower housing boxes handles the input of air and oxygen at high pressure (>3 bar). The other contains the power module, composed of a battery, transformers, and safety fuses and breakers.

A touch screen displays pressure, flow, and volume curves in addition to other important ventilation variables (see **Figures 3A,C**). Ventilation modes and parameters are configurable *via* the touch screen (**Figure 3B**). Operation is started/stopped by pressing a physical button on the front of the ventilator.

Alarms are signaled by sound, light, and a specific alarm text on the display (see the top bar in **Figure 3A**). Alarms need to be acknowledged and muted by pressing another physical button.

Operation

Ventilation mode and parameters are configured *via* the touch display. **Figure 3B** shows the VCV (volume-controlled ventilation) mode configuration screen. Other modes are visible as extra tabs. Once the operation mode is selected and configured,

TABLE 1 | ATENA's overall specifications and control ranges.

Physical characteristics	
Length	600 mm (23.6 in)
Width	500 mm (19.68 in)
Height	1,685 mm (66.3 in)
Weight	53.4 kg
Electrical specifications	
Input power	100–240 Vac (50–60 Hz) 30 W
Battery	Lead-acid battery Nominal voltage−12 V 7 Ah capacity
Usual charge/maintenance time	4 h/10 h
Battery autonomy	Up to 5 h
Sound Pressure Level	40 dB(A) ± 10 dB(A)
Pneumatic specifications	
Medicinal gases	Air and oxygen
Input pressure rated range	3 to 5 bar (300 to 500 kPa)
Maximum transient flow rate (3 s average)	120 L/min (Air: 60 L/min Air) (O2: 60 L/min O_2)
Maximum input flow rate (10 s average)	Air: 35 L/min @ 280 kPa O_2: 35 L/min @ 280 kPa
Control specifications	
Oxygen	21 to 100%
PEEP	0 to 40 cm H2O (0 to 39.2 hPa)
I:E	1:1–1: 4
Breathing rate (RR)	5 to 30 r/min
Peak Inspiratory Pressure (above PEEP)	0 to 40 cm H2O (0 to 39.2 hPa)
Tidal Volume	250–800 ml
Inspiration Pause Time (in% Ti)	0 to 50%
Assistance activation flow	0.2 to 3 L/min
FiO_2 21 to 90% response time	≤65 s
Equipment classification	
Protection class	Class I (Chassis earth connected)
Applied parts classification	Type B (Applied parts in contact with patient are not conductive)
Operation mode	Continuous
Mobility	Mobile Equipment (Can be wheeled but not during operation)
IP protection	IP22 The enclosure of the ventilator is protected against the ingress of solid objects bigger than 12, 5 mm and the ingress of liquids dripping when tilted at 15°.

ventilation can be started by pressing the START/STOP button next to the display.

Air and oxygen enter the system at a pressure of about 4.5 bar (air and O_2 inlets are indicated in **Figure 2**). To ensure adequate availability of oxygen for each inhalation, we installed a 0.75-L buffer tank after the oxygen inlet. Pressure is monitored *via* pressure sensors in each of the high-pressure circuits to detect any fault in the gas supply. Such faults trigger an alarm. These pressures can be checked on the ventilator display (**Figure 3C**).

Piezo-electric valves on the air and oxygen lines control the flow and oxygen content of the mixture delivered to the patient. The control system uses two flow sensors, one for each gas, for feedback control loops. An oxygen cell measuring the fraction of inspired oxygen (FiO_2) allows for mixture correction. Data from pressure sensors on both inspiratory and expiratory circuits are used to estimate the airway opening pressure. Depending on the mode of ventilation, the control system will deliver a constant flow, or variable flow, to reach a set pressure. All the aforementioned sensed variables are shown on the ventilator display (**Figures 3A,C**).

The gas mixture leaves the ventilator through a 22-mm tube outlet, compatible with standard medical tracheas, check valves, and filters. Additionally, two safety mechanisms prevent exposure to overpressure (manually adjustable pressure relief valve, maximum 60 cmH_2O) and suffocation (one-way under-pressure valve). The connection ports for the overpressure and anti-suffocation valves are also standard 22-mm tubes. Under normal operating conditions, the control system will prevent those conditions; the safety mechanisms are redundant systems.

To allow for both an unobstructed exhalation and fine control of flow during the PEEP phase, we selected a pneumatically controlled pinch valve. This valve has a large internal diameter, capable of large flows even in low-pressure conditions. During inhalation, the exhalation valve is closed. At the start of the exhalation, the valve fully opens until the pressure reaches the configured PEEP value. While keeping the PEEP, the exhalation valve is slightly open so that a small bias flow is present. This bias flow is useful for detecting an attempt by the patient to initiate a breath. A flow sensor in the exhalation circuit, in combination with both flow sensors in the inhalation circuit, lets us estimate the actual flow from/to the patient.

Spontaneous breaths are detected by both a variation in pressure and a flow toward the patient during the exhalation period. We found this combined approach to be more robust than a single breath variable measurement.

Requirements and Specifications

ATENA was developed following the clinical requirements for the "minimally acceptable" performance of a mechanical ventilator aimed at the COVID-19 pandemic crisis. Those requirements and specifications were described in the Rapid Manufactured Ventilator System (RMVS) document by the UK Medicines & Healthcare products Regulatory Agency (MHRA) (17) and in the exceptional authorization by the National Authority for Drugs and Healthcare Products (deliberation of 29 June 2020, INFARMED) (18).

The ATENA ventilator can operate in continuous mandatory ventilation (pressure-regulated volume control and pressure- and volume-controlled modes) and in pressure support mode. ATENA's overall specifications and control ranges are presented in **Table 1**.

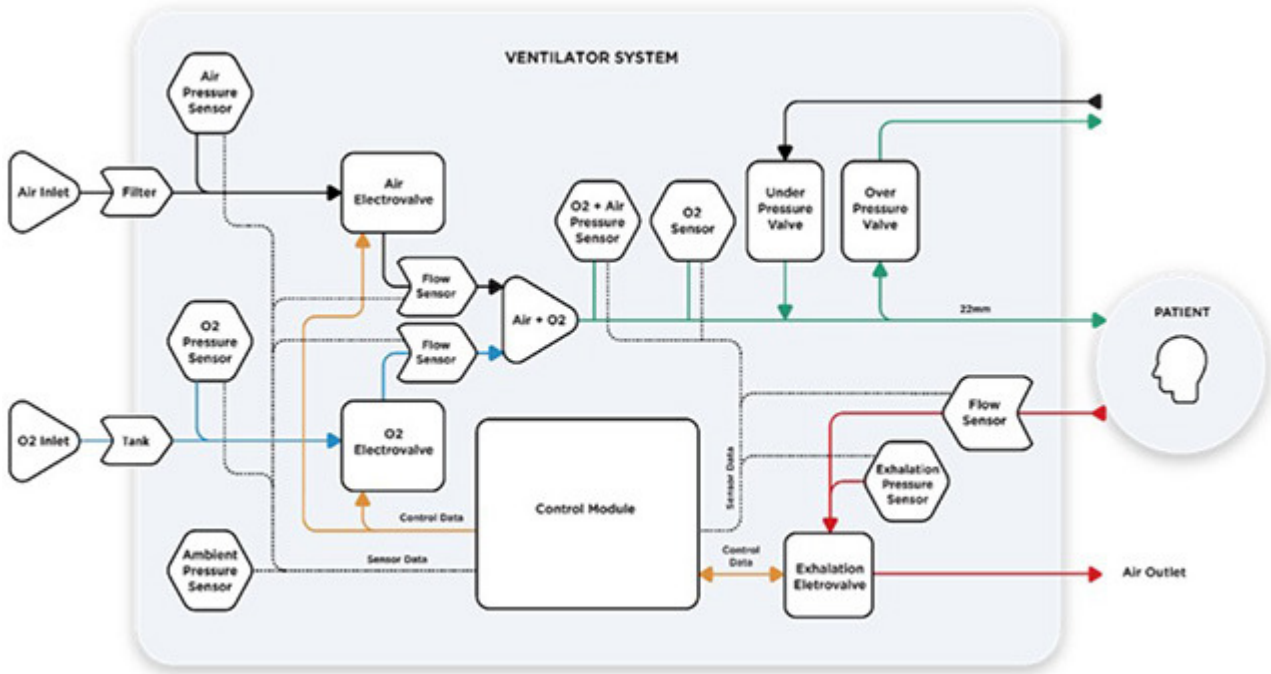

FIGURE 2 | ATENA High-Level Systems Architecture.

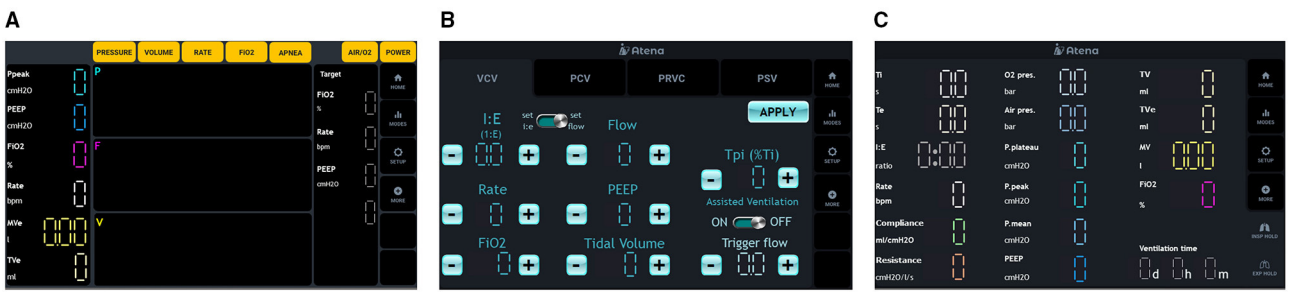

FIGURE 3 | ATENA Graphical User Interface. **(A)** Left panel, **(B)** central panel, and **(C)** right panel.

Testing Protocol

The main objective of the testing protocol was to demonstrate adequate safety and performance by the ATENA ventilator. We evaluated ATENA's accuracy and performance in five steps: (1) MHRA protocol, including endurance testing (17); (2) International Organization for Standardization (ISO 80601-2-12:2020) (19); (3) additional tests for extreme values of tidal volume, PEEP, and FiO_2; (4) pressure support ventilation; and (5) pre-clinical studies.

ATENA was attached *via* the breathing circuit to a calibrated electronic gas flow analyzer ventilator tester (VT900A, Fluke Biomedical) and then to an adult test lung (ACCU LUNG™ Precision test, Fluke Biomedical) that simulates different respiratory systems with variable compliance (C) and resistance (R). The ventilator was also linked to an external computer that allowed the recording of pressure, flow, FiO_2, and volume waveforms.

MHRA Protocol

The assessment of the performance of ATENA was done under controlled conditions following MHRA's RMVS protocol (17). We performed three sets of 36 trials for VC: (i) compliance, (ii) resistance, and (iii) tidal volume, and two sets of 36 trials for PC: (i) plateau pressure at 15 cmH_2O and (ii) 30 cmH_2O.

Concerning endurance testing, ATENA was connected to a passive lung simulator for 24 h. Ventilator settings at the beginning and the end of the test were reported, and the variation of the settings was analyzed.

Electromagnetic compatibility, electrical interference, emission, and immunity tests were made following European

and international standards (EN 60601-1-2, EN 61000-6-1, EN 61000-4-4, EN 61000-4-6, EN 55011, and ISO 80601-2-12).

International Organization for Standardization

Simultaneously, the ATENA ventilator was submitted to ISO requirements testing for basic safety and essential performance of critical care ventilators (ISO 80601-2-12:2020) (19). For volume-controlled ventilation, seven tests were done with variable compliance and resistance lung models, using different tidal volume, PEEP, and FiO_2. To evaluate the performance of pressure-controlled ventilation, seven tests were done also with different compliance and resistance levels, using different airway pressure, PEEP, and FiO_2. Additionally, one set of 14 tests was done to assess ATENA's accuracy in the measurement of tidal volume.

Additional Tests

Following recommendations from INFARMED (19), ATENA performed an additional set of tests with a simulated ARDS lung model (C = 20 ml/cmH_2O and R = 5 cmH_2O/L/s). This allowed us to evaluate the accuracy of the ventilator with an extreme variation of tidal volume (250–800 ml) in VCV and of PEEP (0–40 cmH_2O) in PCV modes. We ran an extra test with a healthy lung model, to analyze ATENA's accuracy on FiO_2 control (21–100%). Those tests were done without pausing the ventilator, to evaluate ATENA's response to a change in configuration parameters. The same breathing simulator and gas flow analyzer were used.

Pressure Support Ventilation

To evaluate the performance of the pressure support ventilation mode, we used an ASL5000 breathing simulator (version 3.6, Active Servo Lung, IngMar Medical, Pittsburgh, PA, USA) with an active lung model in both healthy and ARDS conditions. The settings used for each healthy (C = 50 ml/cmH_2O and R = 10 cmH_2O/L/s) and ARDS patient (C = 30 ml/cmH_2O and R = 20 cmH_2O/L/s) were available from the simulator's patient library and were validated in previous studies (11, 20–22).

ASL5000 tested ATENA's (i) capacity to detect apnea and switch to backup controlled mandatory ventilation (pressure-controlled ventilation) and (ii) performance on the pressure support mode with increasing inspiratory muscle strength. Given that the ATENA ventilator has an inspiratory trigger flow with a sensitivity that varies between 0.2 SLPM (high sensitivity) and 3 SLPM (low sensitivity), we decided to test three trigger points (0.2, 1, and 2 SLPM). For both healthy and ARDS lung models, the same spontaneous breathing parameters were used (respiratory rate: 3/15 cpm; uncompensated residual capacity: 0.5 L; pause: 0%; inspiratory muscle pressure: 0/10/15 cmH_2O; expiratory muscle pressure: 0 cmH_2O; inspiratory rise time: 10%; inspiratory hold: 5%; inspiratory release time: 10%; expiratory rise time: 0%; expiratory hold: 0%; expiratory release time: 0%; effort: sinusoidal). A total of 21 tests were performed on pressure support of 10 cmH_2O with a PEEP of 5 cmH_2O for testing ATENA's capacity to support the weaning process from mechanical ventilation (23, 24).

Pre-Clinical Test

Pre-clinical tests were performed following the EU Directive 2010/63/EU, approved by the Animal Welfare Body (ORBEA EM/ICVS-I3Bs_005/2020) of the institution where the study was conducted (University of Minho) and by the national authority for animal protection—*Direção Geral de Alimentação e Veterinária* (DGAV 008337). Four porcine animals (*Sus scrofa domesticus*) (14 weeks; average weight 32 ± 3 kg) were used to evaluate ATENA's performance *in vivo*, with a special focus on blood gas exchange during the MRHA test protocol. Two animals were allocated to the volume-controlled (group 1), and two animals were allocated to the pressure-controlled (group 2) ventilation. Animals were anesthetized with an intramuscular administration of ketamine (20 mg/kg) and xylazine (2 mg/kg), followed by intravenous propofol administration (4 mg/kg). Total Intravenous Anesthesia (TIVA) was maintained with continuous propofol infusion (4.4 mg/kg) in combination with fentanyl (0.005 mg/kg/h) and midazolam (0.7 mg/kg/h) administered through a central venous catheter, together with the parenteral isotonic fluids administered for maintenance of water and electrolyte balance (6–10 ml/kg/h). Rocuronium (2.5 mg/kg/h) was administered to provide muscle relaxation and improve ventilator adaptation. After intubation, animals were adapted to the ATENA ventilator with a FiO_2 of 60%. An invasive arterial line was achieved for a continuous hemodynamic (Combitrans Monitoring-Set arterial, BBraun, Germany) and blood gas (CG4+ cartridges, i-Stat analyzer, Abbott, Chicago, IL) monitoring.

In both groups, after 5 min of ventilation, arterial blood gas was collected to measure and record pH, PO_2 and PCO_2, and HCO_3, and a new ventilatory setting was selected. At the end of the experiment, with the animals still under deep anesthesia, euthanasia was performed by an intravenous administration of pentobarbital (200 mg/kg), with veterinary support.

RESULTS

MHRA Protocol

In volume-controlled ventilation, a triplet of 36 trials for compliance, resistance, and tidal volume were done. In pressure-controlled ventilation, the same number of tests were completed for PEEP, plateau pressure, and FiO_2 for an inspiratory pressure of 15 cmH_2O or 30 cmH_2O.

The histograms in **Figures 4**, **5** represent the relative frequency of the error (%) in volume-controlled ventilation for different PEEP values (5, 10, and 15 cmH_2O); tidal volume (300–500 ml) and FiO_2 (55–95%) and pressure-controlled ventilation for different PEEP values (5, 10, and 15 cmH_2O); and plateau pressure (15–30 cmH_2O) and FiO_2 (55–95%).

Concerning endurance testing, ATENA ran uninterrupted for 24 h, which represents 28,800 cycles. In volume-controlled ventilation, the set at the beginning of the test was as follows: tidal volume of 500 ml, respiratory rate 20 breaths/min, PEEP 5 cmH_2O, and FiO_2 40%. The average of measured parameters in the first 13 min was a tidal volume of 512.73 ml, FiO_2 = 39.81%, and PEEP = 4.66 cmH_2O. In the last 13 min of the 24 h, the average of the values measured were as follows: tidal volume =

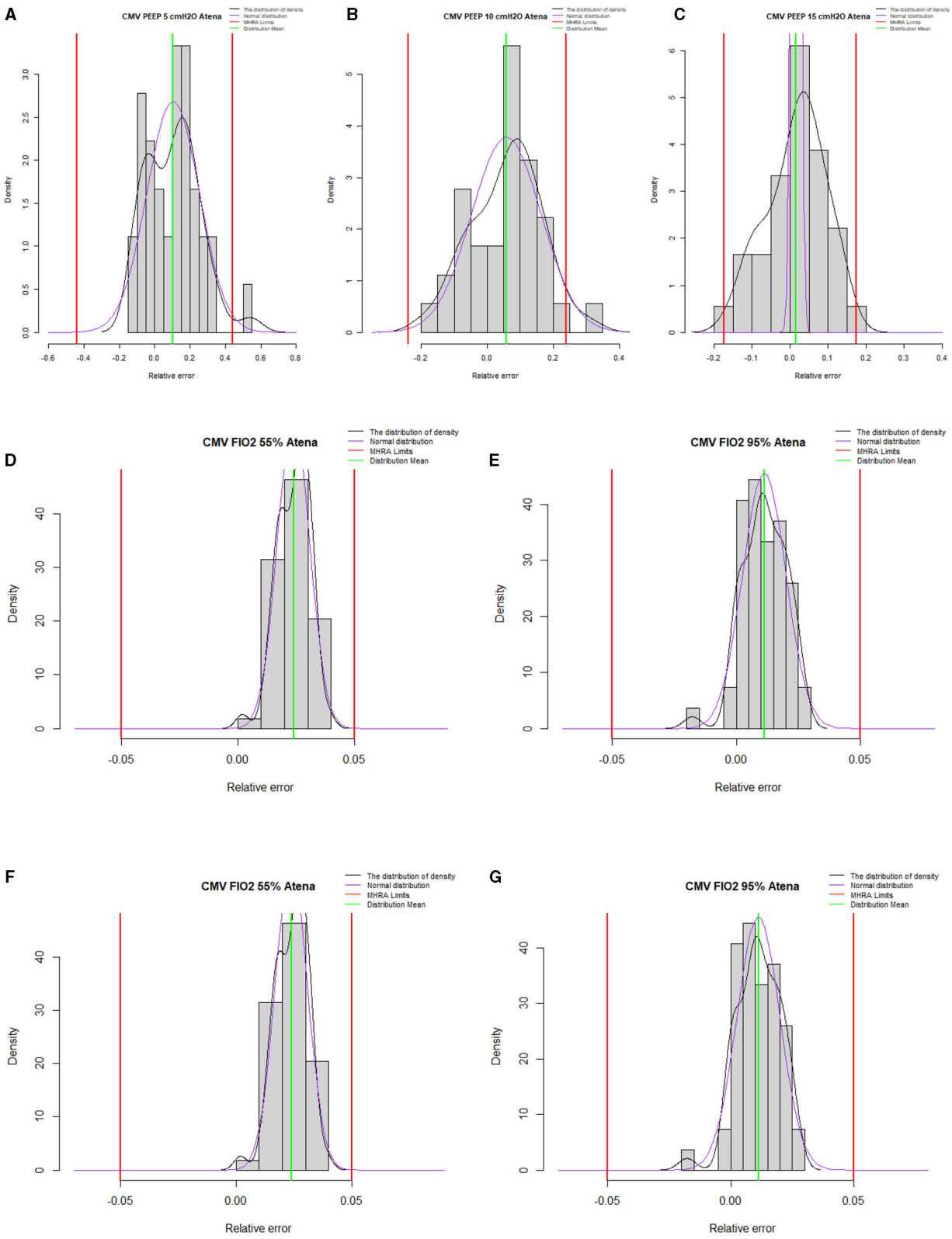

FIGURE 4 | Summary histograms for all volume-controlled ventilation test conditions. **(A–C)** represent histograms for PEEP 5, 10, and 15, respectively. **(D,E)** represent histograms for tidal volume 500 and 300 ml, respectively. **(F,G)** represent histograms for 55 and 95% of FiO_2. Outside the red limits data points out-of-performance.

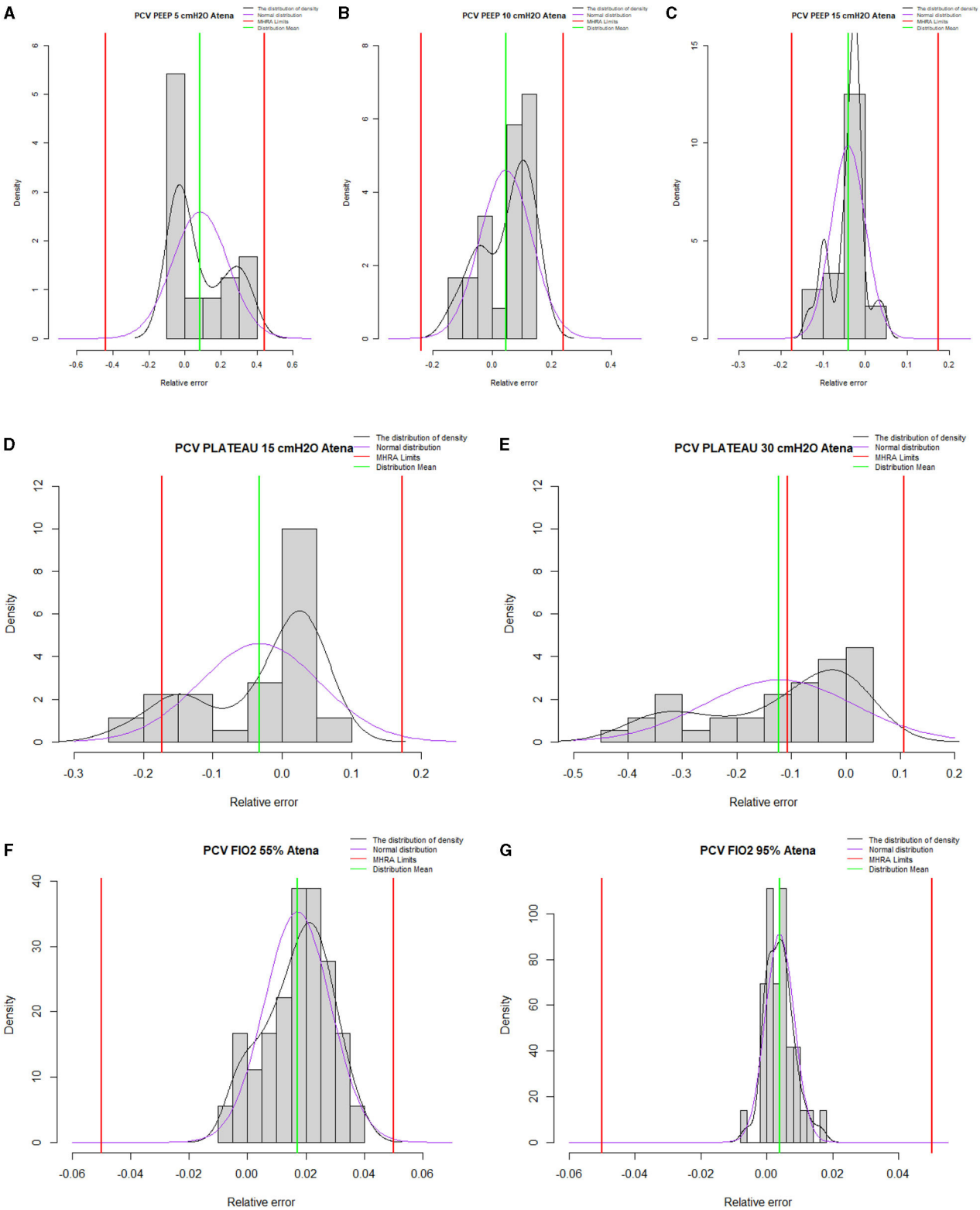

FIGURE 5 | Summary histograms for all pressure-controlled ventilation test conditions. **(A–C)** represent histograms for PEEP 5, 10, and 15 cmH_2O, respectively. **(D,E)** represent histograms for plateau pressure of 15 and 30 cmH_2O, respectively. **(F,G)** represent histograms for 55 and 95% of FiO_2. Outside the red limits data points out-of-performance.

519.57 ml, O2 = 39.72%, and PEEP = 5.47 cmH_2O at the final (time = 24 h).

For the pressure-controlled ventilation mode, a goal was set for the plateau pressure of 20 cmH_2O, respiratory rate of 20 breaths/min, PEEP 5 cmH_2O, and FiO_2 40%. The average values measured after 13 min of ventilation were as follows: plateau pressure = 22.61 cmH_2O, O_2 = 39.81, and PEEP = 4.47 cmH_2O. In the last 13 min of 24 h of ventilation, the average values were as follows: plateau pressure = 22.61 cmH_2O, O_2 = 40.3%, and PEEP = 4.81 cmH_2O.

The relative error values measured between the initial and the last 13 min are tidal volume = 1.3%, FiO_2 = 0.2%, and PEEP = 7.4% for controlled ventilation and plateau pressure = 0%, O_2 = −1.2%, and PEEP = −7.6%.

In terms of electronic safety, the ATENA ventilator complies with the relevant requirements studied (EN 60601-1-2, EN 61000-6-1, EN 61000-4-4, EN 61000-4-6, EN 55011, and ISO 80601-2-12).

International Organization of Standards

ATENA fulfilled the following criteria for basic safety and essential performance of critical care ventilators (ISO 80601-2-12:2020):

- Maximum error of the delivered and monitored tidal volume compared to the set value: ± (4 ml + 15% of the set value);
- Maximum error of the PEEP compared to the set value: ± (2 cmH_2O + 4% of the set value);
- Maximum error of FiO_2 compared to the set value: ± (5% of the set value); and
- Maximum error of $P_{Plateau}$ compared to the set value: ± (2 cmH_2O + 4% of the set value).

Relevant data from volume- and pressure-controlled ventilation, as well as expired volume, measured criteria are presented in **Supplementary Tables 2**, **3**.

Additional Tests

The results of additional tests are presented in **Figure 6**. The data are presented and analyzed in terms of relative error between the values defined by the test conditions, configured in ATENA, and the values measured by the gas flow analyzer. The relationship is linear for all evaluated parameters (tidal volume, PEEP, FiO_2, and $P_{Plateau}$).

Pressure Support Ventilation

The results obtained in tests 1 to 21 show that ATENA had an adequate performance for all trigger levels, for all inspiratory muscle pressures used in both healthy and ARDS simulated lungs (see **Supplementary Table 4**).

Pre-Clinical Test

During the study period, all animals remained hemodynamically stable with no need for vasopressor support. **Supplementary Tables 5, 6** display the relevant ventilatory settings and measures of ventilation variables in pre-clinical testing for volume- and pressure-controlled modes, respectively.

DISCUSSION

Analysis of Results

Test results demonstrated that the ATENA ventilator met the specifications in the MHRA RMVS guidelines. Its accuracy in terms of maximum bias and linearity errors is inside the performance limits for ISO 80601-2-12-2020 requirements.

ATENA can achieve satisfactory performances for all volume-controlled ventilation and pressure-controlled ventilation test conditions with a plateau pressure of 15 cmH_2O. Limited performance was observed in only three tests for plateau pressure of 30 cmH_2O, which explains the outlier values presented in **Figure 5**:

> #1 and 2–In the test with a plateau pressure of 30 cmH_2O, compliance of 50 ml/cmH_2O, resistance of 5 cmH_2O/L/s, and respiratory rate of 20 cpm, both plateau pressure and PEEP were almost achieved. A high instantaneous flow (SLPM) would be required for the PEEP and plateau pressure setpoints to be reached. In fact, during these tests, tidal volumes as high as 1,000 ml were recorded. For a desired FiO_2 of 95%, the required instantaneous flow would exceed the maximum capabilities of ATENA's hardware. Due to the high FiO_2 setpoint, a single piezo-electric valve, the oxygen one, would limit the maximum flow to its capacity, ∼60 SLPM. It is important to notice that ATENA contains two piezo-electric valves, one for air and one for oxygen, each rated to a maximum of 60 SLPM. Again, the tidal volume observed in these tests is not adequate for the protective ventilation that is needed for COVID-19 patients.
>
> #3–For a plateau pressure of 30 cmH_2O, compliance of 50 ml/cmH_2O, and FiO_2 set to 95%, this last parameter could not be reached. This limitation is once again explained by ATENA's hardware capabilities that, when mostly using a single piezo-electric valve, are capable of reaching instantaneous flows of 60 SLPM.

The majority of ISO requirements were met by ATENA. However, for the accuracy tests of volume-controlled ventilation (**Supplementary Table 2**, tests 1 and 2), in a simulated healthy patient (C = 50 ml/cmH_2O and linear R of up to 20 cmH_2O/L/s, tidal volume 500 ml), the PEEP parameter was underperforming. These results were considered to be sufficient for the adequate validation of ATENA since it is not expected that patients who developed bilateral pneumonia due to COVID-19 with the need for invasive ventilation (the scope of use for the ATENA ventilator) present a lung compliance of 50 ml/cmH_2O (25). Furthermore, ATENA displays the accurately measured PEEP, so even if underperforming, it will provide the clinician the required data to make an informed decision.

Simultaneously, the analysis of the small PEEP coefficients of variation in tests performed in volume- and pressure-controlled ventilation allows us to affirm the stability and safety of this parameter in situations that mimic clinical practice.

Taking into account all of the above, it is possible to conclude that the ATENA adequately performed for all test conditions set by the MHRA's RMVS and ISO guidelines, except for a single set of conditions not commonly found in day-to-day clinical practice

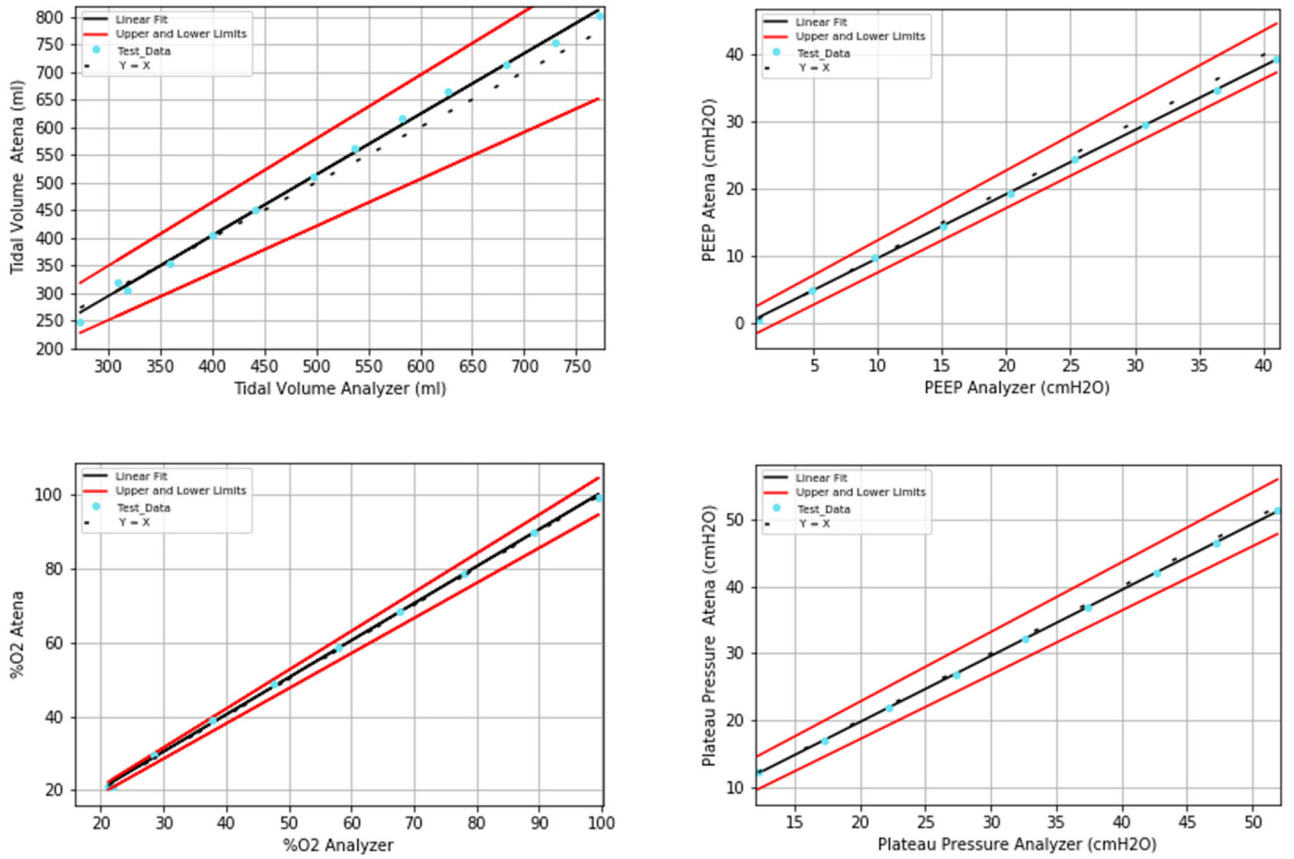

FIGURE 6 | Linear-fit results from additional tests for a wide range of settings (tidal volume, PEEP, FiO_2, and plateau pressure, respectively).

and may therefore be ruled as less relevant for a pandemic COVID-19 ventilator.

Results from the additional tests that extended the setting parameters of tidal volume, PEEP, FiO_2, and plateau pressure to their extreme limits prove that ATENA can perform adequately in an enlarged range of values.

We studied ATENA's performance on pressure support (PS) ventilation mode with the settings commonly used for weaning a patient from the ventilator (pressure support of 10 cmH_2O and PEEP of 5 cmH_2O). The analysis of the results in these settings revealed that ATENA was able to provide PS ventilation in the range of flow trigger values under study and its performance was not impaired when we assessed different levels of inspiratory muscle strength, in both healthy and ARDS lung models.

Noteworthy, even though two HME/HEPA filters were included on the 1.5-m breathing tubes, during the pressure support tests, the muscle pressure required to successfully trigger the ventilator was adequate. This indicates that the trigger sensitivity is robust and is adapted to real working conditions.

During *in vivo* animal model studies, ATENA behaved within expectations for the required standards across the full range of configurations, in both volume- and pressure-controlled modes, maintaining excellent oxygenation and ventilation performance. In both groups, changes in partial gas pressure and arterial pH secondary to changes in ventilatory parameters were biologically expected. In no trial was oxygenation compromised, and an improvement in the partial pressure of oxygen in arterial blood in response to the increase in ventilation/min was always observed. At the same time, the hyperventilation that conditioned the presence of respiratory alkalosis in numerous blood gases assertively demonstrates the effectiveness of ATENA in ventilation.

CONCLUSIONS

The novel ATENA Medical Ventilator, here described, was extensively tested, fulfilling MHRA and ISO requirements and specifications. Additional tests for extended parameter limits, pressure support, and pre-clinical studies demonstrated that it can perform as required. The ventilator is capable of controlled modes VCV, PCV, and PRVC, and mode PSV, and is therefore entirely appropriate for clinical use in adult COVID-19 patients. Further clinical trials must be performed to ultimately and unequivocally validate ATENA in clinical practice.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by EU Directive 2010/63/EU, under project authorization attributed by local ethics committee (Subcomissão de Ética para as Ciências da Vida e da Saúde - SECVS 004/2016, Chairperson Prof. Cecília Leão) and by the National Authority for animal protection (Direção Geral de Alimentação e Veterinária - et al. DGAV 015296, Chairperson Dr. Fernando Bernardo).

AUTHOR CONTRIBUTIONS

TR, FB, HO, JM, JA, JL, JS, MO, PF, RaM, and RuM: CEiiA's engineering team and were responsible for conceiving, developing, prototyping, and testing the ventilator throughout its development and validation. EN, EA, HM, JP, NS, PB, and SG: medical core team and Defined the specifications, tested, and validated the ATENA ventilator throughout its development and validation phases. TR, JA, SG, and JP: study conception and design of the paper. TR, JA, FB, PF, JP, RaM, and SG: acquisition of data, analysis and interpretation of data, and drafting the article. TR, JA, SG, RaM, and JP: in-depth revising the manuscript critically for important intellectual content. All authors contributed to the study and final approval of the version to be published and all agree to be accountable for all aspects of the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.614580/full#supplementary-material

Supplementary Table 1 | Description of each ATENA's component and the corresponding manufacturer.

Supplementary Table 2 | ATENA accuracy of volume and pressure-controlled ventilation (ISO 80601-2-12, clause 201.12.1.102).

Supplementary Table 3 | ATENA accuracy of expired volume indication (ISO 80601-2-12, clause 201.12.4.103.1).

Supplementary Table 4 | Results from ASL5000, on pressure support ventilation in healthy and ARDS lung model.

Supplementary Table 5 | Relevant ventilatory settings and measures of ventilation (average ± standard deviation) in pre-clinical testing for volume-controlled ventilation. TV—tidal volume; RR—respiratory rate; PEEP—positive end-expiratory pressure; PO_2–oxygen arterial partial pressure; PCO_2–CO_2 arterial partial pressure; HCO_3^-–bicarbonate arterial concentration.

Supplementary Table 6 | Relevant ventilatory settings and measures of ventilation (average ± standard deviation) in pre-clinical testing for pressure-controlled ventilation. TV—tidal volume; RR—respiratory rate; PEEP—positive end-expiratory pressure; PO_2–oxygen arterial partial pressure; PCO_2–CO_2 arterial partial pressure; HCO_3^-–bicarbonate arterial concentration.

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Interprofessional Communication Team for Caregivers of Patients Hospitalized in the COVID-19 Wards: Results From an Italian Experience

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Background: During the COVID-19 pandemic, emergency restrictions did not allow clinician family meetings and relatives' visits. In Molinette Hospital, a new communication model between healthcare providers and families of COVID-19 affected patients was developed by a team of physicians and psychologists. The study's aims were to investigate caregivers' distress and to analyse their satisfaction with the communications provided.

Methods: A cross-sectional study was conducted among caregivers of patients of Molinette Hospital COVID wards. Between April and June 2020, all caregivers were contacted 2 weeks after the patient's discharge/death to assess their satisfaction with the communications received through an online survey.

Results: A total of 155 caregivers completed the survey. Caregivers' distress level was found to be higher in women than men ($p = 0.048$) and in caregivers whose relative died compared to the caregivers whose relative was discharged ($p < 0.001$). More than 85% of caregivers defined communication "excellent"/"very good"; being male was associated with higher satisfaction levels than women ($\beta = -0.165$, $p = 0.046$). Besides daily communication, 63 caregivers (40.6%) received additional support from a psychologist of the team.

Conclusions: To our knowledge, this is the first study presenting, in an emergency, a new model of communication provided by a team of physicians and psychologists, and analyzing satisfaction with it. This model was highly appreciated by caregivers and it limited the discomfort caused by the restrictions on relatives' visits. It would be interesting to further evaluate the possibility of extending a communication model that includes doctors and psychologists in routine clinical practice.

Keywords: health communication, caregivers, COVID-19, psychological distress, pandemic

INTRODUCTION

Communication between healthcare providers, patients, and families has been identified as the most important and least accomplished factor regarding quality of care in the subintensive and in the intensive care units (ICU) (1). It was found that effective communication with patients in the ICU improves clinical decision-making (1) and promotes family satisfaction as well as their psychological well-being (2, 3). Clinical practice guidelines for support of the patient and their family report a number of recommendations, including frequent communications and repeated meetings concerning the care of the patient to reduce family stress and to be consistent with communication (4). Several studies have highlighted that communication with the caregivers is one of the most highly valued aspects of care (5–7). The most important family concerns were: having timely information (8, 9), receiving honest information, and support, comfort, proximity, and reassurance (8, 10). Effective communication improves family satisfaction, trust in the ICU physicians, clinical decision-making, and psychological well-being of family members (8, 11).

From January 2020, the novel coronavirus SARS-CoV-2, and the consequent disease Covid-19, has spread all over the world, creating an extraordinary situation of sanitary emergency, evolving in the pandemic that the World Health Organization (WHO) declared on the 11th of March (12). Since the beginning, Italy has been one of the most affected European countries and the Italian government had to drastically introduce new societal rules and legal provisions, limiting population movements, and social life. The increasing number of infected people put a considerable pressure on the Italian National Health System at all levels; hospitals hardly managed the increasing number of infected people who needed different levels of care and, therefore, many extraordinary measures were established such as the prohibition of access to caregivers in hospitals, suspension of non-urgent health services and the improvement of remote working among employees. An important weakness of the health care system was the lack of availability of equipment required for the protection of patients and health care workers. Face masks, for example, were unavailable for many weeks. On one side it was important to reduce any unnecessary potential exposure to infection, but on the other the importance of communication with patients and with their caregivers was valued. Therefore, COVID-19 pandemic restrictions did not allow clinician family meetings and relatives' visits to their beloveds; due to these difficulties, communication with caregivers should be conducted in the most transparent and comprehensive manner, to avoid an increase in the anxiety that the family may experience during this time (13). Thus, to overcome these issues, the hospital adopted telephone communications to allow family members to receive news about their relatives' clinical updates and to contact them, when possible. Phone calls cannot substitute the real presence at the bedside, but they can represent an alternative model of communication between relatives. Clinicians reported that families, during their telephone conversations on COVID-19, experienced the psychological burden and distress of not being able to see and care for their loved ones. This distress also seems to be exacerbated by the lack of information about this disease and the restrictions put in place to prevent its spread (14, 15). Moreover, patients remain alone all day without support, except that provided by the health care workers. It is well-known that family support in a "Mediterranean" country is of paramount importance. Before this crisis, in the hospital care units, family members were allowed to stay alongside their loved ones. In the first 2 weeks after the restrictions enacted by the Health Minister, we have patients and family members been discouraged to do this, drastically changing our way of operating.

Another critical issue was the alternance of the different clinicians due to the work shift who gave information by phone to the patient's relatives. This could leave families that are already stressed by the isolation and the serious condition of their loved one, confused as to who is in charge and to whom they should ask their questions (16, 17). The pandemic has created a public health emergency that is still altering the provision of health care services and affecting the quality and safety of health services. The above-described situation was daily experienced both in COVID and no-COVID wards of our health organization, the Molinette Hospital, inside the University Hospital of "Città della Salute e della Scienza di Torino." The Molinette Hospital is a general, third-level hospital with nine hundred beds, located in Piedmont region, Italy, one of the most affected areas during the pandemic.

At the beginning of the SARS-CoV2 pandemic, the aim of the Health Management of Molinette Hospital and of the Quality and Safety Healthcare Department was to provide clear and consistent communication to the patient's relatives, and therefore decided to begin an experimental project to improve the quality and outcomes of the communication between healthcare providers and families of COVID-19 affected patients, hospitalized in the COVID wards and in the sub-intensive care. Despite a number of resources or guidance proposed by healthcare professionals (18), neither evidence- nor consensus-based guidelines about COVID-19 communication in hospitals and in palliative care in COVID-19 were available. Furthermore, a survey among hospices in Italy revealed that healthcare professionals lacked a communication guideline on care for people dying from COVID-19 (19). The new communication model was developed in accordance with the principles of humanization of clinical care (20), and carried out by a team composed by physicians from the Health Management and psychologists from the Clinical Psychology Unit. The team gave medical information to the families, including daily clinical updates (every day in the early afternoon) through phone calls, accurate but also comprehensible for the relatives (21). At the beginning of each phone call, all relatives were informed of the presence, during the conversation, of a physician and of a psychologist and of the possibility of receiving psychological support by a psychologist of the team. The model was implemented in COVID wards with low intensity of care (not ventilated patients) and subintensive COVID wards (Continuous Positive Airway Pressure and non-invasive ventilated patients); the medical and nurse teams of these wards were heterogeneous and usually not specifically trained in giving information to families and caregivers in emergency situations.

To our knowledge, this is the first collaboration between physicians and psychologists during the pandemic, that provided patients clinical and emotional information about the coronavirus and at the same time faced problems related to the distress and suffering of the relatives.

Therefore, this was a hypothesis-generating study with the aims to analyse caregivers' satisfaction with phone communications provided by a team of physicians and psychologists and to investigate caregivers' distress (anxiety and depression), their emotional experiences and their perception of the adequacy of social support during the COVID emergency.

MATERIALS AND METHODS

Design and Participants

This study is a cross-sectional study including caregivers of hospitalized patients in the COVID wards and subintensive care units of the Molinette Hospital. All caregivers were contacted by phone 2 weeks after the patient's discharge or death to ask for their email address by a psychologist from the Hospital's Clinical Psychology Unit, who was not involved in the communication team, to assess their satisfaction with the daily conference calls. An email with the link to the survey, created with Google Form, was sent to those who agreed to participate. All questions in the survey were mandatory to avoid missing data. Raosoft® was used to determine the minimum sample size of 150, based on a 5% margin of error, 95% confidence level, 50% response distribution, and a population of 245 (total of caregivers of patients hospitalized in our hospital COVID-19 wards between March and May 2020). Data were collected between April and June 2020. The study was approved by the local Research Ethics Committee (no.39960/2020) and written informed consent was obtained from all participants. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (22).

Communication Team Model

Basing on a theoretical and practical analysis of the emergency context, healthcare workers involved in the first line during the emergency period faced long and lengthy work shifts, stressful from a physical and psychological point of view (23, 24). To partially relieve first-line workers, a mixed team composed by medical doctors and psychologists was built by the Health Management and Quality and Safety Healthcare Department; this team, hereafter COVID Communication Team (CCT), aimed to communicate with COVID-19 patients' relatives, to give them a sense of certainty and safety and clear, detailed and daily information on the condition of their loved ones, to allow them to re-elaborate the experience of suffering.

The CCT received daily information in a secure and telematics way (corporate encrypted email) from the ward's doctors after their daily briefing; all reported information shall be communicated to family members through a standardized format personalized by clinicians with patient-specific information. This format contains information about the patient's cognitive state, clinical parameters, ongoing therapy, and clinical activities that will be undertaken in the following days. CCT collectively analyzed and discussed the documents and called the designated family member during the afternoon. During the first interview, a medical doctor (MD) in charge of the team introduced the communication service and explained to the family member what mediated communication means and how the psychological support works. After the introduction phase, the CCT MD communicated the clinical information, taking notes on a special register for the specific requests of the caregivers. These notes were then sent via e-mail to the COVID wards' clinicians, thus ensuring a continuity of communication both within the CCT members and with the COVID wards healthcare staff. Telephone interviews were carried out every day in the same way, from Monday to Sunday. When the patient was in good clinical condition, caregivers could also ask CCT for a direct video call with their relatives, which was made possible by using the tablet computers available in all COVID wards with the help of the healthcare workers.

Moreover, the CCT MD communicated to relatives, in accordance with the medical and nursing staff of the COVID wards, a possible death of the patient in the hospital, supported by the clinical psychologist. Telephone interviews also allowed CCT psychologists to deal with family members with problems related to their own suffering, generated by social isolation, loneliness, and stress inherent to an emerging situation. For these reasons, it was useful to offer a telephone psychological support service for all family members when requested in a dedicated moment at the end of the daily CCT phone calls.

Study Measures

The online questionnaire was anonymous and took about 15 minutes to be completed. The survey was composed of three sections: in the first section socio-demographic data of the caregiver (age, gender, marital status, level of education, and profession) and data on the clinical course of patients (discharged/transferred or deceased) were collected. In the second section, three validated tools were administered to assess caregivers' emotional distress, perceived social support, and satisfaction with the communication received by the doctor-psychologist team. Specifically, the following questionnaires were administered:

- the Multidimensional Scale of Perceived Social Support (MSPSS) (25, 26), a self-report 12-item scale designed to measure perceived social support. The total score range is 1–7, with higher scores indicating greater perceived support.

- the Distress Thermometer (DT), derived from the Distress Thermometer developed by the National Comprehensive Cancer Network (27). It is a one-item, 11-point Likert scale that ranges from zero (no distress) to ten (extreme distress), with which caregivers indicate their level of distress in the past 7 days.

- a set of questions regarding the satisfaction with the communication received by the healthcare team, taken from Supportive Care Need Survey-short form (SCNS-SF 34) (28, 29), a rating scale designed to assess unmet needs in cancer patients. The distribution of answers was on a 5-point Likert scale, which

could vary from "poor" to "excellent," or from "not at all satisfied" to "extremely satisfied" or from "not at all" to "very much," depending on the type of question.

Finally, in the third section, two open-ended questions were asked to collect criticism and possible suggestions to improve the communication service.

Statistical Analysis

Data were processed and analyzed using the Statistical Package for Social Sciences (SPSS version 22.0; Chicago, IL, USA). Percentage values, means and standard deviations (SD) were used to describe the sample. Differences between groups were calculated using Mann-Whitney *U*-test for continuous measures. A multivariable linear regression analysis was performed to determine the association between gender, age, distress level, MSPSS score, and patient clinical course as independent variables and overall satisfaction score as the dependent variable. All tests were two-sided. A $p < 0.05$ was considered statistically significant.

RESULTS

A total of 155 caregivers completed the online survey (response rate: 155/245 = 63%). Of these, 71% were female and 29% were male. The mean age was 53.8 (SD = 12.94), with a range between 21 and 85 years. The other socio-demographic characteristics of caregivers and their relative clinical data are detailed in **Table 1**.

Caregivers reported a distress mean score of 6.59 (SD = 2.88) and a MSPSS mean score of 5.96 (SD = 1.18). The distress level was found to be higher in women than men ($p = 0.048$), and in caregivers whose relative died compared to the caregivers whose relative was discharged from the hospital ($p < 0.001$). No significant differences were found for other variables.

Table 2 describes caregivers' satisfaction with the communication service received by the healthcare team. Possible answers ranged on a 5-point Likert scale. Question number ten, "Did they encourage you to ask questions?", obtained the lowest score (mean=3.83, SD=1.22), while question number seven, "Did they give you all the information you needed?," had the highest score (mean = 4.84, SD = 0.87).

Overall, the daily communication service received was rated as excellent by 63.2% ($n = 98$), as very good by 23.2% ($n = 36$), as good by 9.7% ($n = 15$), as fair by 1.9% ($n = 3$), and as poor by 1.9% ($n = 3$) of the caregivers.

In addition to daily communication with the healthcare team, 63 caregivers (63/155; 40.6%) received additional support from a psychologist of the team. The satisfaction scores regarding this support are described in **Table 3**.

The multiple regression model showed that only gender had a significant predictive value for the overall satisfaction score [$\beta = -0.165$, $p = 0.046$; Model adjusted $R^2 = 0.027$, $F_{(5,148)} = 1.84$, $p = 0.109$], with being male associated with higher satisfaction levels. Age, distress level, perceived social support, and discharge/death of the caregiver's relative had no predictive value on the caregivers' overall satisfaction score with the communication received.

TABLE 1 | Socio-demographic data of caregivers and clinical course of their relatives ($N = 155$).

Variable	*n* (%)
Level of education	
Primary school	2 (1.3)
Low secondary school	39 (25.2)
High secondary school	63 (40.6)
University	51 (32.9)
Marital status	
Single	30 (19.4)
Married/cohabitant	98 (63.2)
Separated/divorced	12 (7.7)
Widowed	15 (9.7)
Employment status	
Unemployed	17 (11.0)
Employed	101 (65.2)
Retired	35 (22.6)
Student	2 (1.3)
Living condition	
Alone	28 (18.1)
With spouse	42 (27.1)
With spouse and children	69 (44.5)
With children	9 (5.8)
With parents	7 (4.5)
Degree of kinship with the patient	
Spouse/cohabitant	59 (38.1)
Parent	41 (26.5)
Son/daughter	23 (14.8)
Grandparent	1 (0.6)
Sibling	11 (7.1)
Other relative	13 (8.4)
Friend	7 (4.5)
Duration of patient hospitalization	
<7 days	31 (20.0)
Between 8 and 14 days	51 (32.9)
Between 15 and 20 days	27 (17.4)
More than 21 days	46 (29.7)
Clinical status of patient	
Discharged	112 (72.3)
Deceased	43 (27.7)

Among the 155 caregivers, only 29 reported some critical issues. The following were the main ones: seven people (24.1%) would have preferred to receive the clinical updates regarding their relative's health status directly from the ward doctors and not only from the CCT. Six caregivers (20.7%) reported that they had received too little information, and five (17.2%) stated that they have received little attention and support after the discharge from the hospital of their relatives, also due to poor information received from the primary care health services.

Finally, 24 caregivers made suggestions to improve the service: six people (25%) suggested to develop a way to communicate directly with ward doctors, four

TABLE 2 | Caregivers' satisfaction with the communication service received by the healthcare team ($N = 155$).

Questions	Mean (SD)[a]
1) Overall, how do you rate the service received? [b]	4.44 (0.89)
2) How satisfied are you with having received daily updates regarding the clinical situation of your relative? [c]	4.59 (0.84)
3) How welcomed you felt by the health team? [d]	4.37 (1.03)
4) Did you feel treated with respect? [d]	4.73 (0.60)
5) Did they understand your main concerns? [d]	4.52 (0.87)
6) Did they let you speak without interrupting? [d]	4.59 (0.80)
7) Did they give you all the information you needed? [d]	4.84 (0.87)
8) Did they use words that were easy for you to understand? [d]	4.58 (0.83)
9) Did they verify that you understood everything? [d]	4.47 (0.94)
10) Did they encourage you to ask questions? [d]	3.83 (1.22)
11) Did they communicate the progress of your relative's treatment? [d]	4.54 (0.089)
12) Did they show attention and interest? [d]	4.52 (0.82)
13) Did they give you the right time? [d]	4.43 (0.93)

[a] *SD, Standard Deviation.*
[b] *distribution of answers was on a 5-point Likert scale from "poor" to "excellent".*
[c] *distribution of answers was on a 5-point Likert scale from "not at all satisfied" to "extremely satisfied".*
[d] *distribution of answers was on a 5-point Likert scale from "not at all" to "very much".*

TABLE 3 | Caregivers' satisfaction with the support received by psychologists of the healthcare team ($N = 63$).

Questions	Mean (SD)[a]
1) How satisfied were you with the communication with the psychologist?[b]	4.37 (0.90)
2) How much did you feel encouraged and supported by the psychologist?[c]	4.24 (0.93)
3) How much support did you feel in dealing with that difficult situation?[c]	4.13 (1.13)

[a] *SD, Standard Deviation.*
[b] *distribution of answers was on a 5-point Likert scale from "not at all satisfied" to "extremely satisfied".*
[c] *distribution of answers was on a 5-point Likert scale from "not at all" to "very much".*

(16.7%) suggested to receive information more than once a day, and three caregivers (12.5%) suggested to increase the level of empathy during phone-calls made by the communication team.

DISCUSSION

Communication with caregivers is one of the most highly valued aspects of care (5–7), especially in a health emergency such as COVID-19 pandemic (30, 31). This study aimed at presenting a new model of communication between healthcare providers and families of COVID patients provided by CCT, a team of physician and psychologists, and investigating the caregivers' satisfaction with it. In addition, it investigated caregivers' distress and their perception of the psychological support received during the COVID emergency.

The satisfaction score is high, as more than 85% of respondents defined the communication "excellent" or "very good." Moreover, the satisfaction level does not appear to be associated with the clinical status of the patient (discharged or deceased). This could be indicative of good bereavement care. According to Morris and collaborators, it is crucial for hospitals to adopt a proactive stance during a public health emergency, to offer universal bereavement care to all families: in the context of the COVID-19 pandemic there is a high possibility that patients will die alone, separated from their loved ones and therefore, there is a sense of urgency for institutions to provide support to bereaved family members (30). To do this, CCT made bereavement calls in the first week after the patient's death, that may have helped grieving families to know that the patient and family were remembered, contributing to the quality of the end-of-life care. Despite this, as expected, the distress level was found to be significantly higher in caregivers whose relative died compared to caregivers whose relative was discharged from the hospital.

Gender was found to be related both to distress and satisfaction levels. Women resulted having higher distress and lower satisfaction levels with the communication service compared to men. This result is in line with the current literature, as higher distress in women was found also in the general population in other studies regarding the COVID pandemic (32, 33).

According to the Italian Istituto Superiore di Sanità report (34), caregivers preferred video calls to communicate with hospitalized patients and with healthcare personnel, because of the possibility of characterizing the face and the aspects of healthcare personnel and to establish a closer relationship (35). Interestingly, none of the caregivers of our sample reported this request. In addition, not all caregivers had the possibility to make video calls. Instead, direct communication between patients and caregivers was encouraged through video calls where possible, or via traditional telephones, with the help of health personnel for patients who needed it. Indeed, recent literature highlights the importance of facilitating communication between patients and family members (30).

Communication between staff and caregivers occurred every day, at about the same time, by the same communication team. This may have contributed to a good level of satisfaction, since family members of a critically ill patient appreciate proactive and regular communication (36), meanwhile frequent communications and repeated meetings concerning the care of the patient could reduce family stress (4). Other studies also highlighted the importance of receiving timely information (8, 10). To confirm this, in our study the satisfaction level of the daily update frequency was very high. Therefore, clear, specific, and detailed information decreased the feeling of insecurity, doubt, and fears of relatives and gave them the opportunity to imagine the situation of the beloved. In addition, good communication reassured families about the optimal care of the patient at a time when trust in a highly pressured health system was often questioned.

Few caregivers would have preferred to receive information several times a day. To analyse this result, it is important to contextualize the study in the emergency period: the request to receive information more than once a day probably also derives from the fact that family members were often all day alone at home, unable to go out to see relatives and friends, with low perceived social support (37). Some authors have recommended contact twice a day if the patient is at imminent risk of life or is dying (38). However, it should be noted that 40% of the caregivers who responded to the survey received additional support from the team of psychologists, with a good level of satisfaction. This additional support was also considered important in previous studies (34, 39).

Satisfaction about the completeness of the information received was highly valued, with only a few caregivers complaining about having received too little information. This may reflect the validity of the communication format between CCT and healthcare professionals in wards, with patients clinical and emotional condition. Completeness of information is an important point of communication; indeed, information should be given in a comprehensive and transparent manner to reduce the caregiver's anxiety (13). On the contrary, some caregivers felt they were not encouraged enough to ask questions. During the peak period of the pandemic, around 70–80 caregivers were called per day, therefore it is possible that despite the CCT willingness to dedicate sufficient attention to all caregivers there was not enough time to address all their questions. This aspect would need further investigation to better understand the specific needs of caregivers.

Some caregivers reported a lack of continuity in support once the patient was discharged from the hospital. This aspect, combined with the fragmented scenario of the emergency period when each care structure adopted its own communication strategy, is a critical point that must necessarily be further addressed. Communication with patients and their relatives is a major issue in medicine and the experience of the COVID-19 pandemic could be a starting point for a common model, adaptable to different health settings. The design and implementation of our communication model was possible also thanks to the human resources made available by the reduction of the workload in non-COVID hospital wards and outpatient services (36).

This study presents several strengths. To our knowledge, this is the first study evaluating the satisfaction of a new model of communication for emergency situations provided by a collaborative team of physicians and psychologists. Moreover, the size of the sample was high, and it was conducted in the biggest hospital in the Italian region most affected by COVID-19 at this time.

However, the present study has some limits that should be acknowledged. First of all, the lack of data on non-responders may have led to possible bias. Responder caregivers could be more satisfied with the communication service than non-responders. This limitation should be taken into account in the interpretation and generalizability of findings (40). Moreover, using an online questionnaire may have limited participation, excluding older caregivers who are less prone to the use of technological tools (41). On the other hand, an online survey was considered the most suitable tool to guarantee the anonymity of participants (42). Moreover, the satisfaction toward the communication model of the clinicians working in the COVID wards was not investigated. The lack of direct interaction with patients' caregivers could have been not easily accepted by all healthcare workers, despite the reduction of the workload.

In conclusion, the communication model presented so far was highly appreciated by caregivers and it limited the distress related to the restrictions imposed on the hospital ward visits. It would be interesting to further evaluate the possibility of extending a communication model that includes a doctor and psychologist even outside the pandemic, in routine clinical practice.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Ethical Committee of A.O.U. Città della Salute e della Scienza di Torino, Italy. Written informed consent was obtained from all participants.

AUTHOR CONTRIBUTIONS

AB and SC conceived the study idea. MC, PRa, PRo, and MS performed the data collection. SC performed the statistical analyses. AB, SC, MF, and EO drafted the first version of the manuscript. All authors contributed to the study design, have discussed the results and revised this manuscript critically for important intellectual content, read, and approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.621725/full#supplementary-material

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REVIEW
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Molecular Hydrogen: A Promising Adjunctive Strategy for the Treatment of the COVID-19

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Coronavirus disease 2019 (COVID-19) is an acute respiratory disease caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has no specific and effective treatment. The pathophysiological process of the COVID-19 is an excessive inflammatory response after an organism infects with a virus. Inflammatory storms play an important role in the development of the COVID-19. A large number of studies have confirmed that hydrogen has a therapeutic effect on many diseases *via* inhibiting excessive inflammatory cells and factors. Recently, a study led by the Academician Zhong Nanshan in China on the treatment of the patients with the COVID-19 by inhalation of a mixed gas composed of hydrogen and oxygen has attracted widespread international attention and hydrogen therapy has also been included in a new treatment plan for the COVID-19 in China. This study mainly describes the mechanism of occurrence of the COVID-19, summarizes the therapeutic effects and underlying mechanisms of hydrogen on the critical disease, and analyzes the feasibility and potential therapeutic targets of hydrogen for the treatment of the COVID-19.

Keywords: COVID-19, molecular hydrogen, inflammation, cytokines, treatment

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CHARACTERISTICS AND RELATED MECHANISMS OF THE COVID-19

Coronavirus disease 2019 (COVID-19) is an acute respiratory disease caused by a novel virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). By the end of August 2021, the number of cases of infection and death has increased to 218 million and 4 million, respectively[1]. COVID-19 is primarily transmitted *via* the respiratory tract and close contact, with the population generally susceptible. The WHO pointed out that the patients whose main symptoms are fever, cough, and fatigue, 80% of the patients have a good prognosis. Their radiological features are the interstitial changes in the lungs. However, about 14% of the patients have a critical illness and 5% of the patients have a severe infection combined with dyspnea and/or hypoxemia followed by the rapid progression to acute respiratory distress syndrome, septic shock, and multiple organ

[1] World Health Organization. https://covid19.who.int/

failure. Patients with severe illness usually require admission to an intensive care unit (ICU) for the treatment with a mortality rate of over 50%. So far, there is little evidence that any drug is effective in treating COVID-19. The current treatment mainly includes symptomatic supportive care, the application of antiviral drugs, and immunotherapy.

Severe acute respiratory syndrome coronavirus 2 is a single positive-stranded RNA virus that enters the respiratory epithelial cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of the tissue cells *via* the S protein on the envelope surface (1–3). After entering the cell, it releases its own RNA, associates with ribosomes for the translation process, and uses the material of the host cell to synthesize its own structural proteins, functional proteins for nucleic acid replication, and viral nucleic acids. Enough structural proteins and viral genomic ribonucleic acid combine to form a progeny virus and then the vesicles are released outside the cell to continue infecting the other cells (4, 5). After the virus breaks through the first barrier, the innate immune response of the host is activated. Subsequently, the macrophages recognize the pathogen-associated molecular patterns (PAMPs) of the virus through the pattern recognition receptors on their surface and then phagocytose the virus. Meanwhile, the activated macrophages produce the pro-inflammatory factors such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), which act on the vascular endothelial cells to increase the expression of the adhesion molecules and activate the chemokines. Under the action of the chemokines, the inflammatory cells migrate to the inflammatory focus to cause inflammation. Infected cells also synthesize and secrete interferons that inhibit viral replication. Cytokines released outside the cells recruit and activate the more immune cells to participate in the "antivirus war." Immune cells will also continue to secrete the cytokines, guiding the more immune cells to the focus, forming a positive feedback regulation. If the immune system beats the virus, the inflammatory response will gradually subside and the body will recover. Once this positive feedback regulation is out of control, the immune cells of the body will be massively activated to secrete more cytokines, causing an uncontrolled inflammatory response and destroying the own structure of the body.

Autopsy of the deceased cases revealed that the lung tissues were congested, edematous, and enlarged in size with various degrees of consolidation (6). The consolidated areas were mainly the diffuse alveolar injury and exudative alveolar inflammation. There are seriflux, fibrin, and hyaline membranes in the alveolar cavity. The exudative cells are predominantly the monocytes and macrophages as well as the abundant mucous secretions in the distal bronchioles and alveoli of the respiratory tract (7). Mucus plugs of the respiratory tract leads to ventilatory dysfunction and hypoxemia. The number of the macrophages in lung tissue of the patients with the COVID-19 increased significantly, including IL-6, IL-18, interferon-γ (IFN-γ), IL-15, TNF-α, IL-1α, IL-1β, and IL-2, which potentially contribute to a "cytokine storm." Subsequently, the cytokine storm is positively correlated with the severity of the disease (8, 9).

Simultaneously, Erlich et al. found that the excessive activation of the immune cells and persistent inflammation caused by the viral infection generate large amounts of reactive oxygen species (ROS) (10). Pro-inflammatory mediators increase the production of ROS in the mitochondria and immune cells by activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (11). After the virus infects the body, its replication depends on the energy metabolism of the host cells and the glycolytic pathway of the host cells is significantly enhanced, resulting in the production of a large number of ROS (12). In the course of the COVID-19, the direct injury caused by the virus and ROS produced by the above two pathways leads to diffuse alveolar damage, which limits the efficiency of the alveolar gas exchange and leads to dyspnea and hypoxemia. Therefore, the lung is more prone to secondary infection (13). Therefore, preventing the virus from binding to the receptors, inhibiting the development of uncontrolled inflammation *in vivo*, and reducing cell damage caused by the products of inflammatory response can become the potential therapeutic targets of the COVID-19. Inflammatory storm and ROS are both the targets of hydrogen therapy.

CLINICAL APPLICATION AND CHARACTERISTICS OF HYDROGEN

Hydrogen, the lowest density gas known in the world, has the smallest molecular mass and some degree of reducibility. Biological research on hydrogen began in 1975 using 97.5% hydrogen and 2.5% oxygen mixture to treat the UV radiation-induced squamous cell carcinoma of mouse skin (14). In 2001, the French scholars used high-pressure hydrogen (eight standard atmospheric pressure) to treat the liver parasitic diseases, demonstrating for the first time that hydrogen has anti-inflammatory effects and proposed that the direct reaction of hydrogen with hydroxyl radical (•OH) is the molecular basis for its treatment of inflammatory damage (15). Until 2007, the Japanese scholars reported that inhalation of 2% hydrogen gas in the animals could effectively eliminate the toxic free radicals and significantly ameliorate cerebral ischemia-reperfusion injury (16), which attracted extensive international attention. Hydrogen gas has begun to become a research hotspot in the biomedical field. Hydrogen has been found to have therapeutic effects on various diseases such as tumors, sepsis, organ injury, and ischemia-reperfusion injury (17–19, 59).

There are many ways to use hydrogen such as inhalation of hydrogen, drinking hydrogen-rich water (HRW), injection of HRW, bathing with HRW, and eye drops containing dissolved H_2. Initially, the hydrogen element used in the clinical trials was mainly in a non-gaseous form. Clinical studies have shown that drinking HRW is safe and well-tolerated and HRW containing 0.8 or 5 mM dissolved H_2 improves the clinical symptoms in the patients with Parkinson's disease (20–22). HRW containing 7 ppm H_2 (3.5 mg H_2 in 500 ml water) could protect the vascular endothelium from ROS (23). Healthy adults drink 4 weeks of HRW at 1.5 L per week, which can reduce cell death and inflammation by regulating the Toll-like receptor-nuclear factor-kappa B (TLR-NF-κB) signaling and enhance the antioxidant capacity of the body. When measured by using the dissolved H_2 analyzer, the hydrogen concentration of HRW was 0.753 ±

0.012 mg/l (24). A hydrogen-rich saline injection containing 1 ppm H_2 can safely and effectively reduce the active phase of rheumatoid arthritis (25). Frequent use of hydrogen-rich tablets can effectively treat soft-tissue injuries in male occupational athletes (26). Oral hydrogen-rich capsules made of a blend of the hydrogen-generating minerals (46 mg of calcium and 40 mg of magnesium) can improve the insulin resistance in obese patients and H_2 can be produced in the intestine by the following reactions: $Mg + 2H_2O \rightarrow Mg(OH)_2 + H_2$ supplying 6 ppm of H_2 per day (27).

Hydrogen can be quickly absorbed and utilized; thus, it is more suitable for emergency patients because oral administration in emergency patients always limits liquid. Therefore, inhalation of hydrogen gas is the best option for the combination of safety and feasibility. In recent years, clinical trials have also confirmed the therapeutic effects of the inhalation of hydrogen gas. Patients with end-stage colorectal cancer treated simultaneously with 68% hydrogen and 32% oxygen were found to have an increased ratio of programmed cell death-1 (PD-1)-/CD8+ T cells in the peripheral blood, significantly longer progression-free survival, and improved prognosis (60). In addition, 3% concentration of hydrogen inhalation for the treatment of the patients with acute cerebral infarction found that the vital indications of the patients were not significantly different from those of the control group, the oxygen saturation was higher, and the degree and scope of brain injury were smaller, which could achieve the therapeutic effects after the optimal clinical therapeutic window (28). In addition, several clinical trials have confirmed that hydrogen inhalation has a positive implication on the reduction of the adverse events in the progression and treatment of postcardiac arrest syndrome after the acute myocardial infarction and non-small cell lung cancer as well as on ventricular remodeling (29–32). With respect to viral diseases, there is no evidence that hydrogen can directly act on the virus, which needs more research. Currently, the treatment with the COVID-19 consists of inhalation of a mixture of the hydrogen and oxygen (66% hydrogen; 33% oxygen) at 6 L/min *via* nasal cannula by using the Hydrogen/Oxygen Generator (model AMS-H-03, Shanghai Asclepius Meditec Co., Ltd., China). H_2-O_2 inhalation for 7.7 h on the basis of standard of care significantly improved the severity of the disease on day 2, including dyspnea scale, chest distress, chest pain, cough scale, and resting oxygen saturation, compared with the control group of the patients who received daily standard of care with oxygen therapy. This may be related to the reduction of inhalation resistance by hydrogen/oxygen mixture (66). Nevertheless, the trial still had some limitations, namely there was no random allocation of the patients, which may cause selection bias due to the emergency situation and, in addition, no further study of the underlying mechanism was conducted. Hydrogen inhalation reducing inhalation resistance was also demonstrated in the patients with acute severe tracheal stenosis (33). Moreover, there was a multicenter, randomized, double-blind, and parallel group controlled trial showing that inhalation of a hydrogen/oxygen mixture can significantly improve the acute exacerbation of the chronic obstructive pulmonary disease symptoms, including dyspnea, cough, and expectoration, compared with oxygen, with acceptable safety and tolerability profile (34).

POTENTIAL TARGETS OF HYDROGEN FOR THE TREATMENT OF THE COVID-19

Neutrophils

Neutrophils, as the first defense part of the innate immunity, are considered to play a protective role upon the bacterial or fungal infection. They kill the bacteria or fungi through phagocytosis and neutrophil extracellular traps (NETs) (35). However, their role in viral infection is unclear. An autopsy of the patients who died of the COVID-19, the neutrophils infiltrated the pulmonary capillaries and alveolar cavities. The lung tissue showed acute capillaritis with fibrin deposition and mucositis with neutrophil infiltration, which was associated with the pathogenesis of the lung injury (36, 64). Transcriptome sequencing analysis of the SARS-CoV-2-infected cells showed that the infected cells expressed the neutrophil chemokines. Transcriptome sequencing analysis of bronchoalveolar lavage fluid cells of the patients also revealed upregulation of the neutrophil genes and chemokines such as TNF receptor (TNFR), IL-8, CXCR1, and CXCR2 (37). Since neutrophils are not the main inflammatory cells in the viral infection, their appearance undoubtedly aggravates inflammatory damage in the lung tissue. In the patients with the COVID-19, neutrophilia tended to predict a poor prognosis (63) and an increased neutrophil-to-lymphocyte ratio was an independent risk factor for severe disease (38). Tomar et al. found that increased mortality in patients with diabetes and cardiovascular disease was also associated with neutrophilia (39). It is found that inhalation of hydrogen gas can reduce the infiltration of the neutrophils in lung tissue, so as to alleviate inflammatory damage to the lung tissue in the disease states. Xie et al. treated mice with severe sepsis by inhalation of hydrogen gas and found that after inhalation of hydrogen gas, lung structural damage caused by inflammatory cell infiltration was significantly improved and neutrophil infiltration in the lung interstitium and alveolar space was reduced, thereby improving the survival rate of the severe septic mice modeled with cecal ligation and perforation (CLP; (58)). In the rat model of the hemorrhagic shock and resuscitation, it was found that the lung tissue myeloperoxidase (MPO) activity was lower in the 2% hydrogen inhalation group compared than in the control group and the levels of inflammatory initiation cytokine, TNF-α, and IL-1β were also reduced. Briefly, the inhalation of 2% hydrogen gas after the hemorrhagic shock and resuscitation reduced MPO activity and suppressed the pro-inflammatory mediators by reducing the infiltration of the inflammatory cells into lung tissue, thereby minimizing the degree of lung injury (40). Therefore, we hypothesized that the neutrophils could be a target for the COVID-19 hydrogen therapy.

Macrophages

Macrophages phagocytose the damaged cells and pathogens in inflammation within the body by releasing the chemokines, leukotrienes, and prostaglandins that increase the vascular permeability and attract more inflammatory cells (41). They

present the antigens to activate the adaptive immune responses. We performed single-cell RNA sequencing of the immune cells from bronchoalveolar lavage fluid of the patients with the severe COVID-19 and found that they were enriched in the pro-inflammatory monocyte-derived macrophages (42). Therefore, inhibiting excessive activation of the macrophages may be an effective way to attenuate inflammatory injury. Chen HG et al. cocultured RAW264.7 macrophages in hydrogen-rich medium with 1 μg/ml lipopolysaccharide (LPS) to obtain a sepsis cell model. The results showed that the hydrogen treatment increased the activity of heme oxygenase-1 (HO-1) in the macrophages compared with the control group and reduced the levels of pro-inflammatory factors [TNF-α, IL-1β, and high mobility group box 1 (HMGB1)] stimulated by LPS in a concentration-dependent manner, increasing levels of the anti-inflammatory factor IL-10, and decreasing levels of cellular inflammation (43). Wang et al. found that LPS induced an increase in human umbilical vein endothelial cell (HUVEC) adhesion to the monocytes, an increase in vascular cell adhesion molecule-1 (VCAM-1) and E-selectin release, and a decrease in the expression of vascular endothelial cadherin (VE-cadherin). However, hydrogen-rich fluid coculture can reduce the release of the adhesion molecules and the changes in endothelial permeability caused by LPS and prevent further development of the inflammatory responses (44). Hydrogen reduces monocyte adsorption by the endothelial adhesion molecules under inflammatory response, thus preventing the blood-borne monocytes from passing through vascular endothelium and activating into the macrophages, resulting in excessive inflammatory damage. In ovalbumin-induced asthma model of mice, inhalation of hydrogen could reverse the phagocytic defect of the macrophages in the asthmatic mice *via* nuclear factor-erythroid 2-related factor 2 (Nrf2) pathway and significantly reduced ovalbumin-induced airway hyperreactivity and inhibited inflammation and goblet cell proliferation (45). It can be seen that hydrogen can stabilize the function of the macrophages and avoid damage to the body caused by excessive activation and phagocytic defects.

Cytokines

Cytokines play an important role in regulating the inflammatory cells by binding to the specific receptors on the target cells. Chemical mediators released by the inflammatory cells can cause vasodilation, increased permeability, and leukocyte exudation and play an important role in the initiation and progression of inflammation. Current studies suggest that the COVID-19 has a pathophysiological process similar to sepsis, i.e., the immune pathogenesis and microcirculatory dysfunction caused by systemic inflammatory cytokine storm (46). Wilson et al. found that in the serum of the patients with the severe COVID-19 or sepsis, the levels of five cytokines related to "cytokine storm" were as follows: IL-1β, IL-1RA, IL-6, IL-8, and TNF-α and there were no significant differences (47). The protective effect of hydrogen on organ injury in sepsis has been demonstrated in a variety of animal models. Xie et al. found that 2% hydrogen inhalation had therapeutic effects on acute lung injury (ALI) caused by a systemic inflammatory response model induced by intraperitoneal injection of zymosan. Hydrogen can reduce the levels of the early inflammatory factor TNF-α and the late inflammatory factor HMGB1 in the serum and lung tissue, alleviate lung tissue damage, and improve the survival rate of mice (62). The main mechanism is that hydrogen inhibits the expression of HMGB1 and alleviates tissue damage by upregulating Nrf2-mediated HO-1 pathway (48, 61). Wang et al. found that the levels of monocyte chemoattractant protein-1 (MCP-1), IL-4, and IL-6 in peripheral blood decreased significantly after inhalation of 2.4% hydrogen gas *via* a nasal catheter for 45 min in the patients with chronic obstructive pulmonary disease. Hydrogen reduces airway inflammation by reducing cytokine levels (65). According to the above studies, the use of hydrogen gas can reduce the destructive cytokine storm and lung injury caused by SARS-CoV-2 in the early stage of the COVID-19, stimulate sputum drainage, and ultimately reduce the incidence of severe disease (49).

Reactive Oxygen Species

Reactive oxygen species are a collective term describing the chemicals formed upon by the incomplete reduction of oxygen, derived from the molecular oxygen, and formed by the redox reactions or electronic excitation including non-free radical and free radical (at least one free electron) species (50) such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and •OH (51). The elevated formation of different ROS leads to molecular damage denoted as "oxidative distress." Excess ROS can directly or indirectly destroy DNA and proteins and induce gene mutations, which are considered to be related to the development of many diseases. Despite their cytotoxic effects, •OH and H_2O_2 play important physiological roles at the low concentrations: they function as regulatory signaling molecules; participate in many signal transduction cascades; and regulate the biological processes such as apoptosis, cell proliferation, and differentiation (16). Similar to the other infectious diseases, large amounts of ROS are released during the COVID-19 process (13). Hydrogen is a reductive gas with selective antioxidant effects in living organisms. Ohsawa et al. first found that H_2 has a very strong scavenging effect on •OH, a much smaller scavenging effect on nitric oxide (NO•), and a negligible scavenging effect on other reactive oxygen species such as superoxide anion radical (O_2•) (16), which means that hydrogen can only eliminate harmful ROS while retaining other physiological ROS that plays an important role in cell signal transduction. Dong et al. found that in a CLP-induced murine sepsis model, 2% hydrogen inhalation could alleviate lung tissue damage caused by ROS and increase the oxygenation index by improving the mitochondrial function (52). However, Hancock et al. found that the direct reaction of hydrogen with the free radicals is not very active (53). Therefore, we speculate that the antioxidant effect of hydrogen in different diseases or disorders is not exactly the same. Consequently, hydrogen may work through removing toxic ROS directly and then improving the antioxidant activity of the body indirectly. In addition, ROS are also an initial signaling molecule that initiates the inflammatory response and its cascade-amplifying effects. ROS and inflammatory

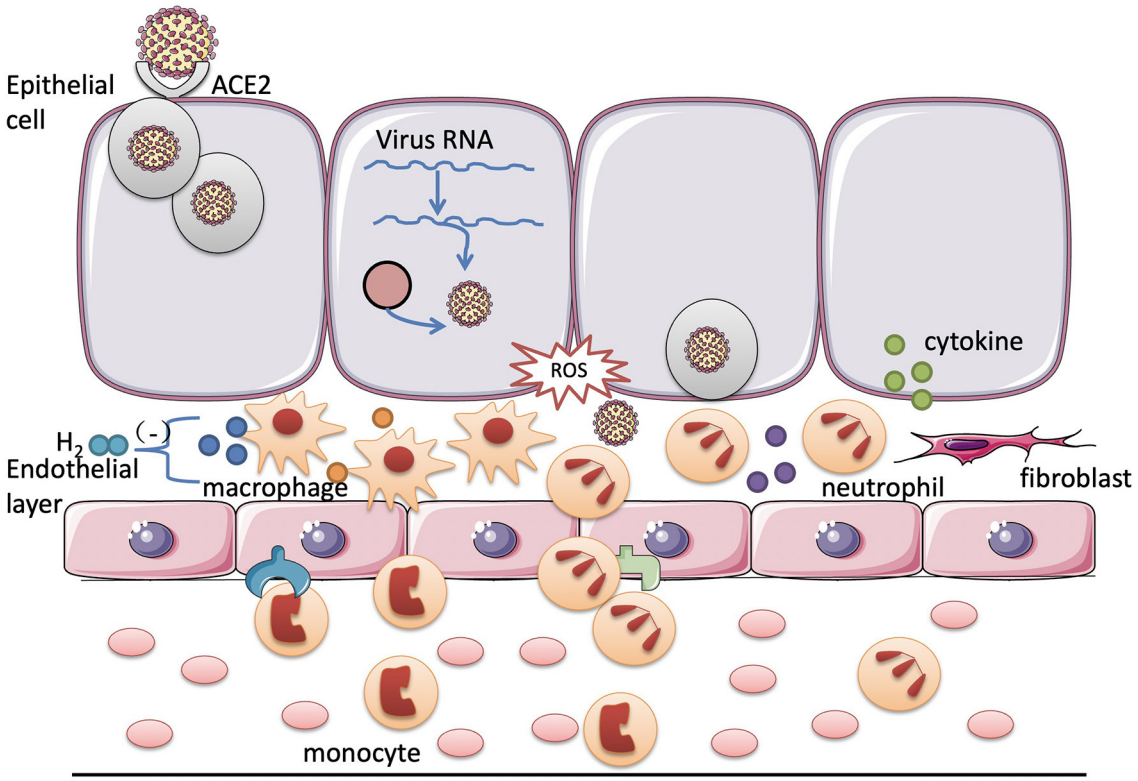

FIGURE 1 | Potential targets of hydrogen for the treatment of the coronavirus disease 2019 (COVID-19). After the viral infection, the inflammatory cells in the tissues and blood are activated to destroy the virus through phagocytosis and the release of cytokines. However, excessive inflammation causes uncontrollable body damage. In the COVID-19, hydrogen may exert its protective effect on the respiratory system by inhibiting the excessive activation of the neutrophils and macrophages and reducing the release of the cytokines.

TABLE 1 | The current clinical trial about hydrogen therapy in patients with COVID-19.

Study	Title	Status	Condition	Intervention	URL	Country
1	Hydrogen-Oxygen Generator With Nebulizer in the Improvement of Symptoms in Patients Infected With COVID-19	Recruiting	COVID-19	Device: oxyhydrogen Device: Oxygen	https://ClinicalTrials.gov/show/NCT04336462	China
2	Hydrogen/Oxygen Mixed Gas Inhalation for Coronavirus Disease 2019 (COVID-19)	Completed	Covid-19 Hydrogen/Oxygen Mixed Gas Dyspnea	Device: Hydrogen Oxygen Generator with Nebulizer Other: Standard-of-care	https://ClinicalTrials.gov/show/NCT04378712	China
3	Hydrogen-oxygen Gas Mixture Inhalation in Patients With Convalescent Coronavirus Disease 2019 (COVID-19)	Not yet recruiting	Covid19 Hydrogen-oxygen Gas AMS-H-03	Device: Hydrogen-Oxygen Generator with Nebulizer, AMS-H-03 Device: OLO-1 Medical Molecular Sieve Oxygen Generator	https://ClinicalTrials.gov/show/NCT04594460	China
4	Evaluation of the Daily Intake of 0.5 L of Water Saturated With Molecular Hydrogen for 21 Days in COVID-19 Patients Treated in Ambulatory Care	Recruiting	SARS-CoV-2 Covid19 AMBULATORY CARE	Dietary Supplement: MOLECULAR HYDROGEN Dietary Supplement: PLACEBO MAGNESIUM	https://ClinicalTrials.gov/show/NCT04716985	France Morocco Serbia
5	Hydrogen Therapy in Patients With Moderate Covid-19	Not yet recruiting	Covid-19	Drug: Mixture 3.6% H2 in N2 (96.4%)	https://ClinicalTrials.gov/show/NCT04633980	

response can proceed in a cyclical manner, wherein ROS promotes inflammatory response and inflammation produces more ROS. This is one of the mechanisms of parenchymal tissue damage in the patient (54). Therefore, hydrogen may exert its anti-inflammatory and antioxidant effects in the COVID-19.

PROSPECTIVE

Recently, there are other reviews analyzing the possibility of hydrogen as an adjuvant treatment to the COVID-19. Russell et al. concluded that hydrogen acts on a variety of pathways to exert its anti-inflammatory and antioxidant effects in the treatment of chronic inflammatory lung diseases. Therefore, it may alleviate the severe pulmonary symptoms of the COVID-19 (54). Russell et al. found that all the domains of life have an intrinsic biological need for hydrogen from the perspective of biological evolution and hydrogen plays a therapeutic role in a variety of respiratory diseases including the COVID-19 (11). Moreover, the COVID-19 has also been reported to induce Kawasaki-like disease, which occurs in children and leads to coronary artery damage. Chen et al. considered that hydrogen can improve macrophage function and reduce myocardial ischemia-reperfusion injury *via* its anti-inflammatory effect, which may be a therapeutic target for its treatment of Kawasaki-like diseases caused by the COVID-19 (55). COVID-19 could be served as virus-induced sepsis. The main reason for the patients with COVID-19 respiratory disorders is that SARS-CoV-2 attacks the pulmonary capillary endothelial cells and triggers an immune response. Massive cellular and mucus exudate accumulation cause airway obstruction and the patients experience dyspnea. Hydrogen may inhibit tissue damage by the inflammatory cells and inflammation factors at all the stages of the inflammatory response (**Figure 1**). Since hydrogen can play a potential antiviral effect such as hydrogen sulfide, it remains to be further studied (56).

However, as a novel medical gas molecule, hydrogen may have the following advantages in the treatment of the patients with the COVID-19: (1) Hydrogen can directly enter the lung tissue through respiratory activities. If inhaled in combination with oxygen, oxygen can be brought into the deeper bronchus space, reducing airway resistance, increasing oxygen dispersion, and improving the respiratory function of the patient; (2) Hydrogen has a selective antioxidant effect that neutralizes the hydroxyl radicals without affecting the functional reactive oxygen. When mixed with oxygen, the potential damage from the high concentrations of oxygen can be reduced; (3) After hydrogen enters the lung tissue, it exerts anti-inflammatory effects at the multiple stages of the inflammatory response, alleviating the airway damage caused by the excessive activation of the inflammatory cells and the massive release of inflammatory factors; (4) Hydrogen can be obtained by electrolyzing water and the raw materials of the reaction are cheap and the resources are extensive. The safety of inhaling hydrogen has been demonstrated in diving medicine (67) and the treatment of the patients with the COVID-19 has also begun to show the results. Another factor must also be taken into consideration: the potential of high-concentration hydrogen to cause an explosion ignited by static electricity (57). I hope that there will be more clinical evaluations on the safety of hydrogen in the future, which will lay the foundation for the clinical application of hydrogen. Furthermore, some clinical trials have been registered on inhalational hydrogen or oral HRW for patients with the COVID-19 in the WHO clinical trials registry[2] (**Table 1**). As adjunctive therapy, the mechanism of hydrogen alleviating the symptoms of the patients with the COVID-19 needs to be further clarified. At the same time, hydrogen has the potential safety concerns for the long-term treatment of diseases that needs further exploration.

AUTHOR CONTRIBUTIONS

YL wrote the first draft of the manuscript. WZ and YW wrote the section of the manuscript. ZW and KX contributed to manuscript revision. All authors contributed to the article and approved the submitted version.

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[2]World Health Organization. http://ClinicalTrials.gov

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