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COVID-19 related acute vascular distress syndrome: From physiopathology to treatment

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COVID-19 related acute vascular distress syndrome: From physiopathology to treatment

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Editorial: COVID-19 related acute vascular distress syndrome: from physiopathology to treatment

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COVID-19, SARS-CoV, AVDS, ARDS, intrapulmonary shunt, right ventricular function, ACE-2, dexamethasone

Editorial on the Research Topic
COVID-19 related acute vascular distress syndrome: from physiopathology to treatment

In the lungs, COVID-19, at least initially, is a vascular insult, leading to overperfusion of affected zones resulting in low VA/Q situation. These changes lead to hypoxia, and consequently to compensatory hyperventilation. Since CO_2 excretion is not affected due to its much higher solubility and to the linear characteristics of the CO_2 dissociation curve, hypocapnia develops, to a point where the respiratory centers do not respond to hypoxia anymore, resulting in the condition of hypocapnic hypoxia without respiratory distress that was termed "Happy Hypoxia". This corresponds to what we have identified with the acronym AVDS (Acute Vascular Distress Syndrome) (1). Later on, when the situation worsens and not only the vessels but also the lung parenchyma is involved, the resulting condition can be identified with the usual ARDS (Acute Respiratory Distress Syndrome) (2). It is worth mentioning that other physiologic mechanisms, somehow falling in oblivion in recent years, may also contribute to the phenomenon of "Happy hypoxia" (3).

Indeed, for us, COVID-19 patients, at any stages of their disease, are characterized by an increased pulmonary blood flow with intrapulmonary right to left shunt associated with alveolar injury of variable severity (2).

Nine articles have been accepted in this Research Topic that refers to different axes:

1. Physiopathology and risk factors

In their review, Cousin et al. have emphasized the role of angiotensin converting enzyme 2 (ACE_2) in the pathophysiology of SARS-CoV-2 infection. ACE_2 is widely expressed in lung vascular cells especially endothelial cells (composing the vessels structure) and pericytes (responsible of microvascular tone). The ACE_2 receptor permits the attachment of the virus. This ligation to the ACE_2 receptor causes its internalization and down-regulates the SARS-CoV-2 cellular entry. In such a case, the decrease in ACE_2 activity creates an imbalance that increases the level of angiotensin 2 which leads to the pro-inflammatory and pro-fibrotic situation responsible

of the severity of COVID-19. Patients with risk factors of baseline increased level of ACE_2 or ACE_2 imbalance (i.e.: male, overweight, diabetes mellitus, hypertension, chronic heart failure, etc...) are particularly exposed to severe forms of COVID-19.

Moreover, Bonato et al. evaluated in cohort study of COPD patients the risk factors of COVID-19. They found that the cardio-metabolic conditions were risk factor for developing COVID-19 (Bonato et al.). Interestingly, respiratory abnormalities (DLCO, emphysema) did not increase the risk of COVID-19 infection but were related to clinical outcome.

2. Bronchial hypervascularization

Pathological studies focusing on lung vasculature in COVID-19 patients have shown ultrastructural damage to the endothelium, the presence of SARS-CoV-2 in endothelial cells and more importantly pulmonary angiogenesis with vascular dilatations (4). In this Research Topic, Jounieaux et al. have shown that such vascular dilatations also concern the bronchial vasculature. The authors used narrow band imaging (NBI) during bronchovideoscopy to unveil bronchial hypervascularization during COVID-19 infection. This bronchial hypervascularization can explain not only some unexplained hemoptysis observed in COVID-19 patients but also, in part, the specific intrapulmonary shunt that we described in this viral infection as AVDS.

3. Thrombosis and pulmonary embolism

COVID-19 vascular involvement is also due to the coagulation impairment associated with SARS-CoV-2 infection with a high risk of venous thrombosis and pulmonary embolism. Kutsogiannis et al. compared patients with COVID-19 related ARDS and patients with ARDS related to other cause. They found that COVID-19 patients had a significant higher incidence of pulmonary embolism. Moreover, the authors found that a high level of D-dimer is a good predictor of PE in these patients. This COVID-19 related coagulopathy seems to involve not only the systemic pulmonary circulation but also portal circulation. Hence, Kheyrandish et al. reported a case series of portal thrombosis following COVID-19 infection or vaccination.

4. Cardiac involvement

Motloch et al. performed a one-year follow-up of patients hospitalized for COVID-19 pneumonia. They found that cardiovascular biomarkers (vascular cells adhesion molecule 1, serum soluble suppression of tumorgenity-2 and high-sensitive troponine I) were associated with mortality. Especially, they found that high-sensitive troponine I, a specific cardiac biomarker, might predict post-discharge mortality. This study emphasizes not only the vascular involvement but also the cardiac injury associated with this disease. In ICU COVID-19 patients, Beyls et al. have performed echocardiography to evaluate right ventricular function. They found that acute cor pulmonale (ACP) was more frequent in this disease even in non-intubated patients. ACP was not related to pulmonary embolism in the majority of patients but appears to be an independent risk factor of mortality.

5. Treatments

The beneficial effects of corticosteroids for hospitalized COVID-19 patients have been extensively proven regardless of the severity of the disease (5). Reindl-Schwaighofer et al. studied the effect of corticosteroids on ACE_2 and fibrin degradation on human volunteers. They showed that dexamethasone reduced ACE_2 upregulation and intra-alveolar markers of fibrinolysis. These findings may explain its beneficial role in COVID-19 (Reindl-Schwaighofer et al.). Regarding ventilatory support, Luján et al. have carried out a narrative review of 74 studies published during the pandemic. They reported that high-flow oxygen therapy, prone positioning and non-invasive ventilation have been extensively used for hypoxemia which appeared refractory to conventional oxygen therapy (Luján et al.). To date, the optimal approach is still debated and individualized strategy is needed.

6. Conclusion

All these articles published in the Research Topic untitled "*COVID-19 related acute vascular distress syndrome: from physiopathology to treatment*" in Frontiers in Medicine are consistent with the hypothesis early evoked during the pandemic (1). COVID-19 is indeed a vascular disease in which lungs vasculature (pulmonary and bronchial vessels) is impaired leading to intrapulmonary shunt and hypoxemia. This specific vascular injury is difficult to observe because it is hidden by concomitant alveolar lesions.

Author contributions

YM, DR, and VJ contributed in conducting the literature review and writing the manuscript. All authors have read and approved the final manuscript.

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.

Publisher's note

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BRIEF RESEARCH REPORT
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Risk Factors for Development and Severity of COVID-19 in COPD Patients

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The impact that COVID-19 could have on patients with COPD is a real concern. In this study we evaluated, in a cohort of longitudinally followed COPD subjects, the incidence of COVID-19, seeking for possible risk factors and prognostic factors predicting the clinical outcome. In our cohort of 370 patients (followed for 5.3 ± 2.7 years), 22 developed COVID-19 (COPD/COVID-19+) between February/November 2020 (5.9%). Cardio-metabolic conditions (hypertension, dyslipidemia, obesity, diabetes) but not respiratory abnormalities (FEV_1, DLCO, emphysema and exacerbation history), were risk factors for development of COVID-19 in COPD patients. Out of the 22 COPD/COVID-19+ patients, 10 needed intensive care. Low DLCO and emphysema, but also metabolic comorbidities, were related to the need for intensive care.

Keywords: COVID-19, COPD comorbidities, clinical outcome, emphysema, DLCO

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2, emerged in late 2019 in China and subsequently became a pandemic. SARS-CoV-2 may lead to pneumonia and respiratory failure. In Chronic Obstructive Pulmonary Disease (COPD) the underlying lung abnormalities, along with impairment of the immune responses to respiratory infections (1), might make these patients more susceptible to the development and severity of COVID-19.

The incidence of COPD in COVID-19 cohorts has been reported to range from 0 to 10% in China and 5.6–9.2% in Italy (2), although how the diagnosis of COPD was made was often unclear (3). However, the risk of patients with known COPD for the development of COVID-19 and its morbid consequences have not been clearly investigated. Underlying COPD may lead to respiratory failure, need for Intensive Care Unit (ICU) admission, mechanical ventilation or death (2).

This study was designed to: 1) evaluate the incidence of COVID-19 in a cohort of known COPD subjects followed longitudinally; 2) study the possible risk factors for the development of COVID-19; 3) identify the pathophysiological factors influencing the clinical outcome.

METHODS

The cohort included 370 subjects with COPD, diagnosed according to GOLD 2020 (4), all routinely followed in the COPD clinics at Padova University Hospital and Treviso City Hospital, Italy. All subjects provided written consent. The mean follow-up duration was 5.3 ± 2.7 years (date of first inclusion October 11th, 2012; date of last inclusion February

12th, 2019). Subjects with asthma or history of asthma were excluded. Subjects underwent yearly clinical evaluation including pulmonary function tests and blood cell count. High-resolution computed tomography (HRCT) was done at diagnosis. Annual frequency of exacerbations was recorded (4). We considered as COVID-19 cases all patients of the cohort who presented at the two public hospitals for symptomatic COVID-19 from February 21st until November 14th, 2020, whose SARS-CoV-2 infection was confirmed by real-time reverse transcription polymerase chain reaction from a nasopharyngeal swab/tracheal aspirate. Notification of cases was obtained by consultation of the electronic registry of all patients of the COPD cohort; inquiries were repeated every 4 weeks until November 14th, 2020. Clinical and functional data refer to the last follow-up visit for each patient before the pandemic outbreak.

In patients who developed symptomatic COVID-19, the following clinical outcomes were considered: disease severity, defined as the need for intensive care (ICU), length of hospitalization, in-hospital mortality and mortality at 6-months. Mann-Whitney, χ^2 and Fisher's exact-test were performed for comparisons between groups, as appropriate; bivariate correlations were estimated using Spearman's rank-correlation coefficient. Statistics were performed using SPSS (v26, IBM Armonk, NY, USA) (level of significance $p < 0.05$).

RESULTS

Twenty-two patients out of 370 (5.9%) developed COVID-19 (COPD/COVID-19+), while 348 did not (COPD w/o COVID-19). **Table 1** shows that age, gender, and smoking history were similar in the two groups and that COPD/COVID-19+ had a higher prevalence of cardio-metabolic comorbidities (obesity, hypertension, diabetes, dyslipidemia, metabolic syndrome) compared to COPD w/o COVID-19. Conversely, lung function, presence of emphysema (**Figure 1A**), history of exacerbations, COPD treatment and blood counts were similar in the two groups (**Table 1**).

Out of the 22 COPD/COVID-19+ subjects, 20 (90%) were hospitalized and 2 (10%) home treated. Among hospitalized

TABLE 1 | Demographic, functional and clinical characteristics of COPD subjects who developed COVID-19 (COPD/COVID-19+) and COPD subjects who did not (COPD w/o COVID-19).

	COPD/COVID-19+	COPD w/o COVID-19	*p*-value
Subjects, *n* (%)	22	348	–
Gender male, *n* (%)	16 (72)	247 (71)	n.s.
Age, years	79 (75–85)	77 (72–83)	n.s.
Smoking: current/ex/never, *n* (%)	4 (18)/18 (82)/0 (0)	94 (27)/243 (70)/11 (3)	n.s.
Smoking: pack-years	40 (19–51)	40 (22–51)	n.s.
Comorbidities, *n* (%)			
• Obesity	8 (36)	47 (14)	0.004
• Hypertension	22 (100)	207 (59)	<0.001
• Type 2 diabetes	9 (41)	62 (18)	0.002
• Dyslipidemia	14 (63)	76 (22)	<0.001
• Metabolic Syndrome	9 (41)	45 (13)	<0.001
FEV_1, %pred.	69 (54–90)	67 (51–86)	n.s.
FEF_{25-75}, %pred.	36 (27–54)	28 (18–44)	n.s.
DLCO, %pred.	45 (32–85)	71 (50–84)	n.s.
Blood eosinophils, cells/μL	120 (37–262)	180 (100–267)	n.s.
Blood lymphocytes, cells/μL	1,820 (1,445–2,302)	1,860 (1,430–2,427)	n.s.
AE in the previous year, *n*	0 (0–1)	0 (0–1)	n.s.
Emphysema on CT-scan*, *n* (%)	12 (60)	133 (58)	n.s.
	n = 20	*n* = 226	
Inhaler therapy, *n* (%)			
• None	4 (18)	16 (5)	n.s.
• LAMA or LAMA/LABA	9 (41)	164 (47)	n.s.
• LAMA/LABA/ICS or LABA/ICS or LAMA+LABA/ICS	9 (41)	168 (48)	n.s.

Data refer to the last visit available before COVID-19.

Data are expressed as median (interquartile range) or absolute numbers (percent). The p-value is referred to the Mann-Whitney-U or Fisher Exact-tests comparisons, as appropriate.

**Data available on 246 out of 370 patients.*

FEV_1, Forced Expiratory Volume in the 1st s; FEF_{25-75}, forced mid-expiratory flow; DLCO, diffusing capacity of the lung for carbon monoxide; AE, acute exacerbations; CT, computed tomography; LAMA, long acting muscarinic antagonist; LABA, long-acting beta2-agonist; ICS, inhaled corticosteroid.

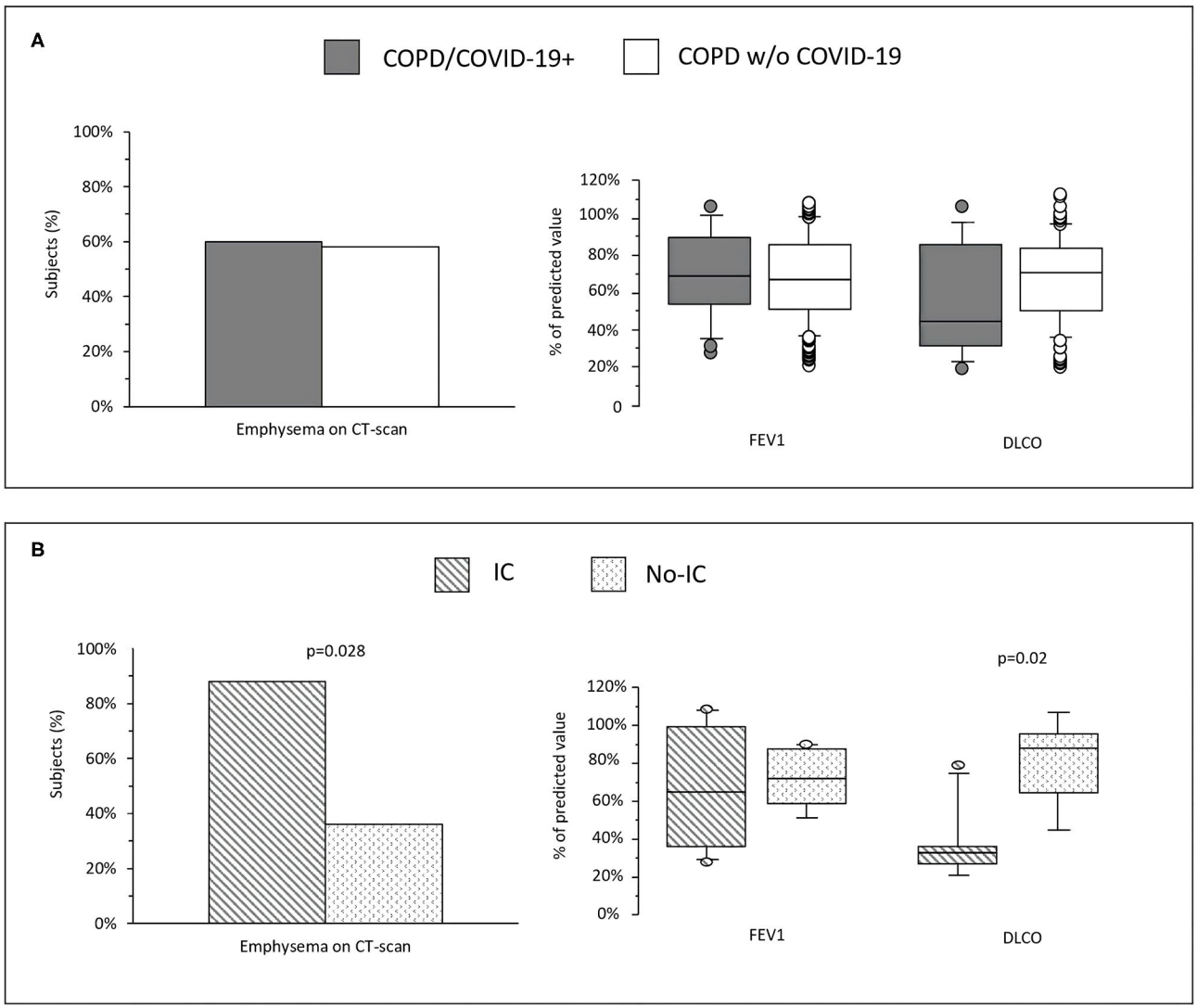

FIGURE 1 | (A) Prevalence of emphysema and values of FEV_1 and DLCO in COPD who developed COVID-19 (COPD/COVID-19+) and COPD without COVID-19 (COPD w/o COVID-19). **(B)** Prevalence of emphysema and values of FEV_1 and DLCO in COPD/COVID-19+ subjects who needed intensive care (IC) and in those who did not (No-IC).

patients, 10 (50%) needed ICU. **Table 2** shows the characteristics of subjects needing (IC) or not needing ICU (No-IC). Dyslipidemia and metabolic syndrome were significantly more prevalent in IC patients than in No-IC. FEV_1 was not related to the need for ICU, however IC subjects had lower DLCO at baseline and higher prevalence of emphysema (**Figure 1B**). When first seen at Emergency Room, PaO_2/FiO_2 Ratio was the only parameter associated to IC and it was inversely related with hospitalization length ($r = -0.63$; $p = 0.013$) (**Table 2**). In hospital mortality rate was 18.1% (4/22), three patients died in IC and 1 in No-IC. Among in-hospital deceased patients, 3 of 4 had emphysema and a very low DLCO (median 35%pred.) even if with mild obstruction (median FEV_1 76%pred). At 6-months, follow-up mortality raised to 36.3% (8/22), 4 patients in IC group (40%), 4 in no-IC (33.3%).

DISCUSSION

Our study shows that the incidence COVID-19 in a cohort of longitudinally followed COPD subjects, was 5.9% [the incidence in Italian population older than 60 years in the same period was 2.8% (5)]. To our knowledge, this is the first time the incidence of COVID-19 in a cohort of COPD patients is described. Only the incidence of COPD in COVID-19 cohorts had been previously reported (2). Despite the small sample size, longitudinal data before COVID-19 allowed

TABLE 2 | Demographic, functional and clinical characteristics of COPD subjects who developed COVID-19 categorized in subjects who needed intensive care (IC) and in those who did not (No-IC).

	COPD/COVID-19+		*p*-value
	IC	**No-IC**	
Subjects, *n* (%)	10	12	
Gender male, *n* (%)	7 (70)	9 (75)	n.s.
BASELINE			
Age, years	78.2 (75.9–80)	79 (72–86)	n.s.
Smoking: current/ex, *n* (%)	2 (20)	2 (16)	n.s.
Smoking: pack-years	45 (32–57.5)	32 (15–45)	n.s.
Comorbidities, *n* (%)			
• Obesity	6 (60)	2 (16.6)	n.s. (0.074)
• Hypertension	10 (100)	12 (100)	n.s.
• Type 2 diabetes	6 (60)	3 (25)	n.s. (0.1)
• Dyslipidemia	9 (90)	5 (41.6)	0.032
• Metabolic Syndrome	7 (70)	2 (16.6)	0.027
FEV_1, %pred.	65 (36.5–99.5)	72 (58.7–87.7)	n.s.
FEF_{25-75}, %pred.	39 (28–77)	36 (26–52.7)	n.s.
DLCO, %pred.	32 (28–35)	88 (64.5–95.7)	0.02
Blood eosinophils, cells/μL	110 (10–270)	120 (90–205)	n.s.
Blood lymphocytes, cells/μL	1,755 (1,450–2,290)	1,820 (1,440–2,325)	n.s.
AE in the previous year, *n*	0.5 (0–2)	0 (0–0.5)	n.s.
Emphysema on CT-scan, *n* (%)*	8 (88.8)	4 (36.3)	0.028
	$n = 9$	$n = 11$	
Inhaled therapy, *n* (%)			
• None	1 (10)	3 (25)	n.s.
• LAMA or LAMA/LABA	5 (50)	4 (33)	n.s.
• LAMA/LABA/ICS or LABA/ICS or LAMA+LABA/ICS	4 (40)	5 (42)	n.s.
ON ADMISSION			
P/F ratio	180 (124–296)	310 (262–364)	0.02
C-Reactive protein, mg/dl	39 (18–117)	43 (17–130)	n.s.
D-dimer, ng/L	238 (167–669)	258 (181–596)	n.s.
BNP, ng/L	224 (94–319)	174 (100–201)	n.s.
Blood lymphocytes, cells/μL	815 (570–1,590)	695 (610–890)	n.s.
OUTCOME			
Hospitalization length, days (all patients)	21 (8–46)	8.5 (6–11.12)	0.05
Hospitalization length, days (discharged alive only)	36 (13.7–53.5)	8 (5.25–10.5)	0.01
In-hospital mortality, *n* (%)	3 (30)	1 (8)	n.s.
6-month mortality, *n* (%)	4 (40)	4 (33)	n.s.

Baseline data refer to the last visit available before COVID-19.

Data are expressed as median (interquartile range) or absolute numbers (percent). The p-value is referred to the Mann-Whitney-U or Fisher Exact tests comparisons as appropriate.

**Data available on 20 out of 22 patients. IC: subjects who needed intensive care. No-IC: subjects who did not need intensive care.*

FEV_1, Forced Expiratory Volume in the 1st s; FEF_{25-75}, forced mid-expiratory flow; DLCO, diffusing capacity of the lung for carbon monoxide; AE, acute exacerbations; CT, computed tomography; LAMA, long acting muscarinic antagonist; LABA, long-acting beta2-agonist; ICS, inhaled corticosteroid; P/F, PaO_2/FiO_2 ratio; BNP, brain natriuretic peptide.

the evaluation of the possible risk and prognostic factors in our cohort.

Among the possible risk factors for the development of COVID-19, we found that patients who developed COVID-19 had higher prevalence of hypertension, obesity, type-2 diabetes and dyslipidemia than those who did not. It is noteworthy that, even in a cohort where comorbidities are highly frequent, their prevalence was still significantly higher in subjects who developed COVID-19. This was particularly relevant for hypertension, that was present in all COVID-19+ subjects, reinforcing the known association between this comorbidity and COVID-19 (6). Of interest, we found that functional and respiratory risk factors (FEV_1, DLCO, exacerbations) were not associated to development of COVID-19 in COPD patients.

When the prognostic factors predicting the severity of COVID-19, defined as the need for intensive care, were assessed,

we found that the presence of metabolic comorbidities was associated with more severe COVID-19, as in the general population (7). In addition, we observed that the presence of emphysema and low DLCO were associated with the need for ICU, while FEV_1 was not. Our observations suggest that, in a context of mild-moderate airflow obstruction, the severity of COVID-19 could be dependent on a decreased DLCO, which reflects a previous impairment of the alveolar-capillary unit secondary to impaired perfusion due to microvascular destruction in emphysema and to compression of the intra-alveolar pulmonary vessels by gas trapping, rather than on the degree of airflow obstruction. The vascular abnormalities reflected by the DLCO in COPD would compound the severity of COVID-19, a disease with an important pulmonary vascular disorder with diffused micro thrombosis or intrapulmonary shunting inducing what has been defined an acute vascular distress syndrome (AVDS) (8). Indeed, there is increasing evidence that the virus can assault directly the capillary endothelium causing diffused micro thrombosis, destroying the lung vascular bed and increasing the dead space (9). Of interest, in a recent follow-up of COVID-19 subjects, patients hospitalized with severe disease had lower DLCO at 3–4 months post-infection compared to those non-hospitalized, probably reflecting the SARS-CoV-2 induced pulmonary vascular disorder, while the FEV_1 was similar (10). Unfortunately, no baseline DLCO was available. If COVID-19 worsens DLCO, it would be expected that a low baseline DLCO ought to be an important risk for severe respiratory failure. Our data points to the value of a baseline DLCO in patients with COPD as a useful predictor of the disease outcome.

Our study has some limitations: first the small sample size did preclude more extensive analyses. Furthermore, our study included only patients presenting at the hospitals for symptomatic COVID-19, which relates to the high hospitalization rate observed in these patients. Although we cannot exclude that mild symptomatic patients were tested outside the public health system, it seems unlikely that patients with chronic respiratory diseases would seek medical care outside of their referral center. Finally, the characterization of our cohort is based on data collected during the routine assessment of COPD patients at outpatient clinics, therefore we did not have any standardized emphysema quantification on CT scan.

In conclusion, in our cohort of COPD subjects, 5.9% developed COVID-19. Cardiometabolic, but not respiratory abnormalities, were risk factors for the development of COVID-19. A low DLCO and the presence of emphysema, but not FEV_1, were prognostic factors for worse outcomes of COVID-19 in COPD. These results highlight the importance of preventive measures and social distancing in patients with COPD with cardiometabolic comorbidities, at risk of developing COVID-19. Moreover, in COPD patients with COVID-19, a low DLCO and emphysema herald unfavorable outcomes, which advises close monitoring in these subjects.

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

MB, US, MR, GT, MC, MS, and SB: contributed to conception and design of the study and drafting, and editing the manuscript. MT, EB, MD, DB, and AC: undertook data collection and performed data analysis. MB, US, EB, MR, GT, MC, MS, and SB: data management and data interpretations. All authors critically revised the manuscript for important intellectual content and approved the final version.

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Pathophysiology of COVID-19: Everywhere You Look You Will See ACE_2!

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Angiotensin converting enzyme 2 (ACE_2) seems to be a central actor in the pathophysiology of SARS-Cov-2 infection. First, it acts as the receptor for the virus and permits its attachment to cells expressing ACE_2. Second, the relative deficiency of ACE_2 during infection could be linked to several clinical features encountered during the disease, like ARDS and coagulation abnormalities. This study explores the strong link between ACE_2 and the majority of risk factors for the severe evolution of COVID-19. It seems that all these risks factors are linked to an increased level of ACE_2 and/or imbalance in ACE/ACE_2.

Keywords: pathophysiology, COVID-19 pandemic, angiotensin-converting enzyme, SARS – CoV – 2, bradykinin - analogs and derivatives, lung injury

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INTRODUCTION

COVID-19 is a worldwide progressing pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus type 2 (SARS-CoV-2). Present pneumonia (pneumonitis) is an acute respiratory illness associated with a new droplet-borne SARS-CoV-2, which caused the global population to be put under lockdown, with many patients clustered in hospitals. It has a wide spectrum of clinical severity, ranging from asymptomatic to fatal outcomes. The virus possesses 4 main structural proteins: spike, membrane, envelope, and nucleocapsid (1). Of special interest for our discussion is the spike protein, which attaches to human cells through the angiotensin converting enzyme 2 (ACE_2) (2). Such a mechanism is common in the two SARS virusus (1, 3). Following host cell binding, with the priming by the transmembrane serine protease 2 (TMPRSS2) and other proteins, the virus and cell membrane fuse, enabling the virus to enter the cell and infect it (1). These interactions with the SARS-CoV-2, ACE_2 play a crucial role in viral pathology since it is the viral receptor that provides the opportunity for the virus to invade cells expressing such enzymes. Other than this role as a viral receptor, the physiological role of ACE_2 is crucial, as it reduces angiotensin 2 levels (breakdown) and so plays a role as a regulator in the renin angiotensin system balance.

ACE_2 ROLE AND IMPACT OF DYSREGULATION

ACE2 has been known for 20 years and has brought major insight to understanding of the complex renin-angiotensin system (RAS) (4, 5). ACE_2 is an enzyme, a carboxypeptidase, which cleaves angiotensin 1 into angiotensin 1–9 and angiotensin-2 into angiotensin 1–7 (6). Through those reactions, ACE_2 plays a crucial role as a regulator of the RAS. If they are both peptidases, ACE and ACE_2 have a different active site and the two enzymes manage to counterbalance each other (5, 7).

ACE_2 reduces the level of angiotensin 2, thereby reducing its capacity of action as a potent vasopressor and pro-inflammatory signal (6). Furthermore, ACE_2 products, mostly angiotensin 1–7, act through a specific pathway to counter angiotensin 2 and mitigate the action of the ligation between angiotensin 2 and the receptor AT1R. The two receptors are of main importance for these pathways. The AT2 receptor (AT2R), Mas receptor (MasR) and induced vasodilation have anti-fibrotic and anti-inflammatory properties (8). Another role of ACE_2 is the cleavage of other bioactive peptides than angiotensin and especially bradykinin, more precisely des-Arg-Bradykinin (9, 10). Bradykinin, especially des-Arg-Bradykinin, binds bradykinin receptor B1 (BKB1R). Ligation to BKB1R induces the release of inflammatory chemokines. It has a role in vasodilatation, cellular proliferation, and fibrosis (9, 11). There is also an intricate role of bradykinin with the coagulation and the complement activation (9, 12). All the present findings emphasize the particular vascular features of COVID-19 disease. In this regard, the authors believe that Acute Vascular Distress Syndrome (acronym "AVDS") seems to be more appropriate for COVID-19 than the usual ARDS (acute respiratory distress syndrome) acronym (13).

ACE_2 is widely expressed inside organs, including, in the lungs, cardiovascular system, gut, kidneys, central nervous system, and adipose tissue. As a result of these roles, it is currently thought that ACE_2 plays a major role as a cardioprotective actor. It has been linked to several situations of heart failure, hypertension, pulmonary hypertension, diabetes, and acute respiratory distress syndrome (5). ACE_2 has well-described associations with better outcomes in the case of cardiac dysfunction and is linked to cardiac fibrosis and inflammation in several studies (5). Moreover, angiotensin 1–7 seems to play a protective role in diabetic cardiomyopathy and nephropathy (14, 15). In this regard, increased expression of ACE_2 protects against hypertension (5). ACE_2 is also strongly involved in acute pulmonary lesions and fibrosis, as a protector, by inducing an imbalance against RAS hyper activation (5, 16).

As we have seen, the cardioprotective effect of ACE_2 could be attributed to several mechanisms, including the degradation of angiotensin 1 and angiotensin 2, and so limits activation of AT1R, production of angiotensin 1–7 and 1–9, which have a direct cardioprotective role, and also contributing to the degradation of bradykinine and thereby limiting its pro-inflammatory effects.

ACE_2 AND COVID-19 INFECTION SEVERITY

There are several described risk factors for the severe evolution of COVID-19, summarized in **Table 1**. The earliest studies on the subject clearly showed such an association (17, 18). An important fact to underline is the strong link between ACE_2 and the majority of these risk factors. It seems that all these risks factors are linked to an ACE_2 increased level and/or imbalance in ACE/ACE_2. A study dosing the soluble ACE_2, as a surrogate marker for the level of ACE_2, showed significantly increased amounts of soluble ACE_2 in patients with diabetes, heart failure, older age, and male gender (19). It could be suggested that such a situation, with an increased ACE_2 at baseline due to an already imbalanced RAS, may be prone to more severe SARS-CoV-2 infection (20). Hypertension was very early reported as a risk factor for fatal outcomes in COVID-19 (21, 22). Hypertension may be linked to a state of hyper activation of ACE_2 to counter regulate the high blood pressure, meaning these patients have a higher number of targets for the virus to attach to. Male gender is also a risk factor for more severe COVID-19 (23). It could be linked to the potential impact of sex hormones on ACE_2 expression, RAS balance, or a difference in the proportion of comorbidities (24). As an illustration, ACE_2 could be found in higher concentrations in the sputum of asthmatic men or plasma of male patients with cardiac failure (25, 26). Patients of Black ethnicity are also at risk of severe COVID-19 and death from COVID-19 (27, 28). However, such risk is currently not well understood, as even if a higher proportion of patients are hospitalized or have fatal outcomes, patients of Black ethnicity seem to have a higher risk when adjusted for multiple factors (28). Patients from Black ethnicities often have comorbidities such as diabetes or hypertension, risk factors that have already been described for severe COVID-19 (28). Moreover, social disparities such as disadvantages in housing and more globally systemic structural disadvantages put such a population at higher risk. This may explain the increased risk for patients of Black ethnicities. Another reason for these comorbidity and population characteristics is that a potential risk factor for severe COVID-19 is decreased levels of ACE_2 at baseline.

TABLE 1 | Risk factors for severe SARS-CoV-2 infection.

Overweight
Black ethnicity
Diabetes mellitus
Hypertension
Chronic heart failure
Male

Table depicting major risks factors for severe COVID-19, all of them linked to a baseline situation at risk linked to increased level ACE2 and/or baseline imbalance in ACE/ACE2 index. Clockwise from the top, these include being overweight, patients of Black ethnicity, diabetes mellitus, hypertension, cardiac failure, and male gender.

An interesting paper by Peters et al. on COVID-19 related gene expression in the sputum in asthmatic patients discusses these points of view (25). Patients of Black ethnicities seem to have an increased expression of ACE_2 in sputum cells, along with male gender and diabetic patients. This raises the question of specific risk linked to increased ACE_2 in Black people. However, the link between COVID-19, ethnicity, and prognosis remains difficult to prove, as underlined by the recent study of Colarusso et al. (9). The authors showed that if Black ethnicities were admitted to ICU they died more frequently during the first "wave". This was not obvious during the second wave, as the authors only had an increased risk of ICU admission without an increase in mortality (29). These papers underline the already discussed risk factors

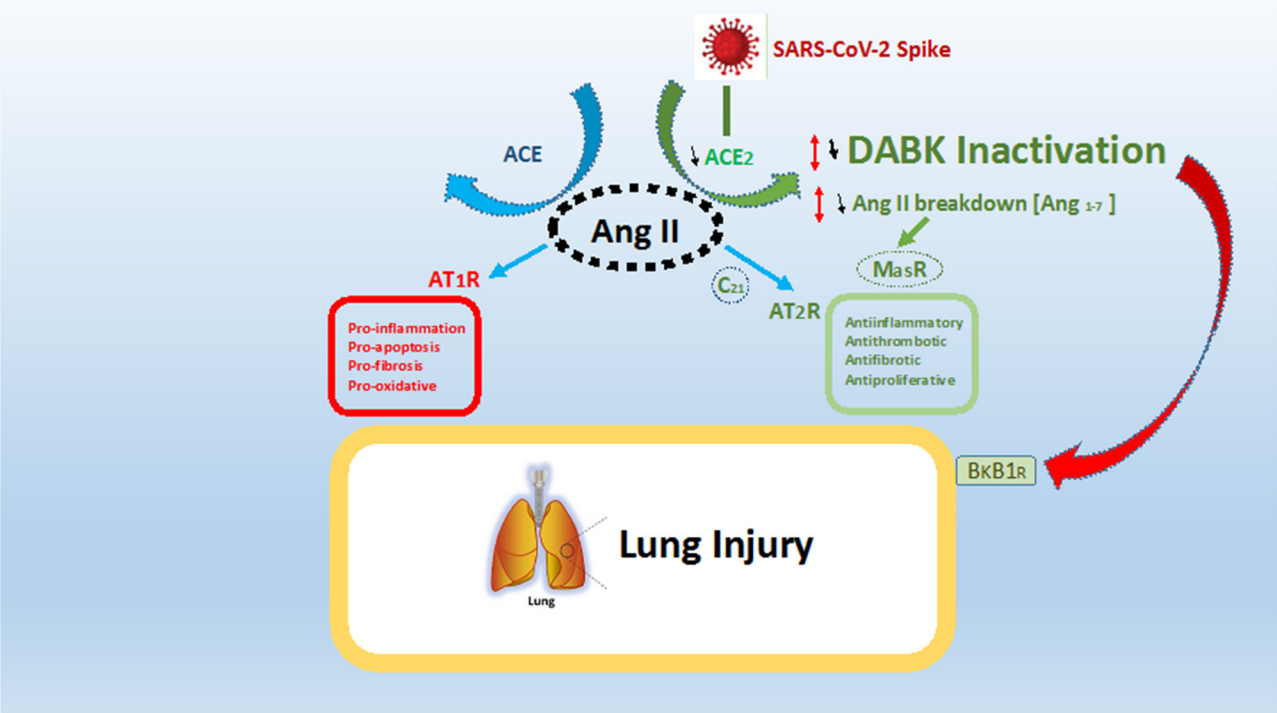

FIGURE 1 | ACE/ACE2 imbalance and effect in case of SARS-CoV-2 infection. SARS-CoV-2 spike protein ligates angiotensin conversion enzyme 2 (ACE_2) and leads to a relative deficiency in ACE_2. Such deficiency leads to both an imbalance in the ACE/ACE_2 system and an over activation of the ACE pathway with over production of angiotensin 2 (Ang II) ligating the receptor AT1R. The present fact leads to a global pro-inflammatory, pro-fibrotic, and pro-oxidative state (in red). ACE_2, through degradation of Ang II to angiotensin 1–7, leads to both a decrease in Ang II levels and stimulation of anti-inflammatory and anti-fibrotic pathways *via* AT2R and MasR (in green). Moreover, ACE_2 inactivate des-Arg-Bradykinin (DABK), which in the case of ligation to receptor Bradykinine-B1-receptor (BkB1R) leads to inflammation and vascular permeability (red arrow). In this regard, the final result of ACE_2 deficiency is both the promotion of lung inflammation and a decrease in lung anti-inflammatory effects, inducing SARS-CoV-2 acute respiratory syndrome.

of male gender and diabetes. Being overweight and obese, are also risk factors. It is common knowledge that obesity is linked to hypertension, diabetes, and heart failure, as already discussed. Moreover, obese patients may have a pro-inflammatory state, predisposing them to a higher impact of RAS imbalance (11).

An important question is the place of treatment for hypertension targeting the ACE, including ACE-inhibitors of Angiotensin receptor blockers. Such treatment is deeply linked to the RAS and has been used in a large proportion of patients with hypertension, diabetes, or obesity, as all these comorbidities are often associated. Interestingly, these medications were linked to less severe disease (and even better outcome) in pneumonia related to influenza infection and so raised the question of their role in COVID-19 infection (30–32). However, such benefits for COVID-19 patients undergoing pneumonia treatment are currently unproven and unfounded (33, 34).

In focussing on ACE_2, we see that all these risk factors could be linked to the more severe features of COVID-19 disease. There are populations for which specific research needs to be done in order to investigate the impact of ACE_2 and therapy aiming at restoring the RAS balance.

IMPACT OF COVID-LINKED ACE_2 DYSREGULATION

In case of a SARS Cov-2 infection, there is ligation of the virus to ACE_2 with its spike protein. Such ligation to ACE_2 caused its internalization and down-regulation following SARS-CoV-2 cellular entry (6, 11). In such a case, the decrease in ACE_2 activity creates an imbalance in signaling by ACE_1 and ACE_2 due to deficiency in ACE_2. As we discussed earlier, such decreases in ACE_2 lead to an imbalance, where angiotensin 2 is the main actor, as shown in **Figure 1**.

A higher level of angiotensin 2 is linked to the pro-inflammatory and pro-fibrotic situation after ligation to AT1R. Moreover, a severe decrease in ACE_2 has a double effect: first, there is a decrease of Angiotensin 1-7, lowering activation of the MasR or AT2R, which impedes anti-inflammatory and anti-proliferation pathways (4, 5, 7). Second, there is an increase of D-Arg bradykinin, with inflammatory and vasoactive properties

through BKB1R (9, 11). This finally leads the RAS equilibrium to imbalanced conditions characterized by pro-inflammatory, pro-apoptosis, and pro-oxidative states. Moreover, the deregulation of RAS, especially in patients who already are in a state of ACE/ACE_2 imbalance, could lead to more severe COVD-19 (5).

If we look specifically at the lung, ACE_2 deficiency is known to be linked to acute lung injury. It has a role in limiting the angiotensin 2 hypoxic vasoconstriction but also pro-fibrotic and inflammatory effect, both meet in case of severe SARS-CoV-2 acute respiratory distress syndrome (1, 7, 11). Diminished levels of ACE_2 and an imbalance in the ACE/ACE_2 system could be a major factor in the outcome of COVID-19, as previously noted in laboratory experimentation on acute lung injury. The effect of imbalance could also explain the significant impact of severe SARS-CoV-2 infection on several systems, especially cardiovascular, including systemic endothelitis, renal, and coagulation (1, 7, 11, 35, 36).

In other pulmonary infections, ACE_2 and angiotensin II were also studied and potentially linked to disease severity. In particular, influenza infection, in which a link between ACE_2 deficiency and lung injury severity has been observed (37, 38). Moreover, increased levels of Angiotensin-II in a patient with severe influenza infection or coxsackie virus, emphasized the key role of ACE_2 in other viral lung infections leading to ARDS (39). The role of the RAS system in potential lung cytokine storm and fibrosis could explain such an association between ACE_2, the RAS system, and viral ARDS (39, 40).

To conclude, ACE_2 seems to be a central actor in the pathophysiology of SARS-Cov-2 infection. First, it acts as the receptor for the virus and permits its attachment to cells expressing ACE_2. Second, the relative deficiency of ACE_2 during infection could be linked to several clinical features encountered during the disease, such as ARDS, vascular inflammation, and coagulation abnormalities (41, 42). Further research is needed to better understand the role of ACE_2 in virus pathophysiology and ACE_2 as a potential therapeutic target. In this regard, a soluble form of ACE_2 may both slow viral entry into cells by competitively binding with SARS-CoV-2 and protect the lung from injury through its unique enzymatic function (2).

AUTHOR CONTRIBUTIONS

KB contributed to the conception and design of the review and **Figure 1**. VC design and first draft. RG designed **Table 1**. All authors contributed to manuscript revision, and read and approved the submitted version.

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CASE REPORT
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Case Reports: Bronchial Mucosal Vasculature Is Also Involved in the Acute Vascular Distress Syndrome of COVID-19

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Background: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which targets the pulmonary vasculature is supposed to induce an intrapulmonary right to left shunt with an increased pulmonary blood flow. We report here what may be, to the best of our knowledge, the first videoendoscopic descriptions of an hypervascularization of the bronchial mucosa in two patients hospitalized for coronavirus disease 2019 (COVID-19) pneumonia.

Cases Presentation: Two patients, 27- and 37-year-old, were addressed to our Pneumology department for suspicion of COVID-19 pneumonia. Their symptoms (fever, dry cough, and dyspnoea), associated to pulmonary ground glass opacities on thoracic CT, were highly suggestive of a COVID-19 disease despite repeated negative pharyngeal swabs RT-PCR. In both patients, bronchoscopy examination using white light was unremarkable but NBI bronchoscopy revealed a diffuse hypervascularization of the mucosa from the trachea to the sub-segmental bronchi, associated with dilated submucosal vessels. RT-PCR performed in bronchoalveolar lavage (BAL) confirmed the presence of Sars-CoV-2.

Conclusions: These two case reports highlight the crucial importance of the vascular component of the viral disease. We suggest that such bronchial hypervascularization with dilated vessels contributes, at least in part, to the intrapulmonary right to left shunt that characterizes the COVID-19 related Acute Vascular Distress Syndrome (AVDS). The presence of diffuse bronchial hypervascularization in the context of COVID-19 pandemic should prompt the search for Sars-CoV-2 in BAL samples.

Keywords: SARS-CoV-2, bronchovideoscopy, NBI (narrow band imaging), intrapulmonary shunt, AVDS

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The presence of diffuse endobronchial submucosal vessels dilation and proliferation, not described until now in coronavirus disease 2019 (COVID-19) disease, was demonstrated using narrow band imaging during diagnostic bronchoscopy in two patients with negative pharyngeal swabs RT-PCR. This unusual finding may prove of value in assessing patients without confirmatory laboratory data. These two case reports show how narrow band imaging (NBI) can help in the

diagnosis of COVID-19 disease by showing diffuse endobronchial submucosal vessels dilatation and proliferation and demonstrating an unknown bronchoscopic vascular aspect of COVID-19-related Acute Vascular Distress Syndrome (AVDS).

CASE REPORT #1

A 37-year-old man was hospitalized for suspicion of COVID-19 pneumonia on January 27, 2021. This non-smoker and athletic patient was only treated for hypertension (Ibesartan) and worked as a host in a nursing home where a COVID-19 cluster raged at this time. His symptoms began on January 17, with fever, dry cough, dyspnoea, headache, myalgia, diarrhea. In this context, the patient underwent two RT-PCR pharyngeal swabs (January 18, 2021 and January 21, 2021) that were negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The symptoms persisted despite a prescription of amoxicillin and he was addressed to our university hospital. The patient presented with fever (39°C), asthenia, headache, and dyspnea. On clinical examination the BMI was 26 kg/m²; blood pressure 135/80 mmHg; crackles were heard bilaterally, and the transcutaneous O2 saturation was 92%. Laboratory tests: WBC = 3,900 cells/mm^3 (57% neutrophils, 32% lymphocytes), CRP: 14.7 mg/L, normal d-dimer value (0.38 µg/ml), arterial blood gas while breathing room air: pH, 7.45; PaO_2, 59.9 mm Hg; and $PaCO_2$, 36.4 mm Hg. Thoracic computed tomography (CT) showed mild evidence of pulmonary lesions related to COVID-19 (15% lung involvement by ground glass opacities). A third pharyngeal swab RT-PCR (January 27, 2021) was negative as well as the blood hemocultures. A diagnostic bronchoalveolar lavage (BAL) was proposed, and performed on January 28 (Olympus bronchovideoscope BF-H190, Tokyo, Japan), 12 days after the onset of symptoms. Bronchoscopy examination using white light (WL) was unremarkable without any abnormal aspect of the bronchial mucosa except a striking unusual presence of bronchial vessels. Narrow band imaging (NBI) bronchoscopy revealed a diffuse hypervascularization of the mucosa from the trachea to the sub-segmental bronchi, associated with dilated submucosal vessels which were developed on the axis of the bronchi (**Figures 1A,B**). Bronchoalveolar lavage (BAL) was performed in RB4 and its RT-PCR analysis confirmed the presence of SARS-CoV-2. The patient received cefotaxim and dexamethasone during 6 days. He became apyretic with an O_2 saturation of 100% and returned home on February 2, 2021.

CASE REPORT #2

A 27-year-old man was hospitalized for suspicion of COVID-19 pneumonia on April 9, 2021. This non-smoker was only treated for hypertension for 10 years (Manidipine) and teleworked as a butcher's instructor. He was married and was the father of a 9-month child. His symptoms began on March 30 with asthenia, headache, and dizziness. The patient underwent a COVID-19 rapid test followed by a pharyngeal swab RT-PCR (April 1, 2021) which was negative for SARS-CoV-2. The symptoms worsened with diarrhea, dry cough, persistent fever despite a prescription of amoxicillin (April 7, 2021), and finally dyspnoea. He was then addressed to our university hospital. The patient presented with fever (38.4°C), diarrhea, and dyspnea at rest. On clinical examination the BMI was 29.8 kg/m²; blood pressure 140/78 mmHg; pulmonary auscultation was unremarkable and the transcutaneous O_2 saturation was 93%. Laboratory tests: WBC = 7,800 cells/mm^3 (85.5% neutrophils, 10.5% lymphocytes), CRP: 96.6 mg/L, d-dimers:.85 µg/ml, arterial blood gas while breathing room air: pH, 7.49; PaO_2, 65 mm Hg; and $PaCO_2$, 29.1 mm Hg. Thoracic computed tomography (CT) showed mild evidence of pulmonary lesions related to COVID-19 (10–25% lung involvement by ground glass opacities). A second COVID-19 rapid test was negative as well as the second pharyngeal swab RT-PCR (April 9, 2021). Blood hemocultures were negative. A diagnostic BAL was proposed and performed on April 10 (Olympus bronchovideoscope BF-H1100), 12 days after the onset of symptoms. Bronchoscopy examination using WL was unremarkable except the unusual presence of bronchial vessels. NBI bronchoscopy revealed a diffuse hypervascularization of

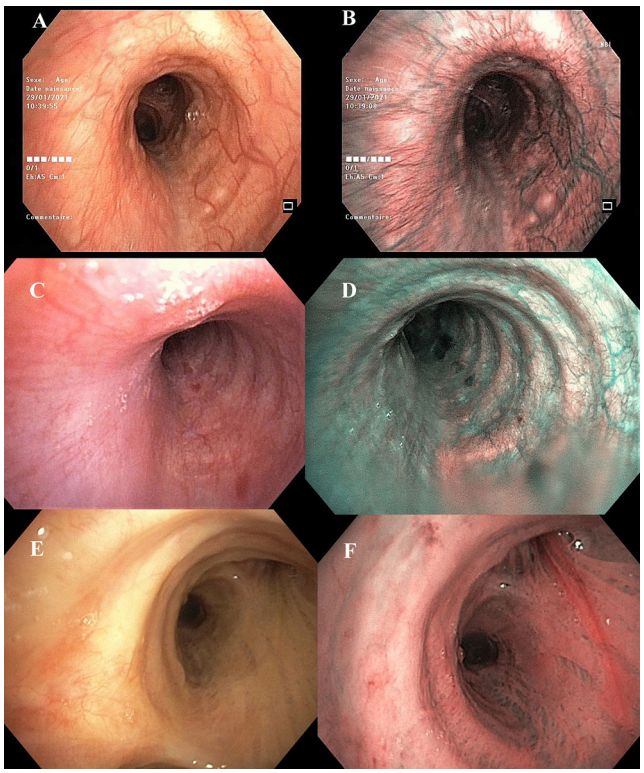

FIGURE 1 | Case report patient #1–Left main bronchus **(A)** white-light, **(B)** Narrow band imaging (NBI) of the same region. Case report patient #2—Left main bronchus **(C)** white-light, **(D)** NBI of the same region. These images show in patients #1 and #2 a bronchial hypervascularization with dilated vessels. Note that in patient #1 the heavy dilated bronchial vessels developed on the axis of the bronchus, without any concomitant bronchial abnormalities. Patient #3—Right main bronchus **(E)** white-light, **(F)** NBI of the same region. These images show an example of the bronchial vascularization in a 77-year-old male patient hospitalized for a non-COVID-19 infection.

the mucosa from the trachea to the sub-segmental bronchi, associated with dilated submucosal vessels (**Figures 1C,D**). BAL was performed in LB4 and its RT-PCR analysis confirmed the presence of SARS-CoV-2. The patient received cefotaxim for 5 days. He became apyretic with an O_2 saturation of 98% and returned home on April 15, 2021.

DISCUSSION

These two cases reported present the first application on bronchovideoscopic NBI to patients with COVID-19, showing a diffuse hypervascularization of the mucosa from the trachea to the sub-segmental bronchi. NBI is generally used in malignant but also, and more, in premalignant airway lesions to detect focal bronchial hypervascularization. Observation of a diffuse hypervascularization with dilated submucosal vessels in patients with COVID-19 is a novel finding which supports the known neo-angiogenesis that leads to an intrapulmonary shunt during COVID-19 infection.

The circulation of the bronchial wall—composed of two different networks (mucosal and submucosal) connected by penetrating vessels—is essential to maintain the homeostasis by conditioning the inspired air (1). The bronchial vessels supply intrapulmonary airways as far as the terminal bronchioles to form anastomoses with the pulmonary vasculature. Two-thirds of the bronchial vein drainage return to the left atrium through the pulmonary veins whereas one- third returns to the right atrium through the azygous vein and superior vena cava (2). NBI is a recent endoscopic technique designed for the detection of pathologically altered submucosal and mucosal microvascular patterns. NBI uses two narrow-bands of light (400–430 and 525–550 nm, respectively). The blue narrow band (390–445 nm) is absorbed by surface mucosal layer capillaries whereas the green narrow band (530–550 nm) is absorbed by the hemoglobin in the deeper submucosal thick blood vessels (3). Their combination allows a detailed image of superficial bronchial vascularization. The combination of magnification video bronchoscopy and NBI has showed great potential in the detection of precancerous and cancerous lesions of the bronchial mucosa (4). NBI is able to detect the onset of angiogenesis during multi-step carcinogenesis of the lung and the meta-analysis by Iftikhar et al. has shown that NBI is better than autofluorescence imaging in the detection of premalignant airway lesions, showing a pooled sensitivity, specificity, and the diagnostic odds ratio of 80, 84, and 31.49%, respectively (3). The video bronchoscopic NBI aspect of the bronchial vascularization is clearly different in patients with COVID-19 and **Figure 1** illustrates the differences when compared to the bronchial vascularization recorded in a 77-year-old male patient that underwent a video bronchoscopy for a non-COVID-19 infection. Based on the endoscopic classification of Shibuya et al. (5), the vascular lesions observed in our patients can be described with NBI as increased vessel growth, complex networks, and some dotted vessels. No tortuous vessels, small spiral or screw type vessels have been observed in our patients as described in angiogenic squamous dysplasia (ASD) or in carcinoma *in situ* (CIS). Because the video endoscopies with WL were normal in these two young non-smoker patients, the bronchial angiogenesis observed with NBI may be related to the ongoing COVID-19 infection. Indeed, it is now well-known that SARS-CoV-2 induces a neoangiogenesis and the histopathologic study of Ackermann et al. has clearly demonstrated in patients with COVID-19 the presence of pulmonary angiogenesis as early as day 4 of hospital admission and significantly increases with time (6). Chau et al. recently found that the median diameter of the bronchial artery at the origin was drastically increased in COVID-19 patients with pneumonia (7). This increase in bronchial circulation could promote the spread of inflammatory mediators throughout the lungs (2) and also increase the specific right to left shunt observed in patients with COVID-19. Indeed, during the first wave, we hypothesized that the cornerstone of COVID-19 disease was a vascular injury with an intrapulmonary shunt [as observed in the hepatopulmonary syndrome (8)] and proposed the acronym AVDS for Acute Vascular Distress Syndrome (9) to describe it. This initial hypothesis of AVDS was further supported by physiological approach and clinical observations (10–14) and reinforced by new imaging techniques (15).

Some limitations must be considered as these two observations, even provoking and illustrative, do not allow for any definitive conclusion. Thus, prospective studies are required to confirm the presence of a diffuse bronchial hypervascularization in patients with COVID-19 (through bronchovideoscopic NBI) and to precise its specificity when compared to non-COVID-19 patients. Indeed, objective tests are lacking that could have supported our hypothesis drawn from the videoendoscopic observations. Invasive investigations (mainly right-heart catheter or central venous catheter with measurements of arterial and venous oxygen contents allowing calculation of the right-to-left shunt) were not performed because our patients presented a non-severe COVID-19 infection and were not hospitalized in ICU. Moreover, dual energy lung CT scan was not available in our institution and data that could have shown pulmonary or bronchial dilated vessels is also lacking in our observations.

The COVID-19 related bronchial angiogenesis differs from those observed during carcinogenesis related angiogenesis. In these two case reports of a COVID-19 pneumonia, we observed a clear-cut bronchial hypervascularization with heavy dilated submucosal vessels developed along the axis of the main and lobar bronchi. These peculiarities, which may be specific of COVID-19 disease, could be interesting for definite diagnosis—in association with RT-PCR on BAL sample—in case of negative pharyngeal swabs RT-PCR.

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 authors.

ETHICS STATEMENT

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

VJ performed the bronchovideoscopies, coordinated of the study and drafted the manuscript. VJ, DB, BT, and CA contributed to the management of these two patients and analyzed tests results. YM and DR contributed in interpretation of the data, in conducting the literature review, and writing the manuscript. All authors have read and approved the final manuscript.

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SYSTEMATIC REVIEW
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Portal Vein Thrombosis Might Develop by COVID-19 Infection or Vaccination: A Systematic Review of Case-Report Studies

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Background and Objective: Infection by the novel coronavirus disease 2019 (COVID-19) has been associated with different types of thrombotic complications same as portal vein thrombosis (PVT). However, by emerging vaccines of COVID, the thrombosis did not seem to be concerning anymore. Until new findings showed that, the vaccine of COVID itself can cause PVT.

Method: We performed an electronic search in PubMed, Scopus, and Web of Sciences to evaluate the possibility of occurring PVT due to infection and vaccination of COVID-19. The results were reported in a narrative method and categorized into tables.

Result: Overall, 40 cases of PVT from 34 studies were reviewed in this article. The prevalence of PVT following COVID-19 was more remarkable in males. However, it was more common in females after vaccinations of COVID-19 in the reviewed cases. Regardless of etiology, 20 of PVT cases reviewed in this article had at least one comorbidity. The most common clinical presentation was abdominal pain (AP). After anticoagulant therapies, most of the patients improved or discharged.

Conclusion: As long as the laboratory findings are not appropriate enough to predict PVT, the diagnosis of this complication with whatever underlying reason is challengeable, while rapid diagnosis and treatment of that are vital. Therefore, by providing available data in an organized way, we aimed to prepare the information of infected patients for better and easier future diagnosis of PVT in new cases.

Keywords: COVID-19, vaccines, liver diseases, portal vein, venous thrombosis, case report

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HIGHLIGHTS

- On the basis of studies we reviewed, PVT following COVID-19 was reported more in males, however; this complication was more mentioned in the females after vaccination of COVID-19.
- Patients with comorbidities were more likely to develop portal vein thrombosis with both underlying reasons.

- Liver CT scan beside laboratory findings were useful solutions in diagnosing this complication.
- We suggest examining more about the underlying mechanism of PVT after vaccination because there was a case mentioned in our study with thrombocytosis so vaccine-induced thrombosis might not be the only mechanism leading to PVT.

INTRODUCTION

The new member of the *Coronaviridae* family has started the novel coronavirus disease 2019 (COVID-19) pandemic, which was first reported in Wuhan, China, appearing as a worldwide health crisis. To date, about 239 million people from 223 different countries in the world have experienced some form of this disease. This dreadful pandemic led to over 4.8 million deaths totally and still, the number keeps on increasing (1–3).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as it was named by the WHO, is a single-stranded RNA virus. Different proteins play roles in the structure and function of this virus. One of the most important ones is the spike glycoprotein, the extrinsic crown-shaped construction of the virus, which is the key connector for the fusion of SARS-CoV-2 and human being cells (4).

The clinical presentations of COVID-19 vary depending upon the immune system, gender, and age of the patients. General symptoms including fever, cough, and fatigue are common in many patients, but several complications such as thrombosis, severe respiratory symptoms, heart, kidney, and multiorgan failure are less prevalent (4–6). The incidence rate of some symptoms was determined by a meta-analysis in 50,466 patients, as followed; fever 89.1, cough 72.2, fatigue 42.5, and abnormal CT in 96.6% of the cases (7). COVID-19 is associated with different types of coagulation abnormalities and is shown to be associated with an increased risk of arterial thrombosis and venous thromboembolism (VTE). It can mainly cause, disseminated intravascular coagulation (DIC), VTE, deep vein thrombosis (DVT), portal vein thrombosis (PVT), and other coagulopathies (8).

Portal vein thrombosis is an abnormal rare condition associated with malignancy, liver cirrhosis, and acute abdominal inflammation (9). PVT cases due to non-cirrhotic reasons are scarce. After cirrhosis, myeloproliferative neoplasms, surgery, and inflammatory conditions are three major triggers leading to obstruction in the portal vein (10). This disorder usually occurs when thrombus blocks the portal vein partially or completely. This obstruction of the portal vein is categorized in different ways. Due to Baveno VI criteria, PVT may happen whether because of extra hepatic portal vein obstruction or the intrahepatic one. However, splenic or super mesenteric veins are not involved. Another categorization demonstrates that in the chronic form of PVT, patients generally develop symptoms such as varicose veins and hypersplenism that are associated with portal hypertension. Nevertheless, in the acute form, local and systemic prothrombotic factors are the main reasons for this complication (9, 11). The clinical presentations of acute PVT, show a wide spectrum of asymptomatic indications to severe intestinal ischemia and infarction (12). Several surveys indicated that activation of the coagulation pathway by COVID-19 infection might be due to the inflammatory response of cytokines to virus invasion (13). For example, IL-6 can increase the expression of tissue factor (TF) from mononuclear cells, which may lead to clot formation. Besides this, other inflammatory cytokines such as tumor necrosis factor alpha- α (TNF-α) and IL-1 can play roles in anticoagulant pathway inhibition (8).

After introducing different vaccines of COVID-19 to the world, in addition to PVT following the COVID-19, several people have encountered with PVT after being vaccinated against this virus all around the world.

Since PVT may happen due to several reasons including infectious disease, by reviewing the available data from other articles, we tried to study the PVT, which is either caused by COVID-19 itself, or vaccination while narrating the differences and similarities.

METHODS

Protocol and Registration

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for developing and reporting this article (14).

Eligibility Criteria

All the case report studies that stated PVT on patients with COVID-19 were included in this study. Every study that reported consequences related to PVT following COVID-19 or all the types of vaccines of COVID-19 was included. Ultrasonography and contrast-enhanced CT are two gold-standard investigations of PVT. All the articles using each of these two diagnostic methods besides the studies which had not mentioned the diagnostic method but been approved and published as a PVT case due to infection of COVID-19 or vaccination were included. All the studies without available English full-text were excluded. Studies that report incomplete data or irrelevant subjects were also excluded.

PICOD:

Population: All patients with COVID-19 or vaccinated people against COVID-19.
Intervention: Not applicable.
Comparison: Not applicable.
Outcome: Portal vein thrombosis.
Design: Case-report studies.

Information Sources and Search

We did an electronic search of PubMed, Scopus, and Web of Sciences to September 7, 2021, without language restrictions. The whole data extracted with these search term combinations "2019 nCoV" or 2019 nCoV or "2019 novel coronavirus" or COVID-19 or "new coronavirus" or "novel coronavirus" or "SARS-CoV-2" or (Wuhan and coronavirus) or "SARS-CoV" or "2019-nCoV" or "SARS-CoV-2" and ("portal vein thrombosis" or "portal venous thrombosis").

Besides this, these mesh terms were also searched COVID Vaccine and Neurology, AstraZeneca COVID vaccine, ChAdOx1

TABLE 1 | Data extraction table of patients suffering from PVT as a complication of COVID-19.

References	Demographic data	Clinical presentation	Covid-19 diagnoses	PVT diagnostic method	Clinical manifestations related to PVT	PVT location	Treatment and anticoagulant therapy	Outcome
Borazjani et al. (15)	M/26y/asthma, alcohol user, cigarette smoker, and occasionally marijuana user	Dyspnea, decrease in the level of consciousness admission with acute asthma attack	Normal CT/positive (RT-PCR) for SARS-COV2	Abdominopelvic CT with IV contrast	AP and abnormal liver biochemistries	Hypo perfused areas in the posterior segment of the right	Prophylactic doses of heparin before PVT (5,000 IU every 12 h) and oral warfarin when discharged	No feedbacks after the patient discharged
de Barry et al. (16)	F/79/none	Fever, deterioration in the patient's general condition, AP in epigastric area diarrhea and dyspnea	Ground-glass opacity in CT/Negative (RT-PCR)	Enhanced CT-scan	AP in epigastric area	Increase of density in Right portal vein	Thrombolysis and thrombectomy of the upper mesenteric artery	Passed away
Franco-Moreno et al. (17)	M/27/none	Serious colic abdominal discomfort, fever and dry cough during 3 weeks before admission	Bilateral consolidations with ground-glass surrounding in both inferior lobes of the lung	Contrast non-enhancing CT-scan	RUQ Tenderness with negative Murphy's sign	Filling defect within the right branch of portal vein	Enoxaparin 1 mg/kg twice daily-acenocoumarol for 6 months	Improved
Jafari et al. (18)	M/26/controlled asthma	Respiratory pain and tiredness	Multifocal patchy consolidations and bilateral pleural effusions in CT scan/Positive RT-PCR	Contrast- enhanced CT-scan	Severe AP located in the RUQ	In portal phase of CT scan	Intravenous heparin infusion (1,000 U/h)	Improved
La Mura et al. (19)	M/72/ Parkinson's disease, anxious-depressive syndrome, mild vascular dementia	Fever, jaundice, and obnubilation	Not reported	Contrast- enhanced CT-scan	Mild AP with bloating and constipation followed by periumbilical tenderness with no rebound reaction nor ascites	Occlusion of the left portal venous system and the secondary branches of the right portal vein	Enoxaparin before PVT diagnosis at 4,000 IU o.d. and after PVT diagnosis increased to 100 IU/Kg b.i.d	Improved
Low et al. (20)	M/51/lower limb DVT	Blood vomiting, respiratory failure	–/–	CT-scan	–	Right and left portal thrombosis and portal vein gas	Intravenous heparin	Improved with no residual portal vein thrombosis
Malik et al. (21)	M/32/obesity and hypothyroid	Hematemesis preceded by fever and cough	Serology tests	CT-scan	Left upper AP	NM	–	Improved
Ofosu et al. (22)	M/55/hyperlipidemia	Fever, dyspnea, altered mental state	Positive PCR/ ground glass opacity main right portal vein	Computer tomography angiography	–	Right portal vein	–	Passed away
Rokkam et al. (11)	F/66/fibromyalgia, gastroesophageal reflux disorder, brain injury due to trauma, high blood pressure, depression, constipation, and anemia	A 10-day diarrhea and 1-day unstable mental status (no respiratory symptoms related to COVID-19)	RT-PCR	CT-scan	mild diffuse tenderness on palpation in abdomen	Left branch of portal vein	Apixaban (5 mg b.i.d)	Improved

(Continued)

TABLE 1 | Continued

References	Demographic data	Clinical presentation	Covid-19 diagnoses	PVT diagnostic method	Clinical manifestations related to PVT	PVT location	Treatment and anticoagulant therapy	Outcome
Abeysekera et al. (23)	M/42/controlled hepatitis B	Fever, oliguric renal failure, supratherapeutic tacrolimus levels, hyponatremia and beside chest discomfort	–	Abdominal ultrasound and contrast-enhanced CT-scan	AP and constant pain in right hypochondrium	Entire portal vein	Apixaban 5 mg two times per day for at least 6 months	NM but symptoms disappeared
Kolli and Oza (24)	F/44/none	AP and bloating	–	CT-scan	Bloating abdomen with pain in RUQ	–	Heparin, coumadin and vitamin K	NM
Petters et al. (25)	F/3/Liver transplant Recipient with history of Caroli disease,treated hepatic artery thrombosis, PVT, EBV infection	Fever, oliguric renal failure, supratherapeutic tacrolimus levels, hyponatremia	RT-PCR	Ultrasound with doppler	Multisystem inflammatory symptoms and abdominal distention	–	Enoxaparin and tacrolimus	Improved
Sinz et al. (26)	M/38/none	Fever, nausea, diarrhea, coughing and pleural irritation	RT-PCR (Negative) but Detectable SARS-CoV-2 serological antibody	Duplex ultrasound	AP and tenderness in RLQ	Extensive PVT and mesenteric vein stasis	Unfractionated heparin	Improved
Miyazato et al. (27)	M/67/Diabetes/alcohol-related cirrhosis/esophageal varices	Fever, respiratory distress	oxygen saturation test-	Contrast-enhanced CT-scan	–	From superior mesenteric vein to the main trunk of the portal vein	No anticoagulants	–
Sharma et al. (28)	M/28/alcohol user	AP, nausea, vomiting, and constipation	RT-PCR	Contrast-enhanced CT-scan	AP	Extensive PVT and mesenteric vein stasis	LMWH, apixaban	–
Rehman et al. (29)	F/33/none	AP	–	CT abdomen with IV contrast	Acute AP in the RLQ	–	Enoxaparin and warfarin	Improved
Agarwal et al. (30)	F/28/pregnancy	Hypertension and general body swelling	–	Contrast-enhanced CT-scan	AP beside distension and tenderness	–	LMWH, diuretics, beta blockers, terlipressin, and anti-biotic	Improved
Jeilani et al. (31)	M/68/pulmonary disease, Alzheimer's dementia and urinary tract infection	AP, constipation, flatus, umbilical hernia with dry coughs and crepitation in chest	–	CT-scan	AP and constipation	Central filling defect within portal vein	LMWH	Improved
Randhawa et al. (32)	F/62/none	RUQ pain	–	Ultrasound	Pain in RUQ but soft and non-tendered abdomen	Right branch of portal vein	Fondaparinux, spironolactone, warfarin	Improved
Rivera-Alonso et al. (33)	M/51/none	AP in RUQ, fever, discomfort	RT-PCR (Negative) but detectable SARS-CoV-2 serological antibody	Enhanced CT-scan	Pain in RUQ	–	Anticoagulants	Improved
Lari et al. (34)	M/38/none	AP, nausea, vomiting, breath-shortness	–		AP	Extensive PVT	Heparin	In charge

COVID-19, coronavirus disease 2019; PVT, portal vein thrombosis; AP, abdominal pain; RUQ, right upper quadrant; RLQ, right lower quadrant.

TABLE 2 | Laboratory data table of patients suffering from PVT as a complication of COVID-19.

References	HB (g/dL)	WBC (*10^3/μL)	PLT (*10^9/L)	CRP (mg/dL)	ALT (U/L)	AST (U/L)	Bilirubin (mg/dL)	D-DIMMER (μg/L)	PT(s) or Ratio	PTT(s)	INR
Borazjani et al. (15)	14.7	18.1 (12%Lymph)	213	–	67	44	1.41	–	19.2	28	–
de Barry et al. (16)	–	12.6 (lymphopenic)	–	12.5	–	–	–	–	–	–	–
Franco-Moreno et al. (17)	RN	18 (8%lymphocyte)	458	24.5	111	64	-	9.530	RN	RN	RN
Jafari et al. (18)	–	7.2 (lymphosyte39%)	–	9.6	–	–	–	500	39s	–	1.34
La Mura et al. (19)	12.1	4.68	330	2.87	28	-	1.13	5,004	1.02	1.13	-
Low et al. (20)	–	–	–	–	–	–	–	–	–	–	–
Malik et al. (21)	12.5	–	–	–	–	–	–	–	–	–	–
Ofosu et al. (22)	14	9.5	518	3	36	50	0.8	>44	–	–	1.2
Rokkam et al. (11)	10.2	31.9	391	–	12	23	–	–	–	–	1.4
Abeysekera et al. (23)	14.7	13.84	364	4.4	31	–	0.37	–	RN	–	–
Kolli and Oza (24)	–	–	RN	–	–	–	–	RN	RN	RN	RN
Petters et al. (25)	–	–	132	18.9	66	132	0.23	7,822	–	–	–
Sinz et al. (26)	17.2	19.5	281	12.2	RN	RN	1.05	6,870	(PT ratio = 0.67)	56	–
Miyazato et al. (27)	–	–	–	–	–	–	–	7,300	–	–	–
Sharma et al. (28)	13.6	10.4	312	–	86	38	0.8	1,533	–	–	–
Rehman et al. (29)	–	RN	RN	1.45	RN	RN	–	610	RN	RN	RN
Agarwal et al. (30)	13.3	17	93	–	–	–	1.89	3,600	11.1	35.5	0.95
Jeilani et al. (31)	15	12.44	318	30.7	41	–	0.76	894	–	–	–
Randhawa et al. (32)	13.1	RN	–	–	RN	RN	–	RN	RN	RN	RN
Rivera-Alonso et al. (33)	–	21.3	–	5.5	472	577	5	–	–	–	–
Lari et al. (34)	–	Increased	–	–	–	–	–	2,100	–	–	–

nCoV-19 COVID vaccine, AZD1222 COVID vaccine, Janssen COVID vaccine, Johnson & Johnson COVID vaccine, Ad26.COV2 COVID vaccine and "portal vein thrombosis" or "portal venous thrombosis" (**Appendix 1**).

Then, we merged them in Endnote V.8. All the reference lists from the included studies and relevant systematic reviews were hand-searched for additional studies.

Study Selection

The duplicate studies were removed and the title, abstract, and full-text of records were screened by two independent reviewers based on pre-mentioned inclusion and exclusion criteria. A third reviewer reviewed the record in case of discrepancy, and disagreement was resolved by consultation.

Data Collection Process and Data Items

Two independent reviewers extracted and tabulated all the relevant data using a researcher-made checklist. Disagreement was resolved by consensus between all the authors. The data extraction checklist includes items such as author name and year of publication, demographic data, clinical presentation, COVID-19 diagnosis test, clinical manifestations related to PVT (same as fever, APs, etc.), PVT location, treatment, and outcome of the therapy (**Table 1**). Besides all these, the data of laboratory experiments of the patients were categorized in a separate table (**Table 2**). As long as not all of these parameters were crucial enough to extract the suitable data from the articles with COVID-19 vaccinated cases, we designed another table with the extra following subheadings: Type of vaccine and diagnostic tests, COVID-19 infection test, number of days until the start of symptoms, and abnormal parameters in laboratory examinations.

A third reviewer rechecked the extracted data.

Quality Appraisal

All the studies were checked in terms of quality by two independent reviewers using an eight-item Joanna Briggs Institute (JBI) checklist for case report studies. The potential disagreement was resolved by consultation with a third reviewer. This checklist includes eight questions and four-rating score (Yes, No, Unclear, and Not applicable). Each question was scored 1 point for yes, 0 points for unclear and no. Then, studies were categorized as having a high risk of bias if the summary score was 0 to <3, moderate risk of bias if the summary score was between 3 and <6 points, and low risk of bias if the summary score was 6 or higher.

Synthesis of the Results

Due to potential heterogeneity between studies, we reported the results in a narrative method and categorized them into several items available in **Tables 1–3**.

TABLE 3 | Data extraction table of cases suffering from PVT as a side effect of vaccination of COVID-19.

References	Demographic data	Clinical presentation	Type of vaccine	PVT diagnostic method	Days until the start of symptoms	PVT location	Abnormal parameters in laboratory examinations	Treatment and anticoagulant therapy	Outcome
De Michele et al. (35)	Case 1: F/57/mild hypothyroidism and treated breast cancer	Left hemiplegia, right gaze deviation, dysarthria, and left neglect, caused by right middle cerebral artery (MCA) occlusion	ChAdOx1 nCoV-19 vaccine (AstraZeneca)	CT-scan	8	Extensive pulmonary artery and portal vein thrombosis	Low platelet count (from 44 to 23 $\times$ 10^9/L)- low Hb levels (5.4 g/dL)- increased levels of Factor VIII while decreased levels of Factor XIII- high levels of PF4–polyanion complexes pan Ab	Thrombectomy, IVIG, plasma exchange, fondaparinux (after increasing of platelet count)	Hospitalized at critical condition
	Case 2: F/55/ mild hypothyroidism	AP and after several days general seizures and coma	ChAdOx1 nCoV-19 vaccine (AstraZeneca)	CT-scan	7	Extensive portal vein thrombosis with occlusion of the left Intrahepatic branches	Elevated D-dimmer (5,441 μg/L)- decreasing thrombocytopenia (from 133 to 59 $\times$ 10^9/L)- increased levels of Factor VIII	IVIG and dexamethasone	Passed away
Kulkarni et al. (36)	M/46/Buddchiary and MPD	Severe AP	ChAdOx1 nCoV-19 vaccine (AstraZeneca)	Contrast-enhanced	7	–	High level of INR (1.7)- negative anti PF4 Ab	Thrombolysis plus venoplasty, LMWH and dabigatran	Discharged
Sorensen et al. (37)	F/30/ migraine	Headache and ecchimose	ChAdOx1 nCoV-19 vaccine (AstraZeneca)	Duplex ultrasonography and CT-scan	8	–	Low platelet count (51 $\times$ 10^9/L) -low levels of fibrinogen, high D-dimer, and marginally increased ALT- increased levels of Factor VIII and VWF-anti PF-4 Ab positive	Tinzaparin 4,500 IU, fibrinogen, fondaparinux, rivaroxaban	Discharged
Öcal et al. (38)	M/41/none	Headache and AP	ChAdOx1 nCoV-19 vaccine (AstraZeneca)	CT-scan	11	Entire portal vein	Thrombocytopenia (64 $\times$ 10^9/L) and increased D-dimer (42 028 μg/L)- anti PF-4 AB positive	Apixaban, IVIG, argatroban,	NM
Greinacher et al. (39)	F/49/none	Chills, fever, nausea, and epigastric discomfort	ChAdOx1 nCoV-19 vaccine (AstraZeneca)	CT-scan	5	–	Thrombocytopenia (18 $\times$ 10^9/L)- high levels of D-dimer (35,000 μg /L)- elevated amounts of CRP and γGT	IVIG, analgesia, enoxaparin, UFH, prothrombin complex concentrates, and recombinant factor VIIa	Passed away
Graf et al. (40)	M/29/NM	Headache, AP and hematomesis	ChAdOx1 nCoV-19 vaccine (AstraZeneca)	CT angiography	9	Extensive PVT	Thrombocytopenia (32 $\times$ 10^9/L), anti PF-4 Ab positive	IVIG, argatroban,	Improved
Scully et al. (41)	Case 1: F/30/ NM	–	ChAdOx1 nCoV-19 vaccine (AstraZeneca)	–	13	–	Thrombocytopenia (27 $\times$ 10^9/L)- elevated D-dimmer (16,280 μg/L)- anti PF-4 Ab negative	–	Alive

(Continued)

TABLE 3 | Continued

References	Demographic data	Clinical presentation	Type of vaccine	PVT diagnostic method	Days until the start of symptoms	PVT location	Abnormal parameters in laboratory examinations	Treatment and anticoagulant therapy	Outcome
	Case 2: F/55/ NM	–	ChAdOx1 nCoV-19 vaccine (AstraZeneca)	–	6	–	Thrombocytopenia (11 × 10^9/L)- elevated D-dimmer (26,689 μg /L)	–	Passed away
	Case 3: M/54/NM	–	ChAdOx1 nCoV-19 vaccine (AstraZeneca)	–	10	–	Elevated PT (13.5s) D-dimmer (80,000 μg/L)	–	Passed away
D'Agostino et al. (42)	F/54/Meniere's disease	–	ChAdOx1 nCoV-19 vaccine (AstraZeneca)	Angio-CT and contrast-CT-scan	12	left portal branch	Elevated D-dimer, normocytic anemia (HB 8.7 g/dL), thrombocytopenia and signs of DIC	–	–
See et al. (43)	Case 1: F/between 18-39/NM	Headache, nausea, Muscle pain, chills, fever, AP, and bloating	Janssen (Johnson & Johnson) ad26.cov2.s	Ultrasound	8	–	Mild thrombocytopenia (127 × 10^9/L), elevated D-dimmer (5,450 μg /L) - anti PF-4 Ab positive	–	Discharged
	Case 2: F/more than 40/NM	Back pain, bruising, AP, fever		Ultrasound	13	–	Thrombocytopenia (13 × 10^9/L), elevated D-dimmer (112,070 μg /L) – decreased fibrinogen (59 mg/dL)–anti PF-4 Ab positive	–	Not discharged
Aladdin et al. (44)	F/36/NM	Fever, vomiting, and severe headache	ChAdOx1 nCoV-19 vaccine (AstraZeneca)	CT-scan	–	Extensive portal vein thrombosis	Elevated WBC (18.7) (mainly neutrophils), low HB at 10.4 g/dL, and clumped platelets- mild elevated liver enzyme-prolonged PT (45 s), PTT (98 s), INR (4.1) -elevated D-dimer (more than 35,000 μg /L)	Enoxaparin	Passed away
Graca et al. (45)	F/62/obesity, asthma and rhinitis	Fever, AP, vomiting, abdominal tenderness	ChAdOx1 nCoV-19 vaccine (AstraZeneca)	Abdominal CT angiography (CTA)	1 (28 days till the PVT occurred)	Left branch of the portal vein	Anemia (HB 7 g/L), thrombocytosis (780 × 10^9/L), leukocytosis 13 × 10^3/μL, elevated CRP (31.07 mg/dL), slightly increased levels of liver enzymes (AST 36 U/L, ALP 126 U/L, GGT 72 U/L, LDH 441 U/L, total bilirubin 1.3 mg/dL	LMWH and endoxaban	Discharged
Umbrello et al. (46)	F/ 36/none	Fever, AP, asthenia and osteoarticular pain	ChAdOx1 nCoV-19 vaccine (AstraZeneca)	Contrast-enhanced CT-scan	17	Complete thrombosis of portal vein	Mild thrombocytopenia (133 × 10^9/L), anti PF4 antibody pos	UFH, IVIG, and argatroban, apixaban	Stable condition

(Continued)

TABLE 3 | Continued

References	Demographic data	Clinical presentation	Type of vaccine	PVT diagnostic method	Days until the start of symptoms	PVT location	Abnormal parameters in laboratory examinations	Treatment and anticoagulant therapy	Outcome
Ciccone et al. (47)	Case 1: F/35/ OCP user	Headache, nausea and vomiting	ChAdOx1 nCoV-19 vaccine (AstraZeneca)	–	6	–	Thrombocytopenia (44 × 10^9/L)- elevated D-dimmer level (>8,000 μg /L)	Mannitol, metil prednisolone, fresh plasma, enoxaparin, plasmapheresis	In coma
	Case 2: F/54/none	Headache and vomiting	ChAdOx1 nCoV-19 vaccine (AstraZeneca)	–	2	–	Thrombocytopenia (13 × 10^9/L)- elevated D-dimmer level (78,254 μg /L)	Enoxaparin, fondaparinux, dexamethasone	Passed away
	Case 3: F/55/none	Headache and fever	ChAdOx1 nCoV-19 vaccine (AstraZeneca)	–	6	–	Thrombocytopenia (31 × 10^9/L)- elevated D-dimmer level (>10,000 μg /L)	Fondaparinux, metil-prednisolone, mannitol, craniectomy	In coma

NM, not mentioned; AP, abdominal pain; γGT, γ-glutamyltransferase; ALT, alanine transaminase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CRP, C-reactive protein; VIG, intravenous immunoglobulin; WBC, white blood cell; HB, hemoglobin; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; RN, reported as normal; Ab, antibody.

RESULTS

Literature Search

The initial search produced 200 articles from three main databases. After removing duplicates, 123 articles remained. These 123 articles were evaluated based on title and abstract and eventually, 53 articles were selected. The full text of these 53 articles was assessed for eligibility criteria. Finally, 34 studies with 40 cases reported the incidence of PVT resulting from COVID-19 (21 cases) or vaccination of COVID-19 (19 cases) due to our inclusion criteria and 19 studies were excluded due to incomplete data, irrelevant subject, or non-availability of full text (**Figure 1**).

Study Characteristics and Demographic Data

The characteristics of the included studies are summarized in the three tables. All of the 34 studies were case reports. The data about patients with the PVT following COVID demonstrates a wide age range of 3–79 years. About 66.7% of 21 cases were male. Thirteen of twenty-one cases (61.9%) had at least one comorbidity. There were five cases with liver disorders (four cases with alcohol consumption and one case with controlled hepatitis) three cases with brain injuries, two cases with asthma, two cases of thrombosis, and one case with pregnancy.

However, these amounts differed in PVT following vaccination. The median age of these cases was about 45 years (range 29–62 years) (the age of two cases were reported as ranges, so they were ignored in calculating median age). Only four cases were male and about 79% of the cases were female. Seven of nineteen cases had the previous history of the disease. Hypothyroidism was reported in two cases, Budd-Chiari syndrome and myeloproliferative disorder (MPD) were reported in one case at the same time. Other previous diseases such as migraine, asthma, Meniere's disease, and oral contraceptive pill (OCP) use were each reported in one separate case. Five had no known comorbidities and in seven cases, it was not mentioned. All of the cases of this complication had received the AstraZeneca vaccine except two of whom were injected with Johnson & Johnson.

Quality Assessment

The JBI tool for quality assessment of included studies yielded scores ranging from 4 to 7. Mean methodological quality was 6.06 out of 8. A total of 31 studies were classified as low risk of bias (77.5%) and 9 studies were with moderate risk of bias (22.5%). Details of the answers to the 8 questions of the tools are given in **Appendix 2**.

Clinical Presentation

As was expected, almost different presentations were observed in PVT following COVID and vaccines of COVID. After infecting with COVID-19, 14 cases presented the APs probably because of their PVT. Ten cases presented fever, which is one of the most common symptoms of both the virus and PVT. Seven cases had respiratory problems. Nausea and vomiting were observed in five cases. Four cases complained from cough and the same number of cases were involved with mental problems. Other

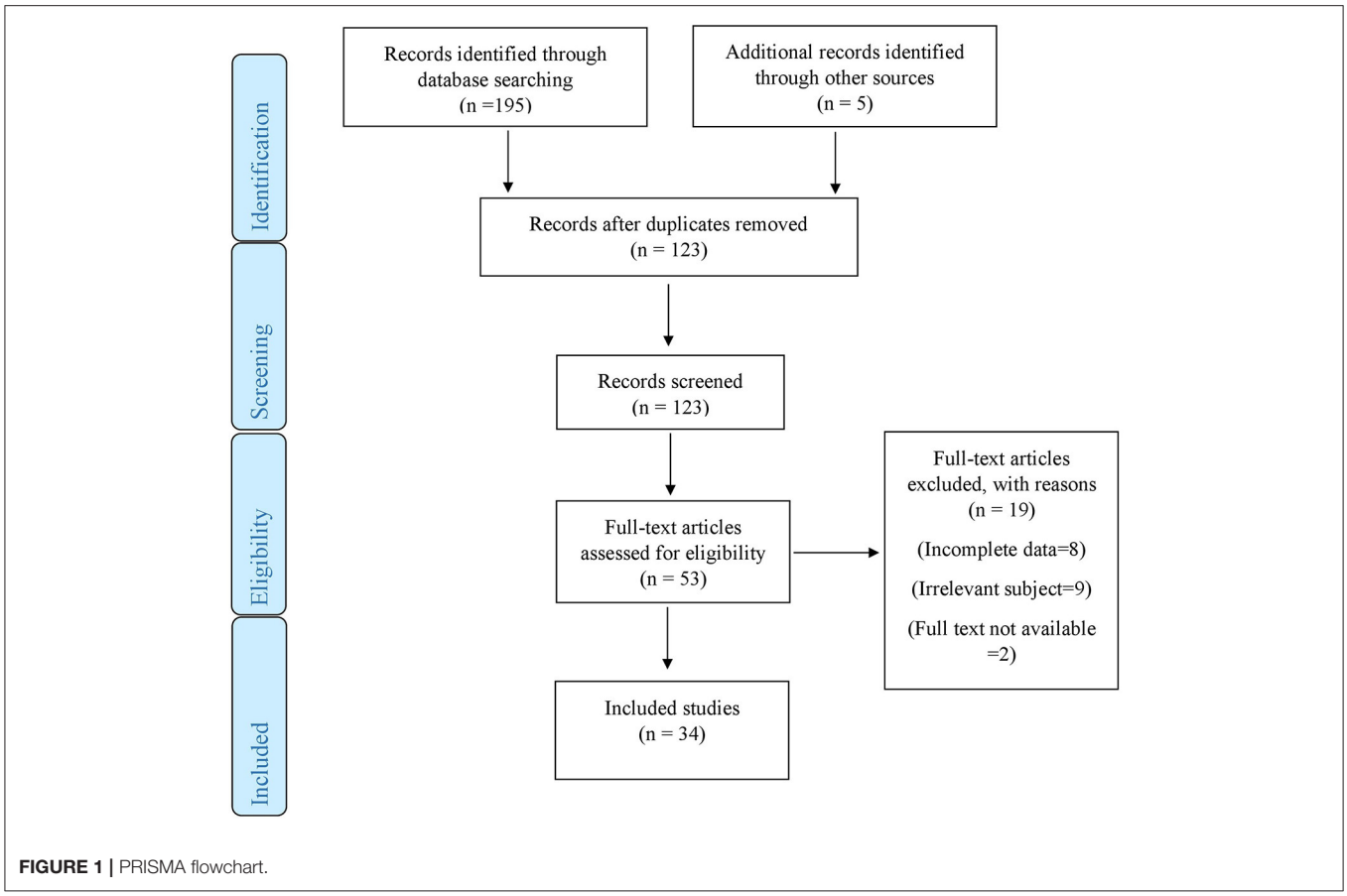

FIGURE 1 | PRISMA flowchart.

presentations same as diarrhea, jaundice, and hypertension were presented in fewer cases.

As the same, the AP was a prevailing manifestation in most cases (eight cases) of PVT following vaccination, especially at the right upper quarter (RUQ), where the liver is located. Then, headache (eight cases) and fever (seven cases) were the most prevalent ones, respectively. Nausea and vomiting were presented in the eight cases. Ecchymosis, chills, and muscle pains were less common.

Laboratory Indices

The most remarkable point about laboratory tests in COVID-19 infected patients was the high level of CRP in all the cases that this index was measured (it was measured in 11 cases).

Only two out of twenty-one patients were associated with abnormal hemoglobin (Hb) levels. Variable platelet counts (PLT) were reported in cases (1 case with decreased, 1 case with increased, and 11 cases with normal counts of PLTs). White blood cell (WBC) counts never dropped under the normal range. Among the cases manifesting PVT following COVID-19, nearly half of the patients (11 cases) appeared with leukocytosis. Liver enzymes were normal (5 cases) to elevated (9 cases) as was expected in PVT disease. Bilirubin was elevated only in three cases. The level of D-dimer was elevated remarkably more than normal in nine patients. Coagulation tests were not performed for most of the patients and did not show a significant increase in performed cases (PT, PTT, and INR were normal in 7, 6, and 5 cases, respectively, and were only elevated in 2 cases).

The results of laboratory experiments in PVT following vaccination showed different algorithms. Thrombocytopenia was a prevalent finding in most of the cases. Fifteen out of nineteen (79%) had experienced low-platelet counts. However, one case was reported with thrombocytosis. The D-dimer level was elevated in 14 cases as a sign of thrombosis. Anti-PF4 antibody was positive in seven cases and negative in two cases. Coagulation tests were abnormal in nine cases. Other complementary data are given in **Table 3** (Only abnormal indices are reported).

Treatments and Outcomes

To treat PVT following COVID-19, different drugs were prescribed depending upon the condition of the patient. Enoxaparin was the most commonly utilized treatment and fortunately, most cases improved after treating it. Six cases used heparin. Moreover, the same number of cases (3) were treated with warfarin or Apixaban. Although in several cases, heparin or enoxaparin were prescribed as prophylaxis therapy before the occurrence of PVT and after the diagnosis COVID-19, PVT developed in some cases. In 1 case, thrombectomy was performed, but finally the patient passed away. Most of these drugs led to improving or discharging the patient. There were

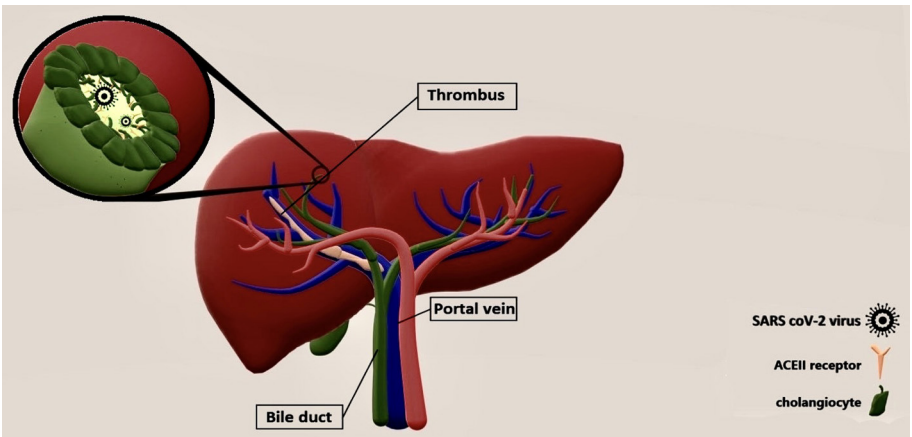

FIGURE 2 | Possible underlying mechanism of PVT by COVID-19 infection. Cholangiocyte is a kind of liver cell which has ACE II receptors presented on the surface more than hepatocytes and endothelium. By direct fusing of COVID-19 to these cells, first the direct injury of the liver happens because of the accumulation of bile acids. Then several inflammatory cytokines (IL6, TNF-alpha) are secreted and they play as inflammation and thrombosis triggers in the liver. Clot formation in the portal vein might be because of the increased expression of tissue factor (TF) from mononuclear cells, possibly done by IL-6. Beside this, other inflammatory cytokines such as tumor necrosis factor alpha (TNF-alpha) and IL-1 can play roles in anticoagulant pathway inhibition.

only two cases with not clear outcomes and two cases who were passed away.

Nevertheless, when PVT was presented after vaccination the most utilized drugs were intravenous immunoglobulin (IVIG) and low molecular weight heparin (LMWH). Argatroban, Apixaban, unfractionated heparin, thrombectomy, and thrombolysis were the other more prevalent treatments used, respectively. From the postvaccination PVT, six cases passed away, five cases were reported as still in charge, and six cases were discharged (the outcomes of two patients were not mentioned).

DISCUSSION

In this study, we review 40 cases with PVT because of new etiologies, the COVID and the vaccines of COVID-19. In this study, the median age was 41 years with the preference sex of males in cases of COVID. However, in PVT following vaccination, the median age of cases was 45 and 79% of them were females. The average number of days until onset of the symptoms was 8.3 days. As long as this is a systematic review of the cases, it is only possible to narrate the existed data. For comparisons, a cohort study is suggested on two homogenate groups. The underlying mechanism of PVT following COVID-19 is not precisely clear but Marjot et al. declared that the attachment of the virus might occur through ACE-2 receptors on the surface of cholangiocytes so the local presentation of COVID-19 in the liver, makes the body to produce different cytokines against it, which leads to the liver injury (**Figure 2**) (48). As portal vein is a vital part of the liver, the thrombosis may be formed because of the same reason. In addition, there is another theory provided by Mohseni Afshar et al. suggesting a mechanism for vaccine-induced thrombosis (VIT). They recommended that thrombi are formed in the vessels dependent or independent of heparin. As long as most of the vaccinated cases were non-heparin users, this heparin-induced thrombocytopenia (HIT) may be happened in a spontaneous or autoimmune way (called aHIT). In aHIT, it is not necessary for heparin to be present and other reasons same as free DNA do job of heparin. The free DNA attaches to PF4, and then platelets to make thrombus (49). The positive anti-PF4 antibody in seven out of nine reviewed cases somehow confirmed these findings. Almost in every type of HIT, the decreased counts of platelets are supposed to observe (**Figure 3**). However, in a 62-year-old woman with PVT that was reported by Graca (mentioned in **Table 1**), the opposite happened. The case was an asthmatic patient with the thrombocytosis of 780×10^3 per milliliter (45). Therefore, still further studies are needed to figure out other underlying mechanisms of the PVT following vaccination and solve this paradox. A recent cohort study stated the incidence of PVT following COVID-19 was 392.3 per million people, which was significantly higher than in PVT following vaccination (AstraZeneca and Jansen vaccines were excluded from this study) (49, 50).

Chronic PVT is a persistent obstruction of the portal vein often more than 6 months from the onset of the presentation. Therefore, the mentioned data suggest that PVT following infection of COVID-19 is of acute form. In PVT, the clinical presentation of the patients are as followed: AP (61%), hepatomegaly (67%), and ascites (83%) while about 20% of the patients have no symptoms (10). Data presented in this study demonstrated that in PVT following both etiologies, the AP was the most prevalent presentation whether after COVID infection or vaccination (66% after COVID-19 and 42% after vaccination).

Examinations of available data demonstrated that laboratory indices are not proper assistances in confirmed diagnosis or prognosis of PVT, and ultrasonography or contrast-enhanced CT scan of the hepatic portal vein is a better way for a valid diagnosis.

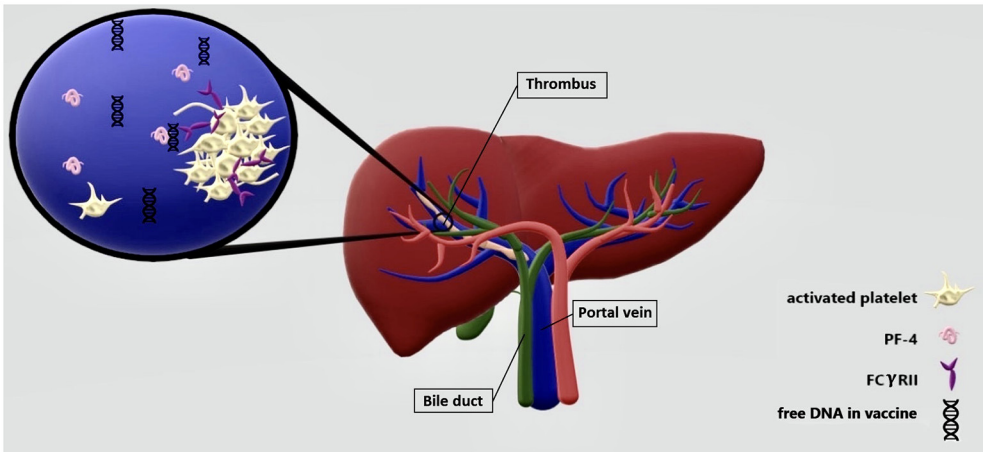

FIGURE 3 | Similar to HIT, vaccine induced thrombocytopenia and thrombosis (VITI) occurs because of free DNA available in COVID-19 vaccines. The free DNA stimulates the production of PF-4 molecules from platelets. The PF4-free DNA attaches to FCRYII on the surface of platelets and the platelet clot shapes.

The Baveno VI criteria suggest that Doppler ultrasound, CT scan and MRI are the best ways to diagnose both the presence and extension of PVT. However, some laboratory indices will be helpful. The elevation of D-dimer was expected, same as PVT cases due to non-COVID-19 etiologies (51). The liver function tests were normal to elevated because in PVT, the liver retrieves the condition by enhancing hepatic arterial flow (52, 53). In accordance with our result, another study suggested that mild elevation of ALT and AST enzymes are estimated in 29–39% and 38–63 % of patients of COVID, respectively (48). There was also a study, which mentioned that in cases of PVT, evaluation of mean platelet volume (MPV) would help as a diagnostic index. They declared that the larger the platelets, the higher the thrombotic conditions (54). However, the MPV amount was not mentioned in any of the studies we examined. As long as PVT is an uncommon complication without pathognomonic clinical manifestations, the mentioned laboratory indices beside general clinical presentations such as fever and AP are helpful in diagnosis of PVT in COVID-19 infected patients. Moreover, these parameters shift to AP and headache beside thrombocytopenia, D-dimer levels, coagulation tests, and anti-PF4 antibody detection in the cases who are suspected to PVT following vaccination.

Up to now, anticoagulants are the suggested treatments for PVT. Due to presence of hypercoagulable states, the treatment can be considered long term or short term. Heparin and low-molecular-weight heparin (such as enoxaparin) was prescribed in more than half of the cases. Nearly all of them were improved except 2 with uncertain feedbacks. While most of the studies suggest these 2 drugs for solving the thrombosis problem in COVID-19 infected patients, there is one case report that advises platelet count monitoring due the probable risk of HIT. In addition, because the similar mechanism (aHIT) underlies the PVT related vaccination of COVID-19, IVIG, LMWH, and fondaparinux were the most utilized drugs for patients with this trouble. Two of COVID-19 infected and six of vaccinated cases were passed away. Due to heterogeneity of the age, sex, and comorbidities of the patients it is not possible to report which condition is associated with less mortality but due to other studies it is clear that vaccine is safe (55) and the mortality rate of thrombosis is much lower than the infection itself. However, in general, the thrombosis morbidity rate is less after vaccination and even when it is occurred, the condition is manageable. Nevertheless, as long as HIT-like mechanisms are suggested as the main responsible of PVT occurrence after vaccination, the use of heparin is with more caution and the wide-spectrum of the utilized drugs somehow confirms this challengeable condition.

However, we were confronted with several limitations same as small numbers of studies and lack of strong evidence, so further examinations are needed in future studies for more information.

CONCLUSION

In this systematic review, we have tried to prepare data available on two new etiologies of acute PVT. Even if the patient is receiving anticoagulants as prophylaxis therapy of PVT, this complication might happen after infection or vaccination of COVID-19. Therefore, it is recommended that upon observing the clinical symptoms mentioned (the most important one is ap), provide a liver CT scan for the patient for checking whether the thrombosis involved this vein or not.

Same as infection of COVID-19, the morbidity rate was higher in male PVT cases after infection with the virus. Although the reviewed cases suggested if the PVT was presented due to vaccination, it is more prevalent in females. As it was the most common comorbidity in the presented cases, liver disorders, might had been deteriorated through drug-induced injury, inflammation or anoxia that resulted from COVID-19 (56).

Further studies are needed to exactly clarify that how the virus and the vaccination can lead to thrombosis of portal vein. Moreover, a cohort study is suggested to compare the data and results in two homogenate groups of patients with PVT following COVID-19 and vaccination of COVID-19.

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.

AUTHOR CONTRIBUTIONS

SK and AR contributed in design, acquisition of data, and drafting the manuscript. MA-Z contributed in the interpretation of data and drafting the manuscript. GS was the study supervisor and contributed to all the aspects of the study. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

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REVIEW
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Non-invasive Respiratory Support in COVID-19: A Narrative Review

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Acute respiratory failure secondary to COVID-19 pneumonia may require a variety of non-pharmacological strategies in addition to oxygen therapy to avoid endotracheal intubation. The response to all these strategies, which include high nasal flow, continuous positive pressure, non-invasive ventilation, or even prone positioning in awake patients, can be highly variable depending on the predominant phenotypic involvement. Deciding when to replace conventional oxygen therapy with non-invasive respiratory support, which to choose, the role of combined methods, definitions, and attitudes toward treatment failure, and improved case improvement procedures are directly relevant clinical questions for the daily care of critically ill COVID-19 patients. The experience accumulated after more than a year of the pandemic should lead to developing recommendations that give answers to all these questions.

Keywords: CPAP, high flow oxygen therapy, non-invasive ventilation, acute distress respiratory syndrome, prone position

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INTRODUCTION

Severe acute respiratory syndrome caused by coronavirus-2 (SARS-CoV-2) emerged at the end of 2019 in Wuhan, China, resulting in an ongoing global respiratory illness pandemic, named Coronavirus Disease 2019 (COVID-19) (1). COVID-19 has a wide spectrum of clinical severity, ranging from asymptomatic to critically ill patients, and ultimately death. The most common feature of severe COVID-19 disease is acute hypoxemic respiratory failure (ARF) requiring oxygen and ventilatory support, and it has been reported that about 5% of the infected patients develop a life-threatening clinical picture (2).

The characteristic pattern of severe disease due to COVID-19 is bilateral pneumonia matching the criteria of acute respiratory distress (ARDS), although some authors defend that there are pathophysiological differences between classic distress and that associated with COVID-19, the so-called C-ARDS (3). C-ARDS is a heterogeneous entity from a clinical point of view, a fact that it shares with ARDS. An attempt has even been made to classify it according to lung mechanics into two different phenotypes. In the first phenotype (L, related to low elastance, low lung weight, and low recruitability), ventilation-perfusion mismatch would predominate, with relatively preserved pulmonary mechanics (compliance around 40-50 ml/cm H2O). In L phenotype, the main pathophysiological phenomena would be the lack of regulation of the pulmonary vasculature, with loss of the hypoxic vasoconstriction mechanism, inflammatory hyperemia of the collapsed areas, and hypoperfusion of the peripheral regions. This phenotype usually corresponds to an early phase of the disease. The second phenotype (or H phenotype) would be like classic ARDS, with high elastance, recruitability, and collapse of dependent areas, often corresponding to a later phase of the disease. In both cases, the presence of thrombotic phenomena at the level of the

pulmonary micro and macrovasculature can further aggravate the ventilation perfusion mismatch (4, 5). Interestingly, despite severe hypoxemia, the infected patients often present with less dyspnea than expected (the so-called "happy hypoxemia" or "silent hypoxemia"), probably due to the preserved pulmonary mechanics, as demonstrated by Chiumello et al. in a comparative study about the features of C-ARDS and non-COVID ARDS (6). Another physiopathological explanation for this "happy hypoxemia" has been proposed by Jounieaux et al. (7). As stated by these authors, the presence of right-to left intrapulmonary shunt induces hypoxemia, leading to an increase in minute ventilation. This increase in minute ventilation may not be enough to increase SpO_2 (as oxygenation increase may be blunted by shunt effect) but may lead to hypocapnia. Hypocapnia has been proven to be a strong driver to decrease dyspnea. For these reasons, the acronym "AVDS" (acute vascular distress syndrome) has been proposed by these authors (7, 8). Other authors have proposed several other mechanisms to explain this silent hypoxemia, such as fever (shifting to the right the oxygen dissociation curve), age, some comorbidities, or pulsioxymetry sampling limitations (9). The underlying vascular abnormalities have also been demonstrated both in autopsy series and in radiological studies (10, 11).

Orotracheal intubation and mechanical ventilation, with protective strategies to avoid aggravating lung injury, have been the main ventilatory support treatments for conventional ARDS, until resolution of the causal process (12). However, in COVID-19, the large number of patients who were infected simultaneously caused the demand for mechanical ventilation to be widely exceeded. In this overwhelming setting, many patients with COVID-19 and ARF required non-invasive respiratory support (NIRS), beyond conventional oxygen therapy (COT). However, there are no unitary protocols regarding when NIRS should be started, what type of support to use, its duration, failure criteria, and treatment withdrawal.

There is a wide range of experience in the use of different non-invasive respiratory support modalities that may need to be reviewed. Non-invasive ventilation (NIV) or CPAP has been used to avoid intubation in hypoxemic patients for more than 20 years (13). Throughout the last decade, another form of NIRS, the high-flow oxygen therapy (HFOT), has gained popularity. It started as a tool mostly used in pediatrics, and jumped to adult use with a growing body of evidence. Nowadays, its use has expanded in an exponential way (14).

For the current narrative review, a PubMed search was performed with the following MeSH headings and search strategy: ((((((“Continuous Positive Airway Pressure”[Mesh]) OR “Respiratory Therapy”[Mesh]) or “Noninvasive Ventilation”[Mesh]) OR “Intermittent Positive-Pressure Ventilation”[Mesh]) OR “Positive-Pressure Respiration”[Mesh]) OR “high flow nasal cannula” [Mesh] OR “high flow oxygen therapy” ([Mesh]) AND ((“COVID-19”[Mesh]) OR (“SARS-CoV-2”[Mesh])))))) AND TREATMENT[filter]. Search was restricted to “Clinical trials,” “Meta-Analysis,” “Randomized Controlled Trial,” “Review,” and “Systematic Review.”

With that search strategy 737 results were screened, and 212 results were finally retrieved. As we did not intend to perform a meta-analysis, we refined the search eliminating case reports or other trials not related to non-invasive respiratory support. **Figure 1** shows the PRISMA-based flowchart (15) for the selection of references.

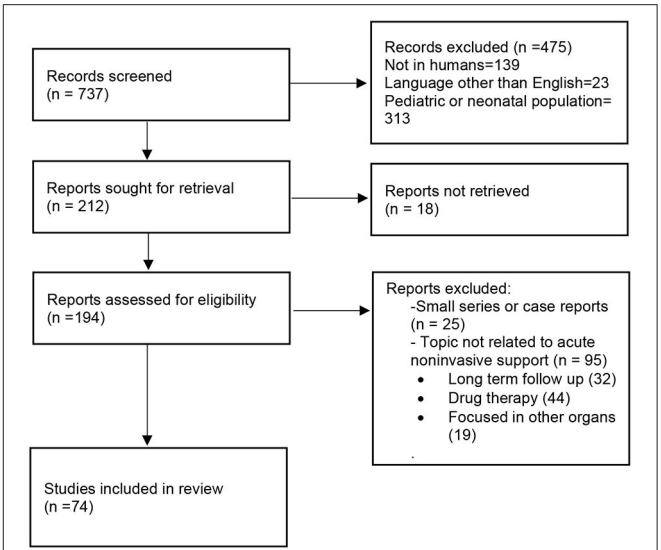

FIGURE 1 | PRISMA-based flowchart for the selection of references.

THE ROLE OF NON-INVASIVE VENTILATORY SUPPORT IN COVID-19

Traditionally, in hypoxemic ARF in acute respiratory distress, one of the main concerns is the increased mortality associated with intubation delay. Thus, NIV has been widely questioned as a support method. In a recent international observational study that included 2,813 patients with acute respiratory distress (ARDS), those initially treated with NIV (15%) and severe hypoxemia ($PaO_2/FiO_2 < 150$ mm Hg) had higher mortality (36.2%) than those ventilated invasively (24.7%) (16). In contrast, HFOT has emerged as a non-invasive strategy for avoiding intubation and invasive ventilation. In the FLORALI study (17), although the result for the primary endpoint (intubation rate) was negative, mortality and the number of days free of mechanical ventilation were significantly lower in the group treated with HFOT. In the subgroup study, the authors found a significant reduction in the intubation rate in patients with more severe hypoxemia ($PaO_2/FiO_2 < 200$).

Based on these previous experiences in hypoxemic ARF and NIRS, as the first phase of the COVID-19 epidemic overflowed, several guidelines from different countries recommended early intubation of critically ill patients with COVID-19 and ARF, also as a means of protecting healthcare workers from cross-infection (18, 19).

One of the main reasons stated for recommending early intubation in patients with COVID and ARF would be the fact that the use of NIRS techniques delays rather than prevents intubation. This delay, while maintaining spontaneous respiratory pattern with tachypnea and high tidal volume,

may lead to the worsening of the so-called patient self-induced lung injury (P-SILI). P-SILI has been linked to various pathophysiological phenomena: (a) increased effort, both inspiratory and expiratory, can lead to an increase in transpulmonary pressure (stress) and strain (increase in volume with respect to its baseline value). The intensity of the inspiratory effort has been correlated as a surrogate of the neural drive associated with relapse in patients with COVID 19 (20); (b) inhomogeneity in gas distribution, with areas with different time constants and intrapulmonary gas redistribution between them (pendelluft phenomenon); and (c) changes in pulmonary perfusion (21).

On the other hand, the defenders of NIRS techniques (high nasal flow and positive pressure, either continuous positive pressure—CPAP- or bilevel) argue that they can avoid unnecessary endotracheal intubations and that the liberal use of invasive ventilation and its associated consequences (muscular atrophy and ventilation associated infections) may lead to increased mortality.

The experience in the use of NIRS in COVID-19 comes mainly from retrospective observational studies, with extremely variable failure rates, ranging between 20 and 60%, and biased populations (i.e., age selected, Intensive care Unit—ICU—or ward environments). A meta-analysis about non-invasive ventilatory support (HFOT was excluded) as a therapeutic option outside the Intensive Care Units included 3,377 patients. Overall mortality was 38%, although it is possible to distinguish the group of patients without therapeutic limitation (19%) from that of patients with orders of no intubation (72%). Mortality in patients with NIV failure who were ultimately intubated was 45% (22).

There are no prospective studies focused on the outcome of patients with direct intubation vs. a previous trial with non-invasive support. A recent meta-analysis that included 8,944 patients showed no benefit of early intubation compared to intubation delayed more than 24 h after admission to the ICU, neither in mortality nor in days of mechanical ventilation. Mortality was also not significant in patients who received treatment with high nasal flow or non-invasive ventilation compared to those who did not receive such treatment before intubation (23).

Therefore, with the available data, the use of NIRS does not seem to lead to a worse prognosis when compared with direct orotracheal intubation.

BEYOND OXYGEN THERAPY. WHEN TO START NON-INVASIVE VENTILATORY SUPPORT

Conventional oxygen therapy has clearly been the main supportive technique in ARF secondary to COVID-19 (24). However, in a percentage of patients this technique may not be enough to ensure proper oxygenation, and it has been necessary to choose between available NIRS techniques: high nasal flow therapy, treatment with positive pressure-CPAP, or bilevel pressure systems (25). A paramount issue is the timing of starting a NIRS. Both positive pressure systems and high nasal flow have a certain unloading effect on the inspiratory musculature, while improving pulmonary gas exchange. On the other hand, the efforts made by the patient in spontaneous ventilation in the presence of respiratory failure can aggravate P-SILI, through increases in transpulmonary pressure, either globally or limited to regional distribution. Therefore, the appropriate timing for the establishment of non-invasive ventilatory support can preclude effects on P-SILI and decrease of the respiratory drive can predict success (26).

The early recommendations at the beginning of the first wave were based on previous experiences in non-COVID patients and the consensus of experts. Some societies recommended starting non-invasive support when oxygen needs exceed FiO_2 of 0.4, in addition to clinical criteria, mainly tachypnoea (27). The early Italian triage led to the identification of four patient categories: (a) green ($SaO_2 > 94\%$, respiratory rate (RR) < 20 breaths/min); (b) yellow ($SaO_2 < 94\%$, RR > 20 but responds to 10–15 L/min oxygen); (c) orange ($SaO_2 < 94\%$, RR > 20 but poor response to 10–15 L/min oxygen and requiring CPAP/NIV with very high FiO_2); and (d) red ($SaO_2 < 94\%$, RR > 20 but poor response to 10–15 L/min oxygen, CPAP/NIV with very high FiO_2 or presenting respiratory distress with $PaO_2/FiO_2 < 200$) and requiring endotracheal intubation and intensive care (28). In this classification, employed in a multicenter retrospective study (29), the indication to start NIV corresponded to the third degree of severity of the ARF (orange). The German position paper suggested starting O_2 or HFOT when $PaO_2 \leq 55$ mm Hg and RR $\geq$ 30/min on room air (30). In the NHS guidelines, the criteria proposed for the initiation of CPAP and O_2 were the inability to maintain SpO_2 between 92 and 94% with an FiO_2 between 0.4 and 0.6 (31). Some experts proposed two different scenarios for starting NIRS: Early start (PaO_2: $FiO_2 < 300$ or $SpO_2 < 93\%$ on $O_2 > 5$ L/min or $SpO_2 < 94\%$ with FiO_2 40%) or late start ($SpO_2 < 92\%$ under O_2 at 15 L) (32). Regardless, definition of early start is not homogeneous, and there is scarce evidence to support it. García Pereña et al. retrospectively compared the use of early HFOT (in patients with $PaO_2/FiO_2 > 100$) vs. patients with $PaO_2/FiO_2 < 100$, finding significant differences regarding the rate of intubations (lower in the group with $PaO_2/FiO_2 > 100$), with mortality at the limit of significance (33). Deng et al. retrospectively compared mortality among elderly patients who received HFOT with a PaO_2/FiO_2 ratio between 200 and 300 (early) with another cohort with a ratio lower than 200 (late). Baseline conditions between both groups were similar and both mortality and complications were significantly lower in the group that received HFOT late (34). Obviously, both studies have the same limitation: in addition to being retrospective, there is a selection bias, since patients with "late initiation" represent a group that has previously failed to respond to conventional oxygen therapy, reflecting disease progression albeit treatment, while in the early group there are patients that may also respond to conventional oxygen therapy. Randomized, high-quality studies, are ongoing to define the effect of early HFOT in patients with ARDS secondary to COVID-19 (35).

On the other hand, randomized controlled studies not directed toward this endpoint also showed heterogeneity

when determining the criteria for initiating NIRS. Thus, the Respiratory Support Recovery trial defined the clinical condition for randomization those patients with a need for $FiO_2 \geq 0.4$ and a peripheral $SpO_2 \leq 94\%$(36), while the HENIVOT study (37) requires a PaO_2/FiO_2 of < 200 as the sole criterion for the initiation of the SRNI. It should be noted, as suggested by Winck and Scala, that the PaO_2/FiO_2 index may not reflect the severity of the exchange, as it does not take into account the baseline $PaCO_2$ value, which is usually decreased in patients with ARF secondary to COVID-19 (38). More accurate seems to be the use of the alveolar-arterial oxygen gradient.

In addition to the opinions of experts, there may be another reason related to the technique of oxygen therapy administered in a Venturi effect mask. It was shown that the gas mixture from FiO_2 of 0.4 can provide up to 50 L/min in the mask, so that in patients with high ventilatory drive that exceed these flow demands, the effective FiO_2 in the mask may be lower (39).

NON-INVASIVE SUPPORT MODALITIES. ESCALATING ALGORITHMS AND THE ROLE OF COMBINED THERAPIES

Since the beginning of the pandemic, heterogeneous recommendations about the most preferred modality (HFOT, CPAP, NIV) appeared in the literature. Whereas some societies emphasized the need for early orotracheal intubation, others recommended a trial with non-invasive ventilatory support, with important differences in the first-line modality: most experts recommended HFOT, although others preferred treatment with positive pressure systems (mainly CPAP) and even with specific interfaces (helmet) (28, 30, 31).

The use of high nasal flow in non-COVID hypoxemic ARF is supported by high-quality controlled studies that show a decrease in mortality compared to conventional oxygen therapy and non-invasive ventilation, especially in patients with a PaO_2/FiO_2 ratio lower than 200. In addition, it is a better tolerated technique when compared with CPAP (17). Moreover, the distribution of tidal volume is more homogeneous than conventional oxygen therapy, protecting the lung against P-SILI (40). On the other side, the PEEP effect achieved is usually less than with true positive pressure systems and it should take into account that the combination of high FiO_2 and low PEEP values maintained has long been associated with de-recruitment phenomena (resorption or denitrogenation atelectasis) in patients with acute lung injury (41). As maintained supraphysiological oxygen levels were associated with an increased mortality in a large, unselected multicenter cohort of critically ill patients (42), a close monitoring and later adjustment of inspired FiO_2 in C ARDS patients seems adequate.

In clinical practice, in a survey that included responses from 502 units from 40 countries, high nasal flow was the most widely used NIRS modality (53%) in cases of mild-moderate ARF, followed by systems of positive pressure (47%) (25). In the same way, a study carried out in an ICU setting highlighted the heterogeneity of treatments between the different origins of the participants, although HFOT was the most used strategy (47%) followed by CPAP/NIV (26%) and early direct intubation (7%) (24). In fact, in an expert consensus based on the Delphi method, 97% of them agreed that HFOT can be considered as an alternative strategy for oxygen support before invasive mechanical ventilation, and should be used in patients who are unable to maintain $SpO_2 > 90\%$ using oxygen delivery through a Venturi mask or may be used in patients with increasing oxygen requirement to avoid endotracheal intubation (43).

Regarding its efficacy, Demoule et al. in a retrospective study with data from the first 2 months of the pandemic, showed a lower intubation rate in the group that received high nasal flow compared to conventional oxygen therapy, although patients with this second group had more severe disease, with a higher rate of acute kidney failure and need for vasopressors (44). Similarly, Bonnet et al. also in a retrospective study, demonstrated an increase in ventilation-free days and a lower intubation rate in patients who received high nasal flow compared to those who received conventional oxygen therapy, but without any differences on mortality between the two groups (45).

The better tolerance and the lack of ICU beds during pandemic peaks have led to increased HFOT use outside the intensive care units, or in patients with do not intubate (DNI) orders (46). Medrinal et al. compared two cohorts of patients, a first group with DNI orders and a second group without therapeutic limitation. In the first group, mortality was 60% (lower in patients who received high nasal flow compared to those who received a miscellaneous group of therapies) while in the second group it was only 26%. In any case, whether HFOT was used in patients as a ceiling therapy or as a first line for *de novo* respiratory failure, it was associated with lower mortality. However, it is not clear whether the patients included in the study underwent sequential escalation treatment in case of failure of high nasal flow (47). In a small study in elderly patients, after adjustment, HFOT was associated with less mortality than conventional oxygen therapy (48).

There are few prospective studies comparing high nasal flow with other non-invasive support modalities. Grieco et al. in a randomized study (37), did not find any differences in mortality between the CPAP modalities with helmet and high nasal flow, although the intubation rate and days free from invasive ventilation were lower in the group that received CPAP. Finally, in the prospective study RS-RECOVERY (preprint), the use of conventional oxygen therapy vs. high nasal flow did not show differences in the composite endpoint intubation or mortality at 30 days (45.1 vs. 44%), while the CPAP group showed a lower incidence of such an endpoint (36).

The second therapeutic option for the treatment of ARF are the positive pressure devices, either CPAP or pressure support. The effect of expiratory positive pressure prevents alveolar collapse and improves ventilation-perfusion relationships and, ultimately, pulmonary gas exchange. The addition of pressure support can theoretically contribute to unloading inspiratory muscles. However, in hypoxemic ARF, the use of positive pressure systems, except for acute cardiogenic lung oedema, remains controversial. In fact, the expert consensus in the respiratory management ARF in COVID-19 recommended only NIV in presence of mixed respiratory failure (hypoxemia and

hypercapnia) and in selected patients with increased work of breathing (43). The increased respiratory drive characteristic in COVID patients and their relatively preserved lung mechanics (compliance) can lead to high tidal volumes when using pressure support. High tidal volumes (>9.2 or 9.5 ml/kg) under NIV are associated with increased mortality (16, 49), probably related to "unprotective" mechanical ventilation. On the other hand, the use of high-quality pressure ventilators equipped with monitoring capabilities can help to monitor reliably and continuously the respiratory rate and the tidal volume, except for helmet interface use.

The early experiences of treatment with positive pressure have already demonstrated a superiority compared to conventional oxygen therapy in terms of the prevention of orotracheal intubation, even with a moderate sample size (50). Positive pressure systems have been recommended as the first line of non-invasive ventilatory support in COVID, especially in countries such as Italy or England (28, 31).

Among the positive pressure modes, the most widely used has been CPAP. In a meta-analysis that included 3,377 patients treated with positive pressure systems outside the Intensive Care Units, a total of 2,764 patients were treated with CPAP and 1,855 with helmet interface (22).

Treatment with positive pressure modes has been used in two different clinical situations: as preventive therapy for orotracheal intubation and as a rescue NIRS in patients with a therapeutic ceiling, mainly DNI orders. In an observational comparative study between both clinical situations, Walker et al. (51), demonstrated a mortality of 25% in the group of patients without DNI orders and 84% in the second, questioning whether CPAP offered an additional benefit in patients with therapeutic ceiling compared to conventional oxygen. In a single-center retrospective study, from 310 patients with ARF treated in the emergency department, 27 had DNI orders and were treated with CPAP, with the overall mortality at 88%. Finally, a UK multicenter study compared conventional oxygen therapy vs. CPAP as a ceiling of care in ward-based patients with COVID-19. Overall mortality showed no differences between the groups that received oxygen (75.6%) and CPAP (77.7%). Nearly 50% of patients who received CPAP chose to discontinue it (52). Despite being considered one of the best interfaces for delivering CPAP, Coppadoro et al. reported 75% of failure in DNI patients receiving CPAP through helmet outside ICUs (53).

In contrast, other studies reported lower rates of failure and mortality: in a prospective single-day study to describe the use of positive pressure systems outside the ICU, 85% received CPAP (68% with a helmet). Overall mortality was 25%, with a success rate of 60% (75% in patients without therapeutic limitation). The failure rate in patients with previous DNI orders was 52% (54). In the second wave, a UK study reported a 56% rate of survival in patients where CPAP was the ceiling of care. Interestingly, the mean time of CPAP use was 9 days (55). Similar results were reported by Aliberti et al. with a mortality of 55% (36/65) in patients with DNI orders using helmet CPAP (56). These discrepancies suggest that the success or failure of the technique is attributable to various aspects, such as the selection of patients, the experience of the team, or the specific protocols of each hospital, with differences in the starting criteria, the interface used, or the level of monitoring. Related to this latter issue, the value of respiratory intermediate care units has been demonstrated both as stepping down (patients transferred from the ICU) and stepping up methods. Matute-Villacís et al. reported 10% mortality in stepping down patients (most of them tracheostomized) and 25% in stepping up ones (57). When available, it would be important, even for selected patients with DNI orders, to organize medical units with basic monitoring capabilities and trained teams for delivering NIRS. In a Spanish survey, the number of existing intermediate care units in the Spanish Public Health System increased from 16 to 41 during the pandemic, bringing the increase in total beds from 112 to 525 (58).

Finally, measurements of activity and quality indicators should be implemented in each service providing NIRS outside ICU to acquire valuable data that may allow to enhance the provided care or determine if any improvement is needed. The final goal would be to use NIRS in selected DNI patients with higher survival probabilities, avoiding at the same time unnecessary extended dying processes in non-responders.

Regarding the efficacy to avoid intubation, in the previously mentioned meta-analysis, from the 75% of survivors in the group of patients who were candidates for intubation, 31% required IMV and 43% only SRNI (22). In a study including patients who were candidates for intubation and invasive ventilation but who could not receive such treatment due to the shortage in the context of massive influx of patients, intubation was avoided in 37% of patients, who were managed only with CPAP (59). Similar results (40% efficacy) were reported by Noeman-Ahmed et al. (60). Fairly better results were reported in a group of patients with moderate ARF ($PaO_2/FiO_2 < 200$ and RR < 30), with 85% of successful management exclusively with CPAP (61). A meta-analysis including more than 4,700 patients showed that CPAP and NIV were equally employed (48.4 vs. 46%). Interestingly, almost half of patients exposed to CPAP/NIV failed the non-invasive support trial and only half of failing cases were eligible for intubation. Finally, mortality was higher in patients treated with NIV (35.1%) than in patients treated with CPAP (22.2%), even though the number of failures was similar in each group (62).

Retrospective comparative studies between techniques of non-invasive support also offer heterogeneous results. The study by Franco et al. showed that there were no differences on mortality between patients who received NIV, CPAP, or HFOT, with mortality and the need for intubation being more related to the severity of respiratory failure ($PaO_2/FiO_2 < 50$), age, and number of comorbidities than with the type of support used (29). The proportion of NIRS failures was between 25 and 30% for the three modalities, despite the patients who were treated with NIV seeming to be in worse clinical conditions (more tachypnea and lower PaO_2/FiO_2 ratio). Interestingly, in all the hospitals that participated in the study, patients were treated in monitored areas by skilled teams. A study conducted in Ireland with a similar design compared oxygen therapy, positive pressure, and HFOT: an improvement in arterial blood gases was documented mainly in patients transitioned from oxygen to CPAP but without

differences on mortality both in patients with and without DNI order (63).

In a matched retrospective of COVID-19 patients admitted to the ICU, the four therapeutic supportive therapies (oxygen therapy, high nasal flow, non-invasive ventilation, and direct intubation) were compared. The group with the highest mortality received non-invasive ventilation (64).

There are a few prospective randomized controlled studies comparing different non-invasive support modalities. Grieco et al. (37), in the HENIVOT study, randomized 110 patients to receive support therapy with HFOT or helmet CPAP. The primary endpoint was the number of days free of respiratory support at day 28. The nine secondary endpoints were related to need for intubation, mortality, ICU stay, and number of days free of invasive ventilation. Among the nine secondary endpoints, only the intubation rate and number of days free of invasive ventilation achieved statistical significance, both favoring the group of helmet CPAP.

The RS-Recovery trial (36) is a three-arm randomized controlled trial on three non-invasive respiratory strategies (conventional oxygen therapy, high flow, and CPAP). The primary outcome was a composite of tracheal intubation or mortality within 30 days. 1,272 patients were randomized. The need for tracheal intubation or mortality within 30 days was lower in the CPAP group (35%) whereas no differences were found in HFOT and conventional oxygen therapy group (44.4 and 45.1% respectively). Interestingly, all interfaces were permitted in the CPAP group, not exclusively helmet. Some crossovers between groups should be noted as a limitation, although they may have favored the conventional oxygen group.

In clinical practice, however, it is not common to find patients with a pure ventilatory support strategy throughout the course of the disease. Patients often receive a variety of supportive treatments, escalating in case of a lack of response or in combination. In the first setting, positive pressure therapy has also been recommended in case of insufficient response to high flow (30, 38). In this regard, it should be noted that a group of English experts considered the use of NIMV as inappropriate in case of failure of the first line of treatment, recommending direct intubation (65).

Both scenarios were retrospectively studied by Colaianni et al. (66) in a clinical study conducted under a careful algorithm for managing ARF in COVID patients. The first step was HFOT and prone position. In case of failure, a CPAP trial, combined with periods of HFOT, was initiated. The first step had a failure rate of 10/65, but mainly due to CPAP intolerance. In the second group (HFOT + CPAP) the failure rate was 20/48. Mortality in intubated patients was 55%. Of note, combination of modalities is not uncommon in clinical practice, especially pauses in CPAP/NIV therapy using HFOT, for example for feeding breaks (29).

Finally, prone position in non-intubated patients has been a complementary strategy for managing COVID patients with ARF. In patients who are intubated and have moderate to severe acute respiratory distress syndrome, prone positioning is an effective intervention to improve oxygenation and reduce mortality, while improving ventilation in dependent lung areas. It is recommended in guidelines for patients with a PaO_2/FiO_2 ratio < 150, in sessions of 16 h/day (67). Awake prone positioning has been associated with improved oxygenation in observational studies of non-intubated patients with acute respiratory distress syndrome (68) and, more recently, it has been demonstrated that it is feasible in patients with COVID-19, with improvements in blood oxygenation that are maintained after re-supination in about half of patients (69). The expert consensus stated that awake self-proning may improve oxygenation when used in patients with C-ARDS requiring supplemental oxygen to maintain oxygen saturation > 90% (43).

The APRONOX study (70), compared outcomes of patients with various sources of oxygen therapy (low-flow, high-flow, and reservoir mask) who underwent prone sessions of at least 2 h duration. The total mean duration of the prone was 12 h during the entire hospital stay and the SpO_2/FiO_2 ratio increased significantly after the prone sessions (from 183 to 212). There were also significant differences in the proportion of intubations (23% in the prone group, 40% in the supine group). Mortality in intubated patients was close to 70%.

Ehrmann et al. (71), in a meta-trial that included patients from six different trials, compared the outcome of 1,126 patients randomized to high flow and prone position or to high flow and standard treatment. Patients with a PaO_2/FiO_2 lower than 300 were included, although the mean PaO_2/FiO_2 in both groups at the time of randomization was around 150. Prone time was variable, with a mean of 5.6 h, but with wide variation among participating countries (from 1.6 to more than 8 h). The composite endpoint (treatment failure or death) was significantly lower in the high-flow and prone group. To avoid treatment failure, a NNT of 15 was required. 28-day mortality was not statistically significant globally or in the group of patients who failed in both groups, which shows that the prone test did not worsen the prognosis of patients who failed. Finally, patients in the prone group were more likely to be released from high flow therapy than the control group.

Despite the beneficial effects on blood oxygenation of awake proning, a proportion of patients, which could be up to 60%, do not tolerate it (69, 72, 73). A variant of postural treatment (Rodin's thinker) has recently been proposed, with the patient sitting on a chair and rest their chest on a flat, elevated surface (semi-prone position). Coppo et al. reported a significant improvement in blood oxygenation in 25 patients with this postural treatment. After re-supination, the blood oxygenation was better than the baseline values (74).

Table 1 summarizes the main studies about NIRS, with emphasis in the NIRS starting criteria, type of support, and results.

EVALUATION OF THE RESPONSE TO SRNI

Early evaluation of the established non-invasive support modality seems to be of the utmost importance when deciding whether to continue with the same therapeutic approach, change the modality, or proceed with orotracheal intubation.

TABLE 1 | Summary of the main studies about NIRS, with emphasis in the NIRS starting criteria, type of support, and main results.

References	*N*	Design	Criteria for starting non-invasive support	Type of support or intervention	Environment/DNI status	Main results
Perkins et al. (36)	1,272	RCT	SpO_2 > 94 on FiO_2 0.4	CPAP (m = 380) HFNC (n = 417) COT (n = 475)	Not stated/full treatment (no ceiling)	CPAP associated with less mortality and intubation than COT (36 vs. 44%). No advantage of HFNC
Griecoet al. (37)	110	RCT	PaO_2/FiO_2 < 200. Non-hypercapnic	Helmet CPAP vs. HFNC	ICU/no ceiling	No differences in 28 d mortality. Helmet CPAP associated with less intubation than HFNC (30 vs. 51%)
Franco et al. (29)	670	Retrospective observational	SaO_2 < 94%, poor response to 10–15 L/min oxygen.	HFNC CPAP NIV	Pulmonary Ward (4% with DNI orders)	30-day mortality HFNC: 16% CPAP 30% NIV 30%/ ETI rate: HFNC 27% CPAP 25% NIV 28%
Aliberti et al. (56)	157	Retrospective observational	PaO_2/FiO_2 < 300 with O_2 at (FIO_2 of at least 0.50) or reservoir mask.	Helmet CPAP	High dependency Unit/41% DNI orders	CPAP failure was observed CPAP failure 45%, 21% ETI (of them, 26% died), 22% dead in HDU. CPAP failure associated with IL-6 levels, and severity scores
Oranger et al. (50)	66	Retrospective observational	SpO_2 < 92% with O_2 6 lx'	CPAP vs. COT	Pulmonary ward/12% DNI orders	57% failure prealgorithm, reduced to 23% post algorithm
Demouleet al. (44)	379	Retrospective observational	RR > 25 Need for $O_2 \geq$ 3 l/min for Spo2 ≥ 92%	HFOT vs. COT	ICU/no ceiling	Higher baseline severity in COT group Intubation rate 56% in HFOT group vs. 75% in COT group
Bonnet et al. (45)	138	Retrospective observational	RR > 25 Need for $O_2 \geq$ 3 l/min for Spo2 ≥ 92%	HFOT vs. COT	IC/no ceiling	Intubation rate 51% in HFOT group vs. 74 % in COT group. No differences on mortality. Higher severity in the HFOT group at ICU admission (higher RR and O_2 needs)
Medrinal et al. (47)	400	Retrospective observational	PaO_2/FiO_2 < 300 or SpO_2 < 94% with at least O_2 10 L/min	Multiple therapies (COT, HFOT, CPAP, NIV, and combinations)	ICU/Intermediate care unit/32.5% DNI orders	Mortality: 60% in the group with DNI orders, 26% in full treatment group. Lower mortality with HFOT in DNI orders.
Walker et al. (51)	294	Retrospective observational	SpO_2 < 94% with FiO_2 0.4	CPAP vs. COT	ICU and ward/DNI orders 53.4%	Mortality: 84% in the group with DNI orders, 25% in full treatment group.
Bradley et al. (52)	479	Retrospective observational	Need for $FiO_2 \geq$ 0.4. Clinical frailty score < 6	CPAP vs. COT	Ward(100% DNI orders)	No differences on mortality (75 % in COT group, 77 % in CPAP)
Coppadoro t al. (53)	306	Retrospective observational	Reservoir mask and: SpO_2 < 93% or RR > 24.	Helmet CPAP	Ward (42% DNI orders)	Helmet CPAP was successful in 28% DNI order group and in 69% full treatment group
Gough et al. (63)	164	Retrospective observational	>4L/min oxygen to maintain SpO_2 > 92%	CPAP = 85 HFOT = 32 COT = 47	Ward (33.5%DNI orders)	Mortality 56% in DNI group without differences on NIRS techniques. No differences on IMV ratio between techniques in full treatment group
Perez Nieto et al. (70)	827	Retrospective observational	SpO_2 < 94 % (room air)	Awake proning vs. no proning	ICU/Ward	Lower intubation and mortality rates in awake proning (both matched and non-matched models). 70% mortality in intubated patients.

In the use of HFOT, one of the most widely used indices in clinical practice is the ROX (SpO_2/FiO_2: RR) at 2, 6, and 12 h after starting treatment (75). An increase in this index has been associated with patient improvement. The cut-off point accepted in the pre-COVID era in patients with pneumonia and hypoxemic ARF (75) was 4.88 in the ranges described (rates higher than 4.88 were associated with treatment success).

Specifically in COVID patients, Chandel et al. demonstrated that a ROX index > 3.0 at 2, 6, and 12 h after initiation of HFOT was 85.3% sensitive for identifying HFOT success (76). On the contrary, Zucman et al. determined that the most sensitive cut-off point for intubation risk was 5.37 at 4 h (77). Finally, in patients with whom high nasal flow was indicated outside the ICU, Vega et al. determined that the value with the highest sensitivity was 5.9, while the classic value of 4.88 was not sufficiently discriminating (78). However, regardless of the specific cut-off point, it seems more reasonable to monitor the trend of the ROX index throughout treatment, as proposed by Xia et al. who demonstrated that the trend to decrease in the ROX index and the increase in the RR over 3 days were predictors of failure (79).

Other authors proposed only the change in respiratory rate as a predictor of HFOT success or failure. Blez et al. demonstrated a discriminant power of the change in RR 30 min after starting the treatment similar to that of the ROX index (80).

In positive pressure treatment, Amati et al. studied the response in the recruitment in a group of patients who were shifted to CPAP and helmet, with PEEP values up to 15 cm H2O. Of the 34 patients included in the study, only nine had a complete response and 17 a partial response. The parameters proposed to consider a response as complete (all of them had to be met) were a 20% decrease in the alveolar-arterial gradient, a decrease in respiratory rate with respect to baseline, an increase in Spo2, and good clinical and hemodynamic tolerance (81). Aliberti et al. defined lung recruitability during helmet CPAP treatment as an increase of PaO_2/FIO_2 ratio of at least 30% from oxygen therapy (baseline) to CPAP treatment (within 6 h) (56). This endpoint was achieved only in 52% of the study population.

Similar short-term criteria were described by De Vita et al. as predictors of CPAP treatment failure (in addition to age and lactate level). While in patients with CPAP failure, the improvement in PaO_2 was 19%, in CPAP success it was 59% (82).

The HACOR score (Heart rate, Acidosis, Consciousness level, Oxygenation, and Respiratory rate) has been proposed as a bedside tool for predicting NIV failure (83). It has also been explored as a predictive score for CPAP failure in a multicenter study. Although the performance was quite good (82%), it was similar to PaO_2/FiO_2 ratio (81.25%) (84).

In an interesting study with continuous measurement of esophageal pressure as a surrogate of patient's inspiratory effort, Coppola et al. demonstrated that the early predictors of failure (measured on the first day of treatment) under CPAP or pressure support treatment were the PaO_2/FiO_2 ratio, the intensity of changes in esophageal pressure, and the total stress lung. This last concept, which was the only independent factor related to failure in the multivariate analysis, is equivalent to the total transpulmonary pressure, and includes concepts such as applied pressure support, changes in esophageal pressure, or set PEEP value (85).

THE DURATION OF NON-INVASIVE SUPPORT. FAILURE CRITERIA. HOW TO DEESCALATE

The duration of NIRS in COVID patients seems clearly longer than in non-COVID patients, but with huge variability. In the meta-analysis by Cammarota et al. (22) the mean time of non-invasive support (CPAP-NIV) until orotracheal intubation in patients with NIRS failure ranged between 72 and 137 h. In responders, the mean time of total duration of NIRS ranged between 2 and 12 days.

This long NIRS time may increase the probability of late failure, with a worsening of the prognosis if intubation is required. This point has been the subject of research in few studies. In an observational study, Boscolo et al. determined that the ventilation time prior to admission to the ICU was one of the determining factors of mortality in patients in whom NIV failed. Although there were no significant differences between patients who were directly intubated and those who underwent failed NIV trial prior to intubation, in patients with a duration of ventilation >48 h outside the ICU, the authors found a significant increase in mortality (86). Similarly, Vaschetto et al. determined that CPAP use time ≥ 3 days was an independent predictor of mortality in the event of CPAP failure and intubation (87).

Given these data, it seems especially important to closely monitor patients under NIRS who are treated for more than 72 h with any supportive therapy. In the event of late deterioration in respiratory conditions in these patients, orotracheal intubation and invasive mechanical ventilation should be considered immediately. In addition to the classic criteria for invasive ventilation (hemodynamic instability, decreased level of consciousness, appearance of signs of muscle fatigue, or development of unmanageable tracheal secretions), predefined respiratory conditions for intubation should be protocolized, especially in late failure. For example, Aliberti et al. proposed a combination of major and minor criteria for considering intubation (at least 1 major or at least two minor criteria lasting for ≥1 h). The reduction of ≥30% of basal PaO_2/FIO_2 ratio, the PaO_2/FIO_2 ratio < 100 and the increase of arterial carbon dioxide tension if basal arterial carbon dioxide tension was ≥40 mmHg, and oxygen saturation measured by pulse oximetry (SpO_2) < 90% a are some of the minor criteria (56). The HENIVOT study defined failure and need for invasive ventilation when two or more were present: the oxygenation worsening was defined as oxygenation and/or SpO_2 below 90% for more than 5 min (37). It is also important to rule out pulmonary embolisms as a potential cause of acute oxygenation alterations, the incidence of which has been shown to be higher in COVID patients under ventilatory support (88).

In summary, it would be cautious to consider orotracheal intubation in those patient candidates who after 48-72 h of NIRS do not present significant clinical improvement, as well as in those patients with acute worsening of a previously stable

situation, or with highly compromised respiratory conditions ($PaO_2/FiO_2 < 100$).

Finally, prolonged treatment times with NIRS may require progressive support withdrawal. Up to now, there have been no definite results about the ideal method. In patients using HFOT, the ongoing SLOWH study protocol proposes the comparison between three branches for the withdrawal of high nasal flow (low FiO_2, low flow, or simultaneous) (89).

For CPAP users, the model proposed and standardized across the three hospitals that participated in the study was as follows: patients who did not show signs of respiratory distress (e.g., respiratory rate < 25 breaths·min^{-1}) and maintained a $SpO_2 > 94\%$ with a $FIO_2 < 50\%$ and a PEEP ≤ 5 cmH2O underwent a weaning trial. Patients maintaining a PaO_2/FIO_2 ratio > 250 on Venturi mask with a $FIO_2 < 40\%$ for at least 24 h were considered successfully weaned from helmet CPAP (56). In the HENIVOT study, weaning was performed by reducing positive end-expiratory pressure and pressure support to 8 cmH2O. If the patient maintained $SpO_2 \geq 92\%$ and respiratory rate equal to or lower than 25 breaths/min for 30 min, non-invasive ventilation was interrupted (37).

CONCLUSIONS

The use of non-invasive support, especially in situations of high simultaneous influx of critical patients, helps to avoid intubations and invasive mechanical ventilation in COVID patients. The decision for starting NIRS is a combination of oxygenation derangement (PaO_2/FiO_2 ratio, alveolar-arterial gradient) and clinical signs (tachypnea and inspiratory effort). Albeit scarce, the few high-quality randomized controlled studies have shown an advantage of Continuous positive airway pressure over other respiratory support techniques. In addition, HFOT plus prone position is a promising first step approach, and for some milder respiratory failure, HFOT alone may be an acceptable approach over COT.

For any kind of respiratory support employed, it is mandatory to monitor the efficacy in a short time frame. In the absence of response, prompt orotracheal intubation and invasive ventilation needs to be considered, if the patient is a candidate for full therapy. If the condition of the patient under NIRS remains stationary after 48-72 h, orotracheal intubation should also be considered. Not all the patients may be candidates for invasive ventilation. For those patients with DNI orders who receive non-invasive ventilatory support, high mortality can be expected. It should be taken into account while starting or maintaining potentially futile treatments (in cases without response) that are not free from secondary effects and may pose relevant discomfort in dying patients.

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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Corticosteroid Treatment Prevents Lipopolysaccharide-Induced Increase of ACE2 and Reduces Fibrin Degradation Products in Bronchoalveolar Lavage Fluid

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The assessment of systemic corticosteroid effects on intrapulmonary disease biomarkers is challenging. This retrospective evaluation of a human endotoxemia model quantified ACE2 and fibrin degradation product (FDP) concentrations in bronchoalveolar lavage fluid (BALF) samples from a randomized, double-blind, placebo-controlled study (NCT01714427). Twenty-four healthy volunteers received either 2 × 40 mg intravenous dexamethasone or placebo. These doses were administered 12 h apart prior to bronchoscopy-guided intrabronchial lipopolysaccharide (LPS) stimulation (control: saline into the contralateral lung segment). We quantified ACE2 concentration, the Angiotensin-II-to-Angiotensin-1-7 conversion rate as well as FDP in BALF 6 h after LPS instillation. In placebo-treated subjects, LPS instillation increased ACE2 concentrations compared to unstimulated lung segments [1,481 (IQR: 736–1,965) vs. 546 (413–988) pg/mL; $p = 0.016$]. Dexamethasone abolished the increase in ACE2 concentrations (p=0.13). Accordingly, LPS instillation increased the Angiotensin-II-to-Angiotensin-1-7 conversion capacity significantly in the placebo cohort, indicating increased enzymatic activity ($p = 0.012$). FDP increased following LPS-instillation [8.9 (2.7–12.2) vs. 6.6 (0.9–9.6) ng/mL, $p = 0.025$] in the placebo group, while dexamethasone caused a shut-down of fibrinolysis in both lung segments. LPS instillation increased ACE2 concentration, its enzymatic activity and FDP, which was mitigated by systemic dexamethasone treatment. Our results strengthen previously published findings regarding the efficiency of corticosteroids for the treatment of COVID-19-induced acute lung injury.

Keywords: randomized controlled trial, acute lung injury, Renin-Angiotensin-Aldosterone System, Angiotensin-Converting Enzyme 2, fibrin degradation products

INTRODUCTION

Corticosteroids are widely used as an anti-inflammatory treatment in lung disease and have emerged as an effective treatment strategy in severe Corona Virus Disease 2019 (COVID-19) (1). Pulmonary edema is present in both COVID-19-induced and other forms of acute respiratory distress syndromes (ARDS), as a consequence of local inflammation and increased vascular permeability. Additionally, the contribution of vascular dysfunction to the pathogenesis of COVID-19 was highlighted (2). Lipopolysaccharide (LPS), a component of Gram-negative bacteria, may be instilled locally to model acute pulmonary inflammation. We have previously shown that dexamethasone reduces systemic inflammatory responses, pulmonary capillary leak and coagulation activation following bronchial instillation of LPS, while having limited effects on pulmonary pro-inflammatory cytokines (3, 4).

Angiotensin Converting Enzyme 2 (ACE2), a central enzyme of the alternative Renin-Angiotensin-Aldosterone System (RAAS), degrades angiotensin II (AngII), a proposed mediator of tissue damage in acute lung disease (5). The Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) uses ACE2 as entry receptor. Downregulation of ACE2 was observed in murine models of lung injury including infection with SARS-CoV-1 and pulmonary LPS stimulation (6, 7). It was subsequently hypothesized that downregulation of ACE2 may disturb the pulmonary and possibly the systemic RAAS, resulting in a certain form of severe lung injury compatible with COVID-19. This pathophysiological concept, however, is primarily based on murine models. Importantly, ACE2 has been identified as an interferon-inducible gene in humans, which contrasts its murine regulation (8). In line, we observed increased systemic ACE2 concentrations in patients with severe COVID-19 that were associated with elevated Interleukin-6 (IL-6) levels (9).

It is well-established that inflammation activates coagulation and fibrinolysis in bacterial pneumonia, the latter primarily mediated by tumor necrosis factor alpha (TNF-α) (10). In COVID-19, a high rate of pulmonary arterial thrombosis has been reported, and elevation of D-Dimer and fibrin degradation products (FDP) were identified as robust predictors of mortality (11).

In the light of the ongoing discussion on ACE2 in lung injury and the relevance of coagulation activation in COVID-19, we quantified ACE2, its enzymatic activity and FDP in bronchoalveolar lavage fluid (BALF) from a pulmonary inflammation model in healthy volunteers. We hypothesized that bronchial LPS instillation increases pulmonary ACE2 and FDP concentrations, which may be mitigated by systemic dexamethasone treatment.

MATERIALS AND METHODS

Between 07/2011 and 06/2012, a randomized, double-blind, placebo-controlled trial was performed in 24 healthy volunteers at the Department of Clinical Pharmacology, Medical University of Vienna, Austria (NCT01714427). The institutional ethics committee of the Medical University of Vienna approved the trial (EK531/2010), which was performed in accordance with the Declaration of Helsinki. This study was initially conducted to investigate the systemic and pulmonary activation of coagulation and the inflammatory response after pulmonary instillation of LPS in healthy human volunteers (3, 4). This is an ancillary analysis of samples generated in this trial. Written informed consent was obtained from all study participants before trial enrollment. In short, in- and exclusion criteria comprised non-smoking healthy volunteers with unremarkable medical history, physical examination and laboratory investigations during screening, as well as normal findings in baseline chest radiography, spirometry and a negative routine drug screening.

Details on study design have been reported previously (3). Subjects were randomized to receive two infusions of 40 mg dexamethasone or saline 12 h apart in a double-blind manner. Prior to the study start, staff not otherwise involved in the study created a randomization list using online randomization software (http://www.randomization.com). Based on this list, two sets of sealed, opaque envelopes were prepared, which were labeled with randomization numbers and contained information on the subject-specific treatment allocation. Eligible subjects were assigned a randomization number. To maintain the double-blind character of the trial, study staff not otherwise involved in the trial prepared the study drug based on the information derived from the sealed envelopes. Another set of envelopes was kept for safety reasons, in case unblinding of subjects was necessary. The investigational medicinal products were not distinguishable from each other based on their physicochemical properties. Subjects received the first infusion 13 h prior to the first bronchoscopy. The second infusion was administered 1 h before the start of the bronchoscopy. Subjects were pretreated with dihydrocodeine (Teofarma, Valle Salimbene, Italy). The first bronchoscopy was performed under sedation with midazolam and propofol, which were titrated to obtain the desired effects. Once the bronchoscope was placed in a subsegment (middle lobe or lingula) a balloon-tipped monitoring catheter (Swan-Ganz catheter, Edwards Lifesciences, Irvine, CA, USA) was inserted and inflated: Ten mL of prewarmed, isotonic saline and 10 mL of air were instilled. Thereafter, 4 ng/kg bodyweight LPS (National Reference Endotoxin, *Escherichia coli* O:113, CC-RE-Lot 3, NIH, dissolved in mL saline), 10 mL prewarmed, isotonic saline and 10 mL air were instilled into the contralateral lung. After 6 h, bilateral bronchoalveolar lavage (BAL) was performed in exactly the same locations. During BAL, a total of 140 mL prewarmed saline in aliquots of 20–40 mL were instilled into both lung segments. The retrieved volumes were comparable between both study drugs and lung sites (median retrieval was ∼45–55 mL).

Vital signs including blood pressure, heart rate, oxygen saturation, and body temperature were closely monitored throughout the trial.

The supernatant of the BALF was obtained as previously described (3). BALF was put on ice after retrieval, centrifuged and the supernatant was aliquoted and stored at −80°C until analysis. Commercially available enzyme-linked immunoassays (ELISA) were performed to quantify concentrations of ACE2 (human ACE2 Elisa, MyBioSource MBS824839, San Diego, CA, USA) and fibrin degradation products (human FDP Elisa, ABclonal

RK 01378, Woburn, MA, USA). Angiotensin II to Angiotensin 1-7 conversion rate in BALF was determined after spiking samples with Angiotensin II as natural substrate and subsequent incubation at 37°C in both the presence and the absence of the specific ACE2-inhibitor MLN-4760. Quantification of Angiotensin II and Angiotensin 1-7 was conducted using LC-MS/MS to calculate the ACE2-specific Angiotensin 1-7 formation rate (Attoquant Diagnostics, Vienna, Austria).

A formal sample size calculation for the here presented exploratory analyses was not performed. The sample size was originally calculated with regards to prothrombin fragment F1+2 concentrations and interleukin-6 concentrations (3, 4). We present medians and quartiles. Furthermore, we present boxplots with whiskers (5–95% percentile). For reasons of robustness, two-group comparisons were performed by non-parametric Wilcoxon-Signed-Rank test or the Kruskal-Wallis test (as applicable). Due to the exploratory nature of the analyses, corrections for multiple testing were not conducted.

RESULTS

Nine women and 15 men were included in the trial. Due to a randomization error, 13 subjects received placebo, while 11 received dexamethasone.

Overall, no severe adverse events occurred, four subjects in the placebo group developed fever after the first BAL. Overall, eight subjects reported cough, three noted throat pain, while two subjects vomited. These results were already presented elsewhere, as two prior analyses have focused on the activation of coagulation and inflammation (3, 4).

ACE2

In placebo treated subjects, median ACE2 concentrations in BALF were ∼3-fold higher in lung areas with local pulmonary LPS instillation compared to the contralateral, unstimulated lung areas [1,481 (736–1,965) vs. 546 (IQR 413–988) pg/mL, $p = 0.016$, (**Figure 1**)]. In contrast, dexamethasone pre-treatment, abolished the LPS-induced increase in ACE2 concentrations observed in placebo treated subjects [857 (326–1644) vs. 884 (522–1,649) pg/mL, $p = 0.13$, (**Figure 1**)]. Comparing ACE2 concentrations in unstimulated lung areas between individuals receiving placebo or dexamethasone did not show a statistically significant difference [546 (413–988) vs. 857 (326–1,644) pg/mL, $p = 0.66$], but suggests intraindividual variation in baseline ACE2 concentration in BALF from unstimulated lung segments.

In line with this, we also found an increased capacity of Angiotensin-II-to-Angiotensin-1-7 conversion capacity in BALF from LPS stimulated lung segments in patients receiving placebo: In unstimulated lung segments the median ACE2-dependent Ang1-7 production capacity was at the lower level of quantification (LLOQ), while following LPS stimulation Angiotensin 1-7 production capacity increased to 26 (22–55) ng/mL/h, $p = 0.012$ (**Figure 2**). In contrast, in dexamethasone treated subjects no difference in Angiotensin 1-7 conversion was found between the LPS stimulated lung side vs. the control [LLOQ (LLOQ-28) vs. 17 (LLOQ vs. 37) ng/mL/h, $p = 0.26$]. Infusion of dexamethasone did not change Angiotensin 1-7 production capacity in unstimulated lung segments compared to placebo ($p = 0.15$). Correlation between ELISA based quantification of ACE2 protein concentration and the LC-MS/MS based quantification of the Angiotensin-II-to-Angiotensin-1-7 conversion capacity was poor ($R = 0.175$; $p = 0.15$).

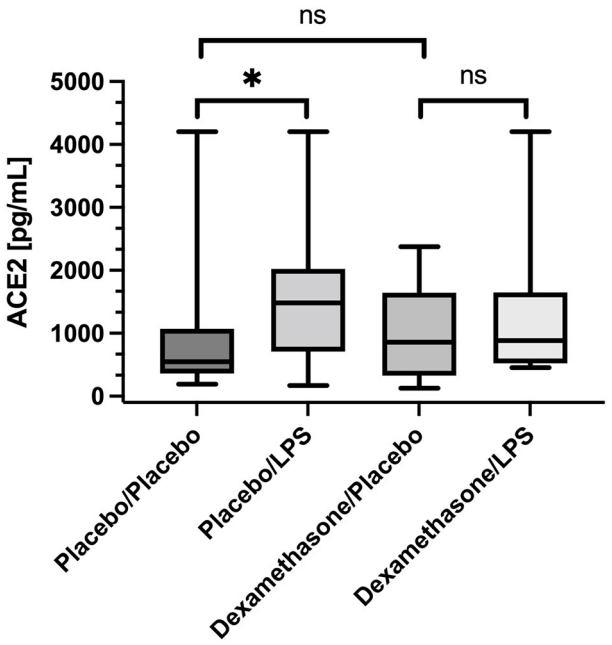

FIGURE 1 | Angiotensin Converting Enzyme 2 (ACE2) concentration in Bronchoalveolar lavage fluid (BALF) samples. Lipopolysaccharide (LPS) instillation resulted in a significant increase in BALF ACE2 concentration (compared to the unstimulated contralateral side, $p = 0.016$) that could be mitigated by systemic application of dexamethasone (no significant difference). We present boxplots and whiskers (5–95% percentile). $N = 24$. * means statistically significant.

Fibrin Degradation Products

In placebo-treated patients FDP concentrations were higher in BALF obtained from LPS stimulated lung segments compared to the contralateral controls [8.9 (2.7–12.2) vs. 6.6 (0.9–9.6) ng/mL, $p = 0.025$, (**Figure 3**)]. However, infusion of dexamethasone resulted in an almost complete shut-down of fibrinolysis in both lung sides [LLOQ (LLOQ-LLOQ) vs. 0.6 (LLOQ-2.3) ng/mL; $p = 0.25$]. In line, dexamethasone reduced FDP concentrations in the unstimulated lungs when compared to placebo [LLOQ (LLOQ-LLOQ) vs. 6.6 (0.9-9.6) ng/mL, $p = 0.005$].

DISCUSSION

Endotoxin-induced lung inflammation increased ACE2, its enzymatic activity and FDP in BALF of healthy volunteers, which was mitigated by dexamethasone. The observed increase in enzymatically active ACE2 in BALF is in contrast to murine models showing decreased ACE2 concentrations in BALF following LPS or virus-induced lung injury (6, 7). We applied two independent methods to quantify ACE2 protein concentration

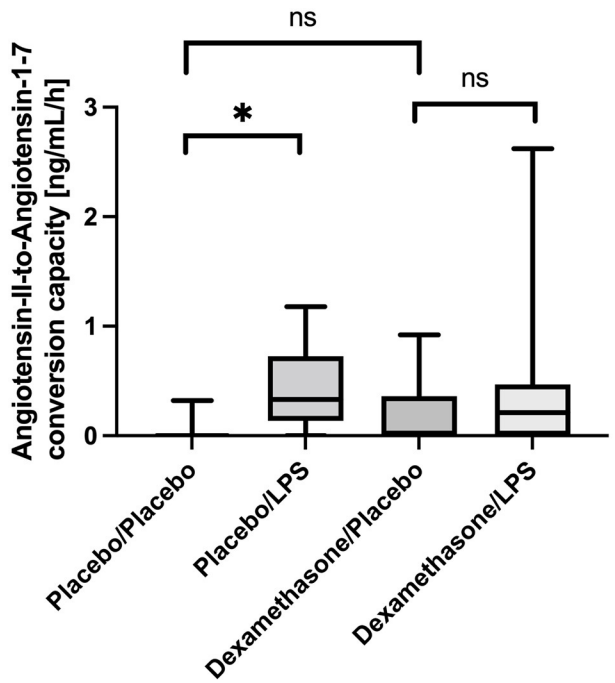

FIGURE 2 | Angiotensin-II-to-Angiotensin-1-7 conversion capacity in ng/mL/h Bronchoalveolar lavage fluid (BALF) samples. Lipopolysaccharide (LPS) instillation resulted in a significant increase in the Angiotensin-II-to-Angiotensin-1-7 conversion capacity compared to the unstimulated lung site ($p = 0.012$) in placebo treated healthy volunteers. No significant difference was observed in dexamethasone treated subjects between LPS-stimulated and control lung sites. In unstimulated lung sites, the capacity was mostly under the lower-limit of detection of the applied assay. We present boxplots and whiskers (5–95% percentile). $N = 24$. * means statistically significant.

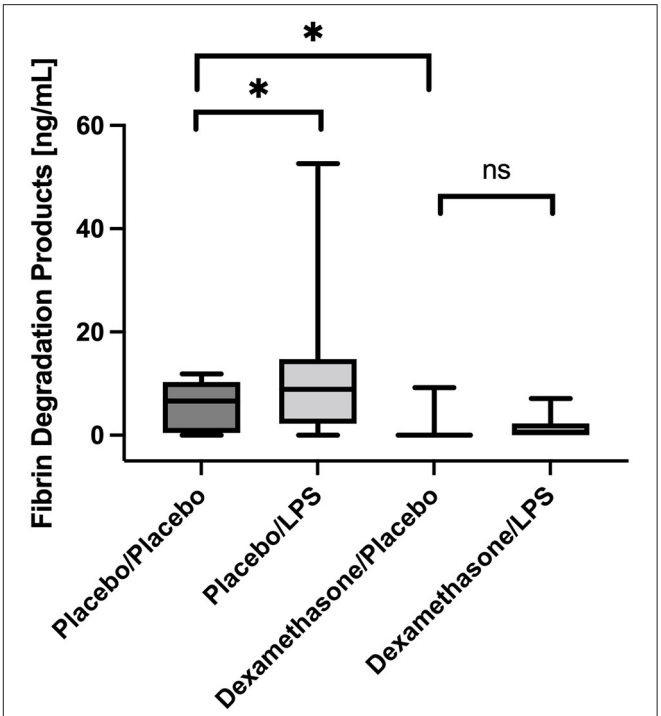

FIGURE 3 | Fibrin degradation products (FDP) in Bronchoalveolar lavage fluid (BALF) samples. In placebo treated subjects, FDP concentrations were higher in BALF obtained from LPS stimulated lung segments compared to contralateral controls ($p = 0.025$). Infusion of dexamethasone resulted in an almost immediate shut-down of fibrinolysis in both stimulated and unstimulated lung segments. No significant increase was observed after LPS stimulation. We present boxplots and whiskers (5–95% percentile). $N = 24$. * means statistically significant.

(ELISA) as well as ACE2-dependent enzymatic activity (Angiotensin-II-to-Angiotensin-1-7 conversion capacity).

In animal models, deficiency of ACE2 enzymatic activity drives lung injury by impaired degradation of angiotensin II (5, 6). In line with this, higher levels of ACE2 were found to be protective in various models of lung injury. Only recently ACE2 was identified as an interferon-inducible gene in humans. This is in contrast with murine data (8).

Onabajo et al. suggested that interferon induces a truncated form of ACE2, not serving as SARS-CoV-2 receptor and lacking endopeptidase activity (12). However, we demonstrated that both ACE2 concentration and enzymatic activity increased in BALF following LPS instillation. Low correlation of ELISA-based quantification of protein concentration and the enzymatic activity may reflect the increase of both active full-length and truncated ACE2. A higher rate of shedding of membrane-bound ACE2 and upregulated gene expression are both plausible mechanisms for the observed increase in BALF ACE2 concentration. Gene expression data in COVID-19 patients showed a ∼200-fold increase in ACE2 expression levels in BALF cells (13). In line with this, systemic levels of enzymatically active ACE2 increased in severe COVID-19 patients compared to less severe cases, and correlated with systemic IL-6 levels (9). The observed mitigation of ACE2 by steroid treatment further supports an inflammation-driven upregulation of ACE2 in humans.

Dexamethasone caused an almost complete shutdown of fibrinolysis (10). It also reduced intrapulmonary prothrombin fragments, which is intriguing since glucocorticoid treatment reduced plasma levels of TNF-α and IL-6 during human endotoxemia, but did not affect LPS-induced activation of coagulation systemically (14). It is possible that dexamethasone reduces pulmonary permeability, which was shown by reduced BALF concentrations of immunoglobulins, as well as a reduced migration of inflammatory cells (3). Since histopathologic studies in deceased COVID-19 patients reported intra-alveolar fibrin deposition, these findings may further support a beneficial role of dexamethasone treatment (10).

Taken together, our data shows that ACE2 increases in human lung inflammation. The apparent species difference in ACE 2 regulation may have important implications for the current pathophysiological understanding of lung disease. Dexamethasone reduced ACE2 upregulation and intra-alveolar markers of fibrinolysis, which, in combination with the previously shown reduced activation of coagulation, may support its beneficial role in pulmonary diseases including, but not limited to, 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

The studies involving human participants were reviewed and approved by the Institutional Ethics Committee of the Medical University of Vienna approved the trial (EK531/2010). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RR-S, FE, and CS designed the study, analyzed the data, and wrote the manuscript. CS performed statistical analysis. JB, BJ, AH, and MH supervised the study and critically read and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Mortality and Pulmonary Embolism in Acute Respiratory Distress Syndrome From COVID-19 vs. Non-COVID-19

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Purpose: There may be a difference in respiratory mechanics, inflammatory markers, and pulmonary emboli in COVID-19 associated ARDS vs. ARDS from other etiologies. Our purpose was to determine differences in respiratory mechanics, inflammatory markers, and incidence of pulmonary embolism in patients with and without COVID-19 associated ARDS admitted in the same period and treated with a similar ventilation strategy.

Methods: A cohort study of COVID-19 associated ARDS and non COVID-19 patients in a Saudi Arabian center between June 1 and 15, 2020. We measured respiratory mechanics (ventilatory ratio (VR), recruitability index (RI), markers of inflammation, and computed tomography pulmonary angiograms.

Results: Forty-two patients with COVID-19 and 43 non-COVID patients with ARDS comprised the cohort. The incidence of "recruitable" patients using the recruitment/inflation ratio was slightly lower in COVID-19 patients (62 vs. 86%; $p = 0.01$). Fifteen COVID-19 ARDS patients (35.7%) developed a pulmonary embolism as compared to 4 (9.3%) in other ARDS patients ($p = 0.003$). In COVID-19 patients, a D-Dimer $\geq$ 5.0 mcg/ml had a 73% (95% CI 45–92%) sensitivity and 89% (95% CI 71–98%) specificity for predicting pulmonary embolism. Crude 60-day mortality was higher in COVID-19 patients (35 vs. 15%; $p = 0.039$) but three multivariate analysis showed that independent predictors of 60-day mortality included the ventilatory ratio (OR 3.67, 95% CI 1.61–8.35), PaO2/FIO2 ratio (OR 0.93; 95% CI 0.87–0.99), IL-6 (OR 1.02, 95% CI 1.00–1.03), and D-dimer (OR 7.26, 95% CI 1.11–47.30) but not COVID-19 infection.

Conclusion: COVID-19 patients were slightly less recruitable and had a higher incidence of pulmonary embolism than those with ARDS from other etiologies. A high D-dimer was predictive of pulmonary embolism in COVID-19 patients. COVID-19 infection was not an independent predictor of 60-day mortality in the presence of ARDS.

Keywords: acute respiratory distress syndrome, pulmonary embolism, recruitment inflation ratio, ventilatory ratio, COVID-19, respiratory mechanics, interleukin-6 (IL-6)

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INTRODUCTION

The worldwide human death toll from the novel severe acute respiratory syndrome coronavirus 2, SARS-CoV-2 disease (COVID-19) has exceeded 302 million. Most people who contract COVID-19 survive, but life-threatening COVID-19 can manifest with acute respiratory distress syndrome (ARDS), multi-system organ failure, venous thromboembolism, and cytokine release syndrome (1–4). COVID-19 patients with ARDS, as defined by the Berlin criteria, currently receive invasive mechanical ventilation and supportive care similar to patients with non-COVID-19 ARDS (5, 6). This study compares respiratory mechanics and laboratory characteristics in patients with ARDS plus COVID-19 vs. those with ARDS but without COVID-19 admitted during the same period.

Initially, two COVID-19-related ARDS phenotypes were suggested: an early L phenotype (low lung elastance, low recruitability), and a late H phenotype (high lung elastance, high recruitability): the latter being reflective of traditional ARDS. Later reports, however, suggested that COVID-19 ARDS patients had similar lung mechanics to patients with ARDS from other etiologies, and similarly, heterogeneous lung recruitability (6–10). It was also proposed that COVID-19 ARDS showed more early disproportionate pulmonary vascular endothelial damage and capillary leak (11). The resultant edema and exudation of proteinaceous fluid into the alveoli causes ventilation-perfusion mismatch, and vascular endothelial damage causes hypoperfusion of oxygenated alveoli (7, 12–15). Conclusions about the respiratory mechanics of COVID-19 ARDS may be complicated by an increased risk of pulmonary embolism (PE), the effects of dexamethasone, and variable use of early proning (16–22). Estimates of dead space, such as the ventilatory ratio (VR), may help in this regard since dead space is a predictor of mortality in ARDS clinical trials but may also be influenced by pulmonary embolism or hyperinflation (23). Potentially, markers like lung recruitability and VR may help clinicians reduce ventilator induced lung injury by maximizing lung unit recruitment and minimizing overdistension (24).

Comparisons of COVID-19 and non-COVID-19 causes of ARDS published so far have used historical controls. The mortality of COVID-19 patients, however, has progressively improved across the time of the pandemic (25). This makes historical comparisons difficult to interpret. We completed a cohort study of patients admitted during the same period in the same center to discern the differences in respiratory mechanics, inflammatory markers, and clinical factors in critically ill patients with ARDS from COVID-19 and other etiologies and understand whether COVID-19 was an independent predictor of mortality in the presence of ARDS. We also investigated predictors of pulmonary embolism.

Abbreviations: ARDS, Acute respiratory distress syndrome; AUC, Area under the receiver operator curve; COVID-19, Severe acute respiratory syndrome coronavirus 2, SARS-CoV-2; CRS, Cytokine release syndrome; CT-PA, Lung computed tomography pulmonary angiography; PaO2/FIO2 ratio, Ratio of arterial oxygen partial pressure to fractional inspired oxygen; PE, Pulmonary embolism; RI, Lung recruitability index; RIFLE, Risk, injury, failure criteria for acute kidney injury; ROC, Receiver operator characteristic curve; VR, Ventilatory ratio; WBC, White blood cell count.

METHODS

Selection and Description of Participants

In this cohort study, we enrolled consecutive intubated patients who met criteria for ARDS arising from both COVID-19 and other etiologies. Patients were admitted to the Level-III 300 multi-unit bed Intensive Care Unit (ICU) (King Saud Medical City, Riyadh, Saudi Arabia) between June 1 and June 15, 2020.The King Saud Medical City ICU department is comprised of several subunits including medical, surgical, trauma, burns and neurocritical care and is the largest referral center for trauma in Saudi Arabia. Inclusion criteria were: (1) age $\geq$ 18 years, (2) requirement for mechanical ventilation, and (3) a diagnosis of ARDS based on the Berlin criteria (5). Exclusion criteria were: (1) intubation for >24 h prior to ICU admission, and (2) transport of a patient to another medical center given a lack of capacity (and not for extracorporeal membrane oxygenation—ECMO). SARS-CoV-2 infection was confirmed or refuted by Real-Time-Polymerase-Chain-Reaction (RT-PCR) assays performed on nasopharyngeal swabs using the Quanti Nova Probe RT-PCR kit (Qiagen, GmbH, Germany) in a Light-Cycler 480 real-time PCR system (Roche, Basel, Switzerland) (26).

The study was conducted according to the principles of the Declaration of Helsinki and approved by our Institutional Review Board.

Respiratory Mechanics and Lung Computed Tomography Angiography

Mechanical ventilation was delivered to each patient using assist control mode as follows: targets: tidal volumes of 4–6 ml/kg, oxygen saturation (SaO2) of 88–95% and pH of 7.30–7.45. Inspiratory flow rate was 60–80 L/min and patients were prone-positioned for at least 16 h per day. All COVID-19 ARDS patients received prophylactic (non-therapeutic dose) heparinoid anticoagulation, intravenous dexamethasone 6 mg once daily, ribavirin, interferon beta 1b, and empiric antibiotics (21). Similarly all patients with ARDS from other etiologies received prophylactic heparinoid anticoagulation and empiric antibiotics. During the first 48-h after intubation, the ventilator settings, respiratory mechanics, and arterial blood gas values were recorded. Plateau pressures were recorded during a 0.3-second end-inspiratory occlusion, and a 1-to-2 second end-expiratory occlusion was used to determine intrinsic positive end expiratory pressure (PEEP). Putative airway closure was determined by measuring the airway opening pressure (AOP) during a low flow ($\leq$6 L/min) insufflation (27). The potential for lung recruitment was determined by the mean value of the recruitment-to-inflation (RI) ratio (ratio of the compliance of the recruited lung divided by the compliance of the "baby lung") using the single-breath drop in PEEP from 15 to 5 cm H2O, as previously described (28). High potential for lung recruitability was indicated by a RI ratio $\geq$0.5. PaO2/FIO2 ratio was calculated based on standard procedures, as was VR [minute ventilation (ml/min) $\times$ PaCO2 (mmHg)]/(predicted body weight x 100 x 37.5) and

driving pressure (DP = plateau pressure − PEEP) (23, 29). Heat and moisture exchanger filters were added on all ventilators to minimize any differences in the measured instrumental dead space. Computed tomography pulmonary angiograms (CT-PA) were performed in subjects with a PaO2/FIO2 ratio < 80 for > 24 h, and PE were categorized as arising from main/lobar, segmental and sub-segmental lung regions (30).

Clinical, Laboratory Investigations, and Outcomes

Within the first 24 h of ICU admission we measured the following in both groups: Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Dysfunction (SOFA) scores, C-reactive protein (CRP), D-dimers, lactate dehydrogenase (LDH), ferritin, interleukin-6 (IL-6), and neutrophil-to-lymphocyte ratio (31–35). Acute kidney injury was defined using the RIFLE criteria (36). The primary outcome was 60-day mortality and the association of mortality with respiratory mechanics, inflammatory markers, and the etiology of ARDS (COVID-19 vs. other etiologies). Secondary outcomes included the incidence of PE and the association between respiratory compliance, lung recruitability, and PaO2/FIO2 ratio within the two subgroups. Additional outcomes included the association between inflammatory markers and respiratory mechanics.

Statistical Analysis

Parametric data were presented as mean ± standard error (SE) and non-parametric data were presented as median with interquartile range (IQR) with comparisons being made using the Student's *t*-test or Wilcoxon signed rank test. Categorical variables were expressed as numbers or percentages and compared using Fisher's exact test. Pearson's correlation coefficient (r) measured the association within and between continuous variables. The association between respiratory compliance and either PaO2/FIO2 ratio or RI ratio was performed using linear regression. Pre-specified and significant ($p < 0.10$) variables were fit into three logistic regression models predicting 60-day mortality. Given the small sample size, we limited our logistic models to four variables to minimize bias in the model's parameter estimates as well as the effects of collinearity (37). Kaplan Meier survival functions were used for 60-day survival, stratified by type of ARDS and compared using the log-rank statistic. All tests were two-tailed with a significance *p*-value of < 0.05. The analysis was performed using SPSS 25.0 (IBM SPSS Statistics for Windows, Version 25.0, Armonk, NY: IBM Corp.), and STATA 15 (Stata Corp, College Station, Texas).

RESULTS

Clinical Characteristics

One hundred and fifteen consecutive patients with ARDS were admitted to the ICU during the observation period. We excluded 10 patients who were intubated for greater than 24 h prior to ICU admission, and 20 who were transported to other ICUs because the existing unit bed capacity was exceeded (not for extracorporeal membrane support—ECMO). No patients had received non-invasive ventilation. The cohort included 42 patients with COVID-19 ARDS and 43 with ARDS from the following etiologies: bacterial pneumonia ($n = 25$), and sepsis syndrome ($n = 18$). There were no significant differences in age, gender, number of comorbidities between patients with COVID-19 and those with ARDS from other etiologies. However, COVID-19 patients had a higher body mass index (BMI), and fewer symptom days prior to ICU admission (**Table 1**).

TABLE 1 | Characteristics of forty-two COVID-19 patients and forty-three patients without COVID-19 and with acute respiratory distress syndrome.

Parameters	All patients ($n = 85$)	COVID-19 patients with ARDS ($n = 42$)	Non-COVID-19 patients with ARDS ($n = 43$)	*P*-value
Age (years)	49.7 ± 0.93	49.5 ± 1.29	49.9 ± 1.36	0.84
Body Mass Index (kg/m²)	25.2 ± 0.37	27.1 ± 0.41	23.3 ± 0.46	0.001*
Sex (Male, %)	63 (74.1%)	33 (78.6%)	30 (69.8%)	0.22
Comorbidities, n (%)				
None	43 (50.6%)	22 (52.4%)	21 (48.8%)	0.64
One	24 (28.2%)	12 (28.6%)	12 (27.9%)	0.92
Two or more	18 (21.2%)	8 (19.0%)	10 (23.3%)	0.51
Symptoms onset to ICU admission (days)	7.24 ± 0.36	6.1 ± 0.28	8.3 ± 0.62	0.001*
SOFA score (baseline)	9.4 ± 0.23	9.7± 0.39	9.2 ± 0.22	0.29
APACHE II score, (baseline)	22.3 ± 0.13	22.4 ± 0.19	22.2 ± 0.72	0.37

*ARDS, acute respiratory distress syndrome; ICU, intensive care unit; APACHE II score, Acute Physiology and Chronic Health Evaluation II score; SOFA score, Sequential Organ Function Assessment score. *P-values ≤ 0.05 were statistically significant (comparisons between the COVID-19 vs. the non-COVID-19 group of patients).*

Respiratory Mechanics

With respect to respiratory mechanics, COVID-19 patients were ventilated with higher respiratory rates and lower applied PEEP, and had lower PaO2/FIO2 ratio, and a higher VR than patients without COVID-19. There was no difference in respiratory compliance; the mean plateau pressure and RI ratio was lower in patients with COVID-19 (**Table 2**). In the COVID-19 patients, fewer patients met the criteria for high recruitability than in other ARDS patients [26 (62%), mean RI ratio 0.58 (0.07), vs. 37 (86%), mean RI ratio 0.59 (0.09); $P = 0.01$]. In patients without COVID-19, there was a linear association between increasing compliance and increasing PaO2/FIO2 ratio (**Figure 1**). Other associations between respiratory compliance and either PaO2/FIO2 ratio or RI ratio may be found in the **Supplementary Figures 1a–c**.

Measures of Inflammation

White blood cell count (WBC) to lymphocyte ratio was over two-times higher, D-dimer over four-times higher, ferritin three-times higher and IL-6 over twenty-times higher in patients with COVID-19 as compared to patients with ARDS from other

TABLE 2 | Respiratory mechanics of forty-two COVID-19 patients and forty-three non-COVID-19 patients with acute respiratory distress syndrome.

Parameters	COVID-19 patients with ARDS (*n* = 42)	Non-COVID-19 patients with ARDS (*n* = 43)	*P*-value
Ventilatory parameters			
Tidal volume (ml/kg) of PBW	5.9 ± 0.04	6.1 ± 0.06	0.71
Respiratory rate (cycles/min)	30.8 ± 0.56	28.2 ± 0.62	0.003*
Positive-end-expiratory-pressure (cm H_2O)	10.6 ± 0.25	12.2 ± 0.42	0.002*
PaO_2/FiO_2 ratio	115.3 ± 5.03	144.7 ± 5.32	0.001*
PaO2/FIO2 < 100, *n* (%)	16 (38)	26 (41)	0.01*
PaO2/FIO2 ≥ 100, *n* (%)	26 (62)	37 (59)	
Respiratory system compliance (ml/cm H_2O)	45.0 ± 0.50	45.6 ± 0.55	0.46
Respiratory system resistance (cm H_2O/l/s)	15.5 ± 0.31	15.1 ± 0.44	0.45
Recruitment-to-inflation ratio	0.49 ± 0.02	0.55 ± 0.02	0.04*
Ventilatory ratio	1.87 ± 0.05	1.62 ± 0.03	0.001*
Plateau pressure (cm H_2O)	23.8 ± 0.35	25.1 ± 0.33	0.01*
Driving pressure (cm H_2O)	10.1 ± 0.16	10.1 ± 0.21	0.85

*PaO_2/FiO_2 ratio, partial arterial pressure of oxygen to fractional inspired concentration of oxygen ratio, Ventilatory ratio = [minute ventilation (ml/min) × PaCO2 (mmHg)]/(predicted body weight × 100 × 37.5), Driving pressure = plateau pressure – PEEP. *P-values ≤ 0.05 were statistically significant (comparisons between the COVID-19 vs. the non-COVID-19 group of patients).*

etiologies (**Table 3**). The ratio of WBC/Lymphocytes was highly correlated with other inflammatory markers including IL-6 (r = 0.84, $P < 0.0001$), D-dimers (r = 0.71, $P < 0.001$), ferritin (r = 0.58, $P < 0.001$), and CRP (r = 0.34, P = 0.001). Likewise, values of D-dimers and IL-6 were highly correlated (r = 0.72, $P < 0.0001$). Increasing values of markers of inflammation were negatively correlated with PaO2/FIO2 ratio and RI ratio and positively correlated with VR. Correlations between the PaO2/FIO2 ratio and VR with biological parameters are shown in **Supplementary Table 1**.

Complications and Mortality

As shown in **Table 4**, COVID-19 patients had a similar prevalence of acute kidney injury but had a higher prevalence of PE than in those with ARDS from other etiologies. Twenty COVID-19 patients and eighteen non-COVID-19 patients underwent CT-PA due to refractory hypoxemia (PaO2/FIO2 ratio < 80 for > 24 h). Fifteen COVID-19 patients had a PE, of which 7 were segmental, and 8 subsegmental. This PE prevalence was significantly higher than the 4 patients with ARDS from other etiologies: 3 segmental PEs and 1 sub-segmental; overall 35 vs. 9%, P = 0.003. Of patients meeting our criteria for refractory hypoxemia, the prevalence of PE was also significantly higher in the COVID-19 group than in the patients with ARDS from other etiologies; 75 vs. 22.2 %, P = 0.003. In patients with COVID-19, the mean VR [2.05 (0.42) vs. 1.77 (0.24), P = 0.001] and IL-6 [721.27 (645.44) vs. 148.89 (179.80), $P < 0.001$] were significantly higher in those who developed a PE (**Table 4**). Inference for PE in patients with ARDS from other etiologies was limited by a low prevalence so the performance of the diagnostic tests in the combined population is outlined in **Supplementary Figure 2**. However, D-dimer performed significantly better than VR for discriminating the presence or absence of PE in patients with COVID-19 (AUC 0.84, 95% CI 0.71 to 0.98, P = 0.03; **Figure 2**). The sensitivity of a D-dimer ≥ 5.0 mcg/ml in discriminating the presence of absence of a PE in COVID-19 ARDS was 73.3% (95% CI 44.8–92.2%) with a specificity of 88.9% (95% CI 70.8–97.6%). As the performance of a CT-PA (the gold standard for diagnosing a PE) was conditional on meeting the prespecified criteria of a PaO2/FIO2 ratio < 80% for > 24 h, we did not evaluate the performance of refractory hypoxemia as a discriminating test nor could we fit this parameter as an independent predictor of PE in our multivariable models. COVID-19 patients had a significantly higher crude 60-day mortality (35 vs. 15%, P = 0.039). COVID-19 patients also had shorter durations of mechanical ventilation, ICU length of stay, and hospital length of stay compared to patients with ARDS from other etiologies (**Table 5**). Shorter lengths of mechanical ventilation and ICU stay were preserved in survivors. Unadjusted Kaplan Meier mean survival of COVID-19 patients (29.64, 95% CI 26.11 to 33.17 days) was significantly shorter than patients with ARDS from other etiologies (48.13, 95% CI 41.31 to 54.94 days, $P < 001$).

In predicting 60-day mortality, APACHE II score was collinear with VR, and VR was collinear with D-dimer and IL-6. Given the small number of patients and collinearity between these variables we fit three separate models to avoid biased estimates of our model parameters. Independent predictors of mortality using Model 1 were, an increasing VR (OR 3.67, 95% CI 1.61 to 8.35, P = 0.002) and a decreasing PaO2/FIO2 ratio (OR 0.93, 95% CI 0.87 to 0.99, P = 0.02). Increasing IL-6 (OR 1.02, 95% CI 1.00 to 1.03, P = 0.047) and D-dimer (OR 7.26, 95% CI 1.11 to 47.30, P = 0.04) also independently predicted mortality in models which included respiratory parameters and ARDS etiology (Model 2 and 3, **Supplementary Table 2**). Having ARDS from other etiologies independently predicted mortality only at the threshold level of significance (P = 0.05) in only one model, and COVID-19 infection was not predictive of mortality in any of the models (**Table 6**, **Supplementary Table 2**).

DISCUSSION

On average, COVID-19 ARDS patients had comparable respiratory mechanics but differing inflammatory markers compared to patients with ARDS from other etiologies. In COVID-19 ARDS, average recruitability was lower than in other ARDS. However, in patients with COVID-19, higher

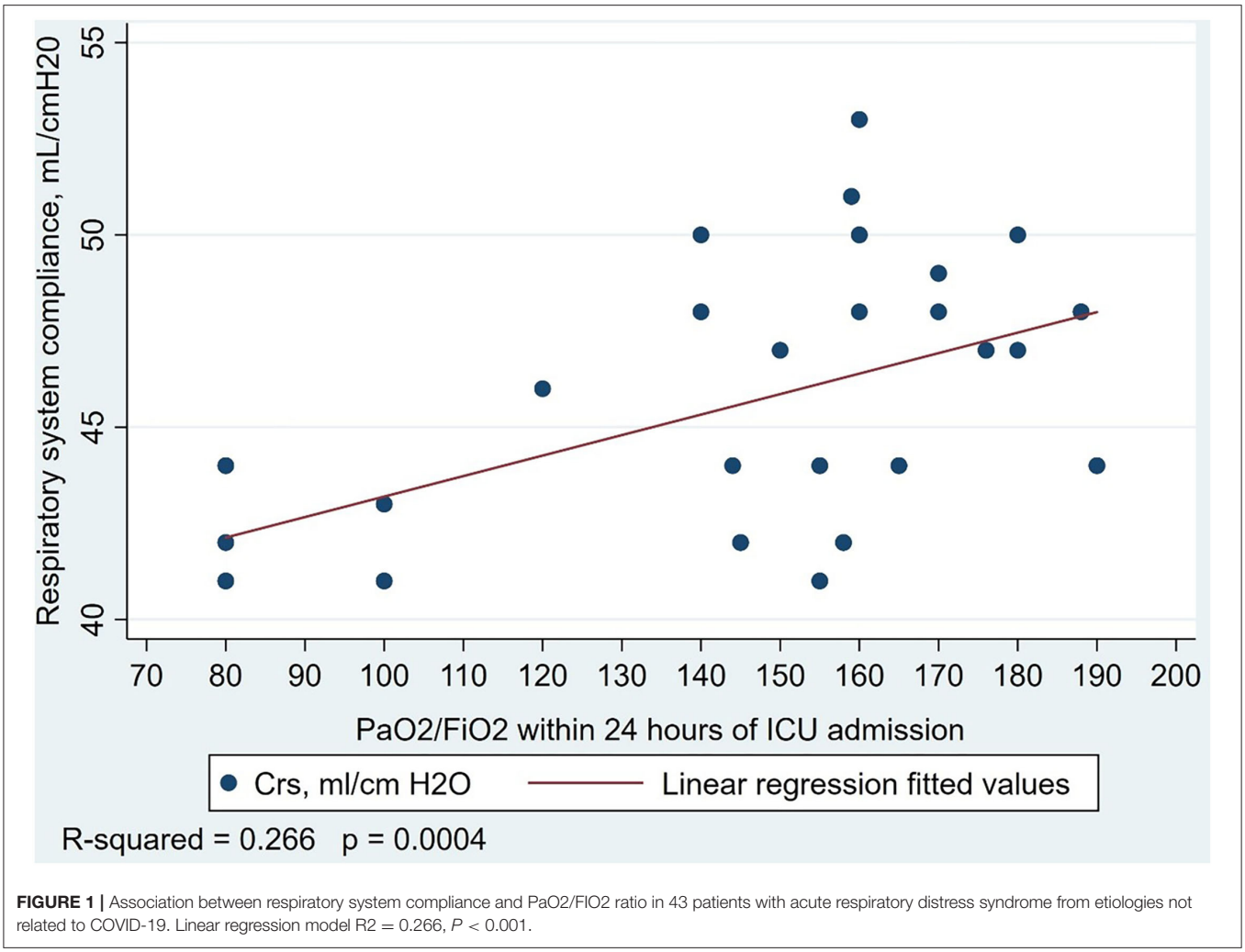

FIGURE 1 | Association between respiratory system compliance and PaO2/FIO2 ratio in 43 patients with acute respiratory distress syndrome from etiologies not related to COVID-19. Linear regression model R2 = 0.266, $P < 0.001$.

TABLE 3 | Laboratory parameters of forty-two COVID-19 patients and forty-three non-COVID-19 patients with acute respiratory distress syndrome.

Laboratory parameters	COVID-19 patients ($n = 42$)	Non-COVID-19 patients ($n = 43$)	*P*-value
Creatinine (mg/dl, normal: 0.6–1.2)	1.05 ± 0.03	1.21 ± 0.05	0.02*
White blood cells (cells/mm^3, normal: 4–10)	13.1 ± 3.5	13.2 ± 2.9	0.84
Lymphocytes (10^9/l, normal: 1.1–3.2)	0.5 ± 0.2	1.5 ± 0.4	0.001*
White blood cells/lymphocytes ratio	29.7 ± 2.44	11.6 ± 1.46	0.001*
Platelets (cells/mm^3, normal: 150–450)	134.5 ± 32.7	156.8 ± 40.8	0.007*
International normalization ratio (normal: 0.8–1.2)	1.19 ± 0.30	1.22 ± 0.35	0.70
D-Dimers (mcg/ml, normal: < 1)	3.6 ± 0.35	0.76 ± 0.11	0.001*
Total bilirubin (μmol/L, normal: 0 to 26)	31.3 ± 1.10	36.4 ± 0.96	0.001*
C-reactive protein (mg/L, normal: 0–5)	127.3 ± 15.75	76.4 ± 18.86	0.04*
Lactate dehydrogenase (u/L, normal: 100–190)	575.9 ± 57.64	233.4 ± 12.86	0.001*
Ferritin (ng/ml, normal: 23–336)	589.1 ± 65.5	190.8 ± 9.94	0.001*
Interleukin-6 (pg/ml, normal: 1–7)	353.3 ± 75.56	16.9 ± 6.26	0.001*

**P-values ≤ 0.05 were statistically significant (comparisons between the COVID-19 vs. the non-COVID-19 group of patients).*

recruitability was associated with increasing compliance and was independent of the PaO2/FIO2 ratio. These findings may indicate that higher recruitabiliy is achievable in less damaged alveolar lung units with higher baseline compliance. The association between compliance and recruitability was not present in our patients with ARDS from other etiologies possibly because of

more heterogeneous pulmonary pathology in this subgroup of ARDS patients. This would suggest that more non-COVID-19 ARDS patients would be required to demonstrate any true association between baseline compliance and recruitability because of increased variability in the underlying pathology. The early phase of ARDS is characterized by alveolar edema and filling by proteinaceous fluid concomitant with the destruction of surfactant producing Type-II alveolar cells. Both alveolar filling with fluid and the reduction in surfactant production results in reduced static respiratory system compliance in injured segments of the lung. Recruitability is largely attributable to an increase in end expiratory lung volume from increases in aerated alveoli with recruitement (38, 39). We found a high proportion of high recruitability in both ARDS subgroups reflective of some preservation of normal alveolar units. However, in our study a significantly lower proportion of COVID-19 ARDS patients had high recruitability. COVID-19 can activate the coagulation cascade, cause vascular endothelial damage, disrupt pulmonary vasoregulation, and create early ventilation-perfusion mismatch and shunt through a mechanism of capillary leak and pulmonary edema resulting in a reduction in static respiratory system compliance. Concomitantly, COVID-19, via its disruption of pulmonary vasoregulation, can also increase dead space in non-perfused alveoli (7, 11, 13, 14, 40). Our findings that 62% of COVID-19 ARDS patients were highly recruitable aligns

TABLE 4 | Characteristics associated with the development of pulmonary embolism in COVID-19 patients with acute respiratory distress syndrome.

Characteristics	COVID-19		
	Pulmonary embolism present *n* = 15	**Pulmonary embolism absent, *N* = 27**	***P*-value**
Ventilatory ratio	2.047 (0.4207)	1.767 (0.2434)	$P = 0.001$*
RI ratio	0.487 (0.164)	0.496 (0.116)	$P = 0.83$
D-dimer, mcg/mL	5.53 (2.07)	2.65 (1.62)	$P = 0.23$
IL-6, pg/ml	721.27 (645.44)	148.89 (179.80)	$P < 0.001$*
CRP, mg/L	145 (122.64)	117.48 (89.767)	$P = 0.41$
Ferritin, ng/ml	661.067 (546.41)	549.22 (345.52)	$P = 0.42$
LDH, u/L	443.4 (348.087)	649.556 (372.877)	$P = 0.09$

**P-values < 0.05 were statistically significant (comparisons between the COVID-19 vs. the non-COVID-19 group of patients).*

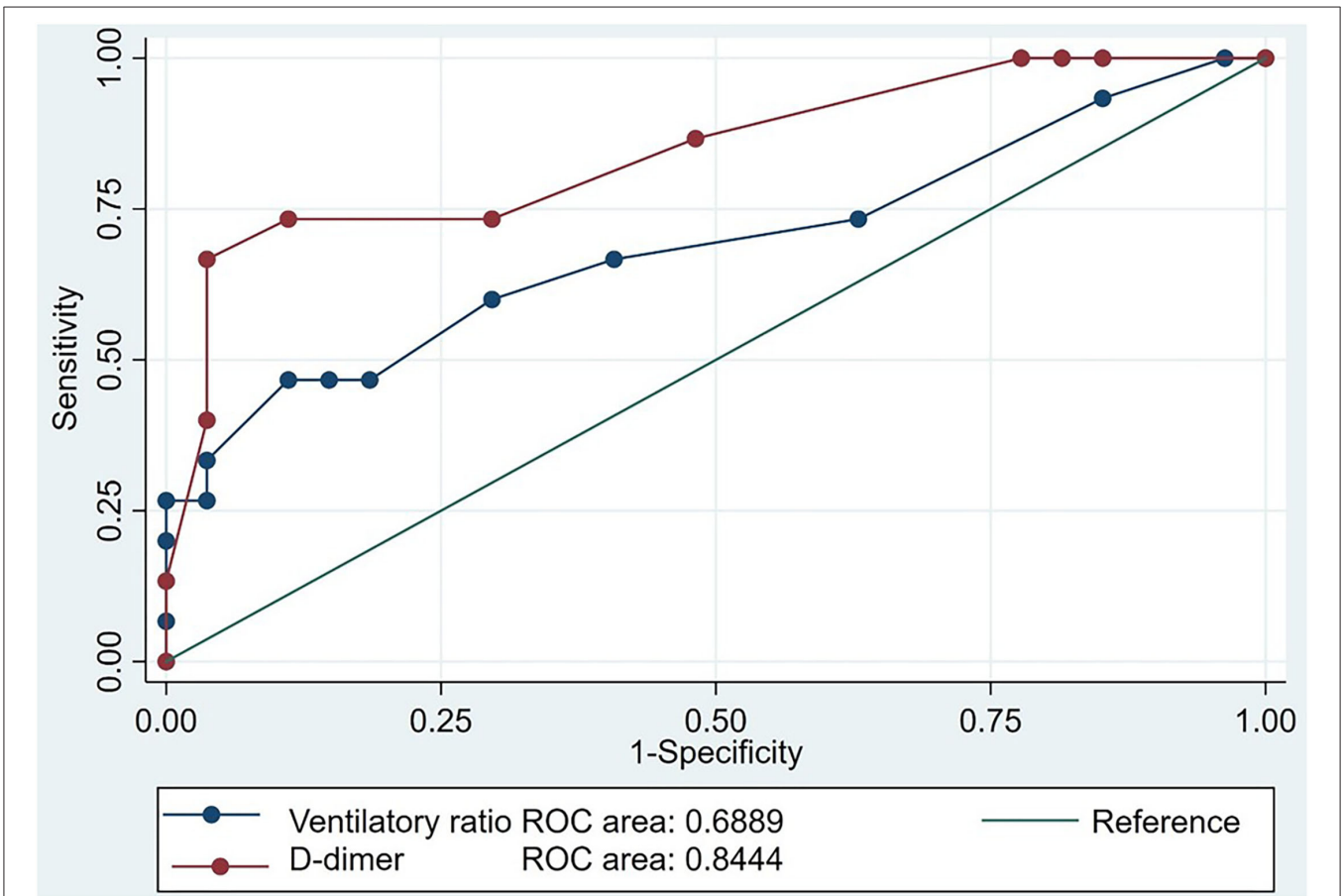

FIGURE 2 | Receiver operator characteristic curve assessing the performance of the ventilatory ratio (VR) and D-dimer in predicting the development of pulmonary embolism in 42 patients with COVID-19 associated acute respiratory distress syndrome. The predictive value of D-dimer was significantly improved over that of the VR when comparing areas under the receiver operator curve (ROC) $P = 0.03$.

TABLE 5 | Complications and outcomes of forty-two COVID-19 patients and forty-three non-COVID-19 patients with acute respiratory distress syndrome.

Characteristic	COVID-19 patients with ARDS ($n = 42$)	Non-COVID-19 patients with ARDS ($n = 43$)	*P*-value
Mechanical ventilation (days)	19.5 (12.4–24.1)	21.6 (15.9–27.3)	0.004*
Survivors (days)	16.8 (12.6–21.0)	21.3 (16.5–25.7)	<0.001*
ICU length of stay (days)	21.5 (17.3–28.3)	27.8 (18.2–31.9)	0.001*
Survivors (days)	21.2 (16.4–26.0)	26.0 (19.5–32.4)	0.002*
Hospital length of stay (days)	30.8 (22.9–37.3)	33.2 (27.8–44.8)	0.001*
Acute kidney injury, *n* (%)	4 (9.5)	7 (8.2)	0.35
Pulmonary embolism, *n* (%)	15 (35.7)	4 (9.3)	0003*
60-day mortality, *n* (%)	15 (35.7%)	6 (14%)	0.02*

*ICU, intensive care unit. Acute Kidney Injury as defined by the RIFLE criteria. *P-values ≤ 0.05 were statistically significant (comparisons between the COVID-19 vs. the non-COVID-19 group of patients).*

TABLE 6 | Univariate and multivariate logistic regression analysis of predictors of 60-day mortality in eighty-five COVID-19 and non-COVID-19 patients with acute respiratory distress syndrome.

Characteristic	Univariate odds ratio (95% CI)†	*p*-value	Model 1 odds ratio (95% CI)†	*P*-value
APACHE II	3.31 (1.87–5.87)	<0.001*		
Non-COVID-19 ARDS	0.29 (0.10–0.85)	0.024*	1.08 (0.06–19.22)	0.05*
Respiratory compliance, ml/cm H20	0.82 (0.69–0.97)	0.021*	0.65 (0.41–1.04)	0.07
Ventilatory ratio, per 0.10 units	3.03 (1.79–5.11)	<0.001*	3.67 (1.61–8.35)	0.002*
PaO_2/FiO_2 ratio	0.97 (0.96–0.99)	<0.001*	0.93 (0.87–0.99)	0.02*
D-Dimer (mcg/ml, normal: < 1)	1.84 (1.40–2.43)	<0.001*		
Interleukin-6 (pg/ml, normal: 1–7)	1.01 (1.00–1.01)	0.001*		

*APACHE II score, Acute Physiology and Chronic Health Evaluation II score; PaO2/FiO2 ratio, partial arterial pressure of oxygen to fractional inspired concentration of oxygen ratio. Ventilatory ratio = [minute ventilation (ml/min) × PaCO2 (mmHg)]/(predicted body weight × 100 × 37.5). *P-values < 0.05 were statistically significant (comparisons between the COVID-19 vs. the non-COVID-19 group of patients). †CI indicates the 95% confidence interval.*

with previous French and Italian studies that reported 64% and 73% (respectively) of COVID-19 ARDS patients as being highly recruitable (9, 10). Our findings differ from those of an earlier Chinese and another French study where only 17 and 30% of COVID-19 patients were highly recruitable (6, 8). Although highly recruitable lung units should be responsive to an increase in PEEP, our population of COVID-19 ARDS patients had significantly less mean PEEP delivered within the first 48 h than did our patients with ARDS from other etiologies. This may be attributable to the fact that significantly fewer COVID-19 ARDS patients were deemed to be highly recruitable and consequently, an escalation of PEEP was not performed. The fact that the mean VR was higher and PaO2/FIO2 ratio was lower in the COVID-19 ARDS group may also indicate that the higher dead space ventilation in the COVID-19 ARDS group would not have been reduced with increasing PEEP levels.

Ventilatory ratio was significantly higher in COVID-19 ARDS than in ARDS from other etiologies. Ventilatory ratio was also associated with the presence of PE in COVID-19 patients, and it was an independent predictor of mortality in the entire cohort. As VR is only a respiratory physiological parameter indicating the degree of dead space ventilation it may only be viewed as a physiological surrogate of disease severity and not as a biological or pathological process characterizing ARDS in either subgroup. In addition, in the COVID-19 subgroup, D-dimer performed better than the VR in discriminating the presence or absence of PE in those patients with refractory hypoxemia who mandatorily received a CT-PA.

We found higher VR in COVID-19 ARDS. This aligns with the findings of Grieco et al. (9). Our findings highlight the importance of VR as an independent predictor of both PE and mortality in COVID-19 ARDS, and duplicates both a recent Italian cohort of COVID-19 patients, and studies of patients with ARDS from other etiologies (3, 23, 41, 42). We also determined a good sensitivity and specificity for diagnosing PE in COVID-19 ARDS by using a D-dimer threshold level of ≥ 5 mcg/ml. These findings align with those of an Italian cohort which showed that higher D-dimer levels predicted PE and mortality in COVID-19 ARDS (3).

Illness severity was comparable between groups, but COVID-19 patients had a higher crude mortality. In the entire cohort, a higher VR and a lower PaO2/FIO2 ratio as well as higher IL-6 and D-dimer levels were independent predictors of 60-day mortality after adjusting for baseline compliance and etiology (subgroup) of ARDS. This suggest that markers of inflammation are strongly associated with the underlying pathophysiology of both ARDS subgroups. Higher levels of inflammatory markers and incident PE were demonstrated in the COVID-19 subgroup, and inflammatory markers were positively associated with incident PE, predominantly in the COVID-19 ARDS patients. Although our findings do not suggest causality, other authors have suggested that inflammation and vasoconstriction resulting in microthrombosis are important factors in COVID-19 ARDS (43, 44). Microthrombosis and extension of this thrombotic process into sub-segmental and segmental pulmonary arteries may account for the findings of these distal pulmonary arteries being predisposed to thrombosis as compared to proximal pulmonary thrombosis seen in non-COVID-19 diseases. Previous authors have described a predominance of CT-PA confirmed thrombus involving distal pulmonary vessels and

located in lung parenchymatous condensations in COVID-19 patients with pulmonary embolus (45).

Given the high prevalence of PE in COVID-19 ARDS, and its associated mortality, our study could encourage early use of VR and D-Dimer as discriminatory tests, confirmation with a CT-PA, and empiric anticoagulation in circumstances where a CT-PA may not be able to be performed safely (43, 46–48). However, our findings of a 75% PE prevalence in those COVID-19 ARDS patients with a PaO2/FIO2 ratio < 80 for > 24 h may question the additional usefulness of the VR or a D-Dimer in deciding on empiric therapeutic anticoagulation. We did not perform a CT-PA in less hypoxemic patients where the prevalence of PE may have been lower and the discriminatory value of VR or D-Dimer may have been higher. We also demonstrated elevated laboratory investigations in COVID-19 ARDS: including WBC/lymphocyte ratio, D-Dimer, C-reactive protein, LDH, ferritin, and IL-6. Although the importance of D-Dimer and IL-6 as predictors of COVID-19 mortality has been noted by others, ours is the first study to confirm the robustness of this association independent of respiratory mechanics variables such as VR and PaO2/FIO2 ratio (3, 34, 46, 49).

A strength of our study was the contemporaneous inclusion of all patients and the use of a uniform strategy for mechanical ventilation. Also, all patients with COVID-19 received a standard dose of dexamethasone, which differ from most previous reports. Our study has limitations including its small sample size, and the fact that we did not directly measure dead space, nor work of breathing prior to intubation. Consequently, we could not conclude whether patients would develop self-inflicting lung injury (50). We also did not sequentially measure respiratory mechanics, so we could not characterize temporal improvement or deterioration. Despite limitations, we did demonstrate that a bedside measurement, VR, predicts both PE and mortality. We have also reaffirmed, although not causal, the predictive value of high D-Dimer and IL-6 levels in predicting the development of PE and mortality in COVID-19. This bolsters the rationale behind clinical studies into IL-6 targeted immunomodulatory therapies for severe COVID-19 (4, 51, 52). However, the significant associations we found between inflammatory markers and respiratory physiological parameters and mortality are in no way causal in nature. Such associations are only hypothesis generating and require further pathophysiological investigations into the biological mechanisms linking these markers to vascular and alveolar injury and death.

INTERPRETATION

In conclusion, in addition to illness severity and PaO2/FIO2 ratio, VR, D-Dimer and IL-6 were independent predictors of mortality in COVID-19 ARDS. D-Dimer at a threshold of ≥ 5 mcg/mL has good sensitivity and specificity in discriminating the presence or absence of PE as confirmed in ARDS patients with refractory hypoxemia. A high proportion of our COVID-19 ARDS patients had high recruitability in whom both oxygenation and ventilation should improve with higher PEEP. In the presence of ARDS we did not find, however, that COVID-19 was an independent predictor of mortality.

IMPLICATION STATEMENT

In a contemporaneous cohort of patients with COVID-19 associated ARDS and ARDS from other etiologies, COVID-19 patients were slightly less recruitable and had a higher level of inflammatory markers and incidence of pulmonary embolism. However adjusted mortality did not differ between groups.

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 Kingdom of Saudi Arabia Ministry of Health, King Saud Medical City. IRB registration number with KACST, KSA: H-01-R-053. IRB registration number U.S. Department of HHS IORG #: IORG0010374. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DKu, AA, AB, FF, JP, SA, ZM, and DKa contributed to the conception and design, drafting and revision, interpretation, and final approval of the study and manuscript. PB and LB contributed to the drafting, revision, interpretation, and final approval of the study manuscript. DKu contributed to the statistical analysis of the study. 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.2022.800241/full#supplementary-material

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Cardiovascular Biomarkers for Prediction of in-hospital and 1-Year Post-discharge Mortality in Patients With COVID-19 Pneumonia

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Aims: While COVID-19 affects the cardiovascular system, the potential clinical impact of cardiovascular biomarkers on predicting outcomes in COVID-19 patients is still unknown. Therefore, to investigate this issue we analyzed the prognostic potential of cardiac biomarkers on in-hospital and long-term post-discharge mortality of patients with COVID-19 pneumonia.

Methods: Serum soluble ST2, VCAM-1, and hs-TnI were evaluated upon admission in 280 consecutive patients hospitalized with COVID-19-associated pneumonia in a single, tertiary care center. Patient clinical and laboratory characteristics and the concentration of biomarkers were correlated with in-hospital [Hospital stay: 11 days (10; 14)] and post-discharge all-cause mortality at 1 year follow-up [FU: 354 days (342; 361)].

Results: 11 patients died while hospitalized for COVID-19 (3.9%), and 11 patients died during the 1-year post-discharge follow-up period ($n = 11$, 4.1%). Using multivariate analysis, VCAM-1 was shown to predict mortality during the hospital period (HR 1.081, CI 95% 1.035;1.129, $p = 0.017$), but not ST2 or hs-TnI. In contrast, during one-year FU post hospital discharge, ST2 (HR 1.006, 95% CI 1.002;1.009, $p < 0.001$) and hs-TnI (HR 1.362, 95% CI 1.050;1.766, $p = 0.024$) predicted mortality, although not VCAM-1.

Conclusion: In patients hospitalized with Covid-19 pneumonia, elevated levels of VCAM-1 at admission were associated with in-hospital mortality, while ST2 and hs-TnI might predict post-discharge mortality in long term follow-up.

Keywords: COVID-19, long COVID-19, post-discharge mortality, cardiovascular biomarkers, sST2, VCAM-1

INTRODUCTION

The novel coronavirus disease COVID-19 still represents a major clinical challenge to date. COVID-19 primarily involves the respiratory system and severe COVID-19 typically leads to bilateral pneumonia with consequent acute respiratory distress syndrome and high mortality rates (1). As the Spike protein S of the ACE-2 receptor serves as the binding site for SARS-CoV-2, cells with a high expression of the ACE-2 receptor are primarily affected by COVID-19, resulting in a broad range of clinical symptoms in COVID-19. Several clinical parameters including laboratory, electrocardiographic and radiology findings have been used to stratify mortality risk (1–3), yet monitoring parameters and long-term prognostic markers for COVID-19 remain scarce.

COVID-19 was reported to have a considerable impact on the cardiovascular system, including not only cardiac injury but also thromboembolic events. Given the correlation of myocardial injury and disease severity in COVID-19, novel cardiovascular biomarkers might prove to be an effective prognostic tool in COVID-19 patients.

High-sensitive troponin is released in response to myocardial injury and represents the gold standard for cardiovascular risk assessment (4). Previous studies studies found that myocardial injury, defined by increased serum cardiac high-sensitive Troponin (TnI) levels, was associated with a mortality rate of >50% in COVID-19 patients (5), while other studies have reported that 19.7% of all COVID-19 patients presented with myocardial injury. Moreover, these patients had a significantly higher mortality rate compared to COVID-19 patients with normal TnI (51.2 vs. 4.5%) (6). This finding is further emphasized by a meta-analysis which reported significantly higher TnI levels in severe COVID-19 compared with patients with mild COVID-19 (7).

Soluble suppression of tumorgenity-2 (sST2) is a member of the interleukin-1 receptor family and has recently emerged as a potentially useful tool for improving the assessment of cardiovascular disease (8–10). There are two isoforms of ST2, the membrane-bound ST2L, mediating cardio-protective effects through binding of its only known ligand IL-33 (11), as well as sST2, the soluble form of ST2, acting as a decoy receptor for IL-33, thereby inhibiting its potential cardio-protective effects (11). Of note, the IL-33/ST2 axis was also reported to play a potential role in the COVID-19 pathogenesis (12–14). sST2 itself was shown to be elevated in numerous clinical scenarios, including heart failure and cardiac remodeling, myocardial infarction, atherosclerosis as well as in inflammatory disease such as sepsis (8). Recent studies reported high levels of sST2 in COVID-19 patients, also correlating with CRP levels, a standard marker of COVID-19 activity (15). Similarly, Sanches et al. (16) reported a significant correlation between levels of sST2 and ICU admission as well as death, emphasizing its prognostic potential.

Several studies have revealed a potential link between COVID-19 and endothelial dysfunction. On this regard, also the term "Acute Vascular Distress Syndrome" was introduced, to account for the vascular pathophysiology in COVID-19 pneumonia (17, 18). This comprises vasoplegia along with a reduced ventilation-to-perfusion ratio, leading to an increased pulmonary blood flow with intrapulmonary right to left shunt (18). Accordingly, also an analysis of vascular biomarkers might contribute to diagnosis and prognosis in COVID-19.

Vascular cells adhesion molecule-1 (VCAM-1) is a protein acting as a cell adhesion molecule of vascular endothelium for lymphocytes, monocytes, eosinophils, and basophils. In a study on the effect of SARS-CoV-2 spike S1 protein on the activation of human lung microvascular endothelial cells, the incubation of HLMVEC with the S1 protein significantly induced the expression of VCAM-1 (19). In further trials, VCAM-1 was associated with COVID-19-related mortality (20). Moreover, in a meta-analysis (n = 2,213), VCAM-1 levels were linked with increased disease severity in COVID-19 patients (21).

Given the involvement of sST2 and VCAM-1 in inflammatory processes and the previous reports on their role in COVID-19, their potential impact on prognosis also in the long term seems plausible. Accordingly, we undertook a comparative analysis of novel cardiac biomarkers sST2 and VCAM-1 as well as high-sensitive Troponin I (TnI) in a 1-year follow-up of COVID-19 patients. We hypothesized that these cardiovascular biomarkers might be helpful in predicting 1-year mortality. Therefore, the aim of our work was to establish an possible association between the investigated cardiovascular biomarkers and in-hospital as well as post-discharge mortality, which could help to identify patients at risk.

Therefore, the aim of our work was to establish an association between biomarkers and mortality.

METHODS

The study was approved by the Local Ethical Committee (N5, 2020) and was performed in accordance with standards of good clinical practice and the principles of the Declaration of Helsinki. Written informed consent was obtained from all study participants prior to inclusion.

This prospective, non-randomized, single-center study enrolled 288 consecutive patients between June 2020 and September 2020, who were hospitalized due to COVID-19-associated pneumonia in a tertiary care center during the 1st "wave" of the COVID-19 pandemic. Initial diagnosis was established via CT-scan, PCR testing and specific antibodies at admission and COVID-19 specific medical treatment was applied according to current national COVID-19 guidelines (22).

Included were patients 18 years or older with confirmed COVID-19 disease and related pneumonia. Exclusion criteria included: acute ST-elevation myocardial infarction at admission, acute stroke at admission, active malignant disease within the last 3 years, and acute kidney failure at admission defined as glomerular filtration rate (GFR) <30 mL/min/1.73 m^2, as well as pregnancy or lactation. In total, eight patients met the exclusion criteria and were therefore excluded (acute ST-elevation myocardial infarction: $n = 2$, acute stroke: $n = 1$, active malignant disease: $n = 2$, and acute kidney failure: $n = 3$).

Patient enrollment and the design of the study are presented in **Figure 1**. Upon hospital admission, venous blood was drawn,

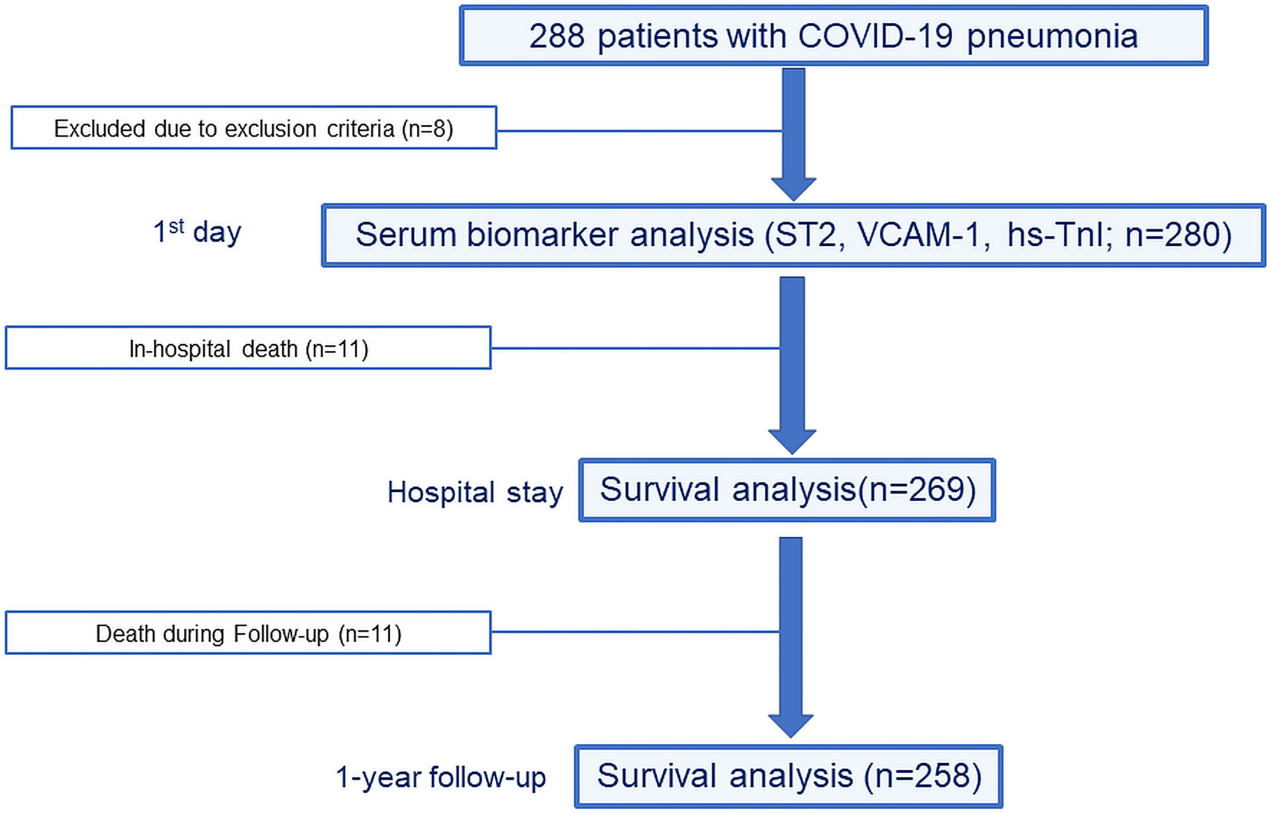

FIGURE 1 | Design of the study.

subsequently centrifuged, and the serum frozen at −20° C for further analyses. The concentration of biomarkers ST2, VCAM-1 and TnI was analyzed by enzyme immunoassay as indicated by the manufacturer (Thermo Fisher Scientific, USA for VCAM-1, Critical diagnostics, USA, for ST2, and Hema Ltd, Russia for TnI). In addition to the investigated biomarkers, further laboratory parameters were routinely measured according to current guidelines (**Table 1**).

A detailed medical history was obtained at admission for all enrolled patients, including current symptoms, as well as previous illnesses and current medications. The study was carried out between June 2020 and September 2020. Follow-up (FU) analysis was conducted during the acute phase of disease defined as the total hospital stay and after hospital discharge for a median of 366 days (356: 373) for the study endpoint with the help of the regional medical information analytical system "ProMed" (23). This web-based medical records system enables remote online monitoring of hospitalization discharge notes including death certificates. The study endpoint was defined as all-cause mortality as indicated by discharge notes and/or death certificate during the FU period. The FU endpoints were analyzed in September 2021.

The mathematical model for statistical analyses is summarized in **Figure 2**. All data were tested for normality. Normally distributed continuous variables were expressed as mean values (M) and standard deviations (SD). Non-normally distributed data were expressed as median (interquartile range Q1–Q3), and the non-parametric Mann-Whitney test was used for comparison between the two groups. Categorical variables were expressed as frequencies and proportions. Differences among groups were assessed with the Chi-squared test.

Prediction of biomarkers for prognosis in COVID-19 patients was analyzed as follows. At the preliminary stage of the analysis, univariate Cox proportional hazards models were evaluated. Biomarkers values were taken as independent variables. To remove the bias of estimates, age of the patients was also considered as a control factor. Then statistically significant factors with $p > 0.1$ were selected. The first multivariate model of survival was built for all-cause mortality during in-hospital stay, and the second for all-cause mortality after hospital discharge during a FU of 1 year. Gsslasso Cox Bayesian hierarchical models (24) were used to obtain reliable estimates of the models' coefficients. Application of this model was possible since it offers satisfactory results in the case of a correlation between cardiovascular risk predictors. The predictive power of the model was reassured by proximity to the Harrell concordance CI-index. R^2_{mer} measure of explained risk was used as model quality metric. The interpretation of the model's results was based on the hazard ratio (HR) of survival for each risk predictor. To determine the predictive value of addressed serum cardiovascular biomarker as mortality risk predictors, two variants of models were

TABLE 1 | Characteristics of the study cohort.

Parameter	Median (Q1; Q3) or %
N	280
Gender, m/f	42.5 / 57.5%
Age, years	60 (50; 67)
Hospital stay + FU analysis, days	366 (357; 373)
BMI, kg/m^2	27.9 (25.3; 32.6)
Clinical presentation at admission	
SpO_2, %	97 (95; 98)
Body temperature at admission, °C	36.7 (36.5; 37.45)
SAP, mm Hg	130 (120; 143)
DAP, mm Hg	83 (79; 90)
HR, beats / min	90.5 (76; 102)
BR, breaths /min	19 (18; 20)
Lung tissue damage on CT, %	36 (22.5; 52)
Relevant concomittant disease:	
AH, % (*n*)	38.9 (109)
DM, % (*n*)	7.5 (21)
CKD, % (*n*)	1.4 (4)
CHD, % (*n*)	6.4 (18)
CHF, % (*n*)	2.1 (6)
History of Stroke, % (*n*)	0 (0)
Obstructive lung disease, % (*n*)	7.5 (21)
History of AF, % (*n*)	0 (0)
Laboratory parameters	
Hb, dg/l	12.9 (119; 137.75)
WBC, *10^9/l	4.55 (3.64; 6.65)
Platelets, *10^9/l	266 (172.25; 277)
ESR, mm/sec	29 (18; 40.75)
CRP, mmol/l	41.8 (18.8; 76.9)
Procalcitonin, ng/ml	0.09 (0.05, 0.16)
Albumin, g/l	40.3 (37.8; 42.5)
CK, mmol/l	120.0 (72; 213)
Urea, mmol/l	5.33 (4.38; 6.62)
Creatinine, mmol/l	85.8 (77.5; 99.1)
GFR, ml/min/m^2	65.9 (57.1; 78.1)
D-Dimer, ng/ml	641 (505; 824)
Sodium, mmol/l	143 (141; 145)
Potassium, mmol/l	4.2 (3.9; 4.4)
Serum cardiovascular biomarkers	
TnI, ng/mL	0.03 (0.01; 0.07)
VCAM-1, ng/mL	13.84 (9.79; 17.5)
ST2, ng/mL	52.5 (32.4; 77.9)
Events during hospitalization	
Oxygen therapy, % (*n*)	64.3 (180)
NIV, % (*n*)	6.4 (18)
ET, % (*n*)	3.2 (9)
In hospital mortality, % (*n*)	3.9 (11)
Total 1-year mortality, % (*n*)	7.9 (22)
Hospital stay, days	11 (10; 14)

AH, arterial hypertension; BA, bronchial asthma; CK, creatine kinase; CHD, coronary heart disease; CHF-congestive heart failure; CKD, chronic kidney disease; CRP- C-reactive protein; CT computer tomography; DBP, diastolic blood pressure; DM, Diabetes Mellitus type 2; ET-endotracheal intubation; ESR, erythrocytes sedimentation rate; Hb, hemoglobin, HR, heart rate;, MI, myocardial infarction; NIV-non-invasive mechanical ventilation; SBP, systolic blood pressure; CK, creatine kinase; ST2 - suppression of tumorigenicity 2; TnI – highly sensitive Troponin I, VCAM-1; vascular cells adhesion molecule-1; WBC, white blood count.

considered: 1. a model which included all significant clinical and laboratory risk factors compared to 2. a model which additionally included the investigated cardiovascular serum biomarkers as risk predictors. The predictive value of both models was compared by quality metrics (Harrell concordance CI-index, measure of explained risk) of models with the inclusion/exclusion of biomarker values. A p-value < 0.05 was regarded as statistically significant. All statistical analyses were performed on R software (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria, https://www.r-project.org).

RESULTS

Demographic characteristics, clinical presentation at admission, relevant concomitant disease, and laboratory markers of our 280 hospitalized COVID-19 patients are presented in **Table 1**. COVID-19 relevant in-hospital therapies and relevant post-discharge therapies are presented in **Supplementary Tables 1**, **2**. Arterial hypertension (AH) was the most frequent comorbidity. While 64.3% of patients required oxygen therapy, 6.4% needed support by non-invasive mechanical ventilation and 3.2% by endotracheal intubation. Hospital stays averaged 11 (10, 14) days, with an in-hospital mortality rate of 3.9%, whereas overall mortality at 1 year was 7.9%.

In Hospital Survival Analysis

The in-hospital mortality rate was 3.9% ($n = 11$). This patient group was significantly older than patients surviving COVID-19 pneumonia ($p < 0.001$) and had lower oxygen saturation ($p < 0.003$) resulting in higher rates of non-invasive mechanical and invasive mechanical ventilation (both $p < 0.001$). Similarly, comorbidities were more common in these patients, including significant impairment of renal function. Among the investigated biomarkers, only VCAM-1 ($p < 0.001$) was significantly elevated in non-survivors, while no significant differences were observed for sST2 but a strong trend toward a statistical significance was evident for TnI ($p = 0.05$, **Table 2**).

In the next step, investigated biomarkers were analyzed with the help of univariate Cox regression with age as the control variable. The endpoint in-hospital mortality using each biomarker was further analyzed with the help of univariate Cox regression, where age was the control variable. **Table 3** presents coefficients of univariate Cox regression proportional hazards for investigated biomarkers according to in-hospital mortality. Of note, the most accurate mortality risk predictor was VCAM-1 (HR 1.086, $p < 0.001$). We further analyzed the differences in hospital survival rates in groups, according to the presence / absence of indicator or based on the normal / out of range laboratory and clinical parameters in patients by univariate Cox regression model analysis (**Supplementary Table 3**). The following variables were associated with hospital mortality with $p < 0.1$: age, SpO_2, arterial hypertension, coronary heart disease, chronic heart failure, procalcitonin and GFR. A significance has been also shown for creatinine, urea, and existence of chronic kidney disease, but considering their direct association with GFR, only the latter was included into the multi-marker model. Furthermore, since WBC and platelets showed significant differences between non-survivors and survivors when applying the Mann-Whitney test (**Table 2**), we also decided

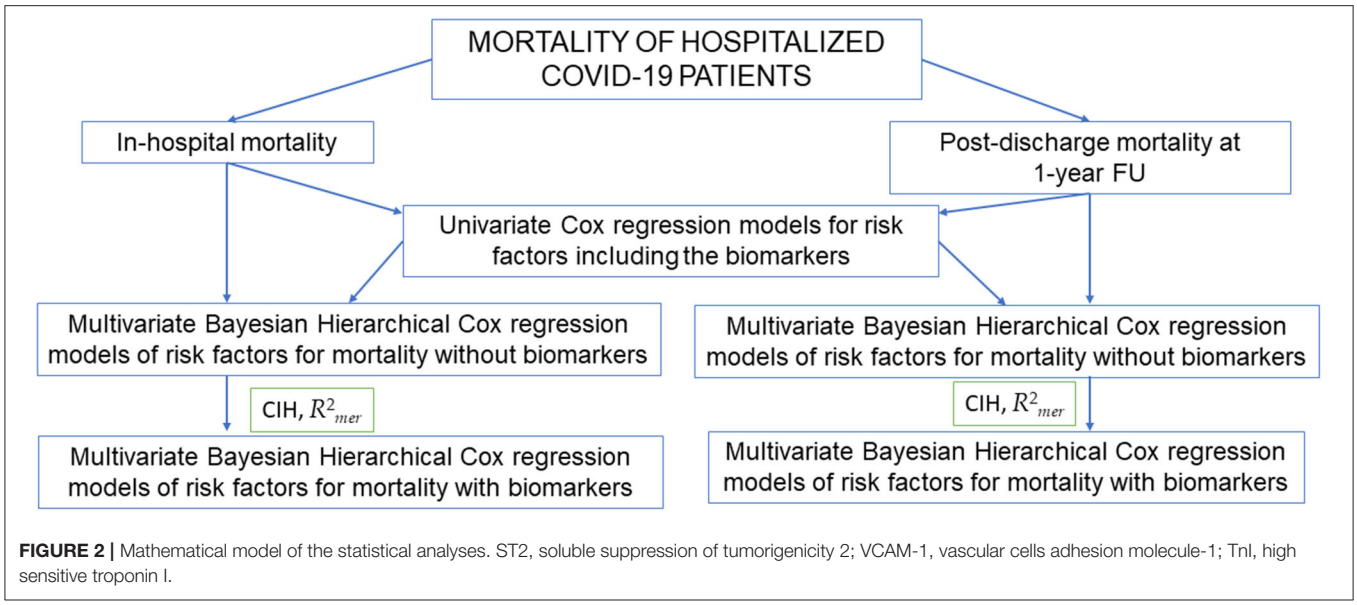

FIGURE 2 | Mathematical model of the statistical analyses. ST2, soluble suppression of tumorigenicity 2; VCAM-1, vascular cells adhesion molecule-1; TnI, high sensitive troponin I.

to include them into the multivariable model, although no association ($p > 0.1$) was revealed when using the univariate Cox regression for patients with high WBC and low platelets (**Supplementary Table 3**). The variables WBC and platelets were added to the multivariable model as dummy variables (as 1 if WBC was $> 8*10^9$ and also as 1 if platelets were $<150*10^9$ or as 0 in the rest of the cases).

The Gsslasso Cox Bayesian hierarchical model was based on identified risk factors for in-hospital mortality. It was constructed to assess their combined impact on survival in a multi-marker model. VCAM-1, age and gender as control variables were also added to the pool of risk factors to create the multi-marker model (**Figure 3**). By creating the preliminary multifactor model, risk factors arterial hypertension, coronary heart disease and chronic heart failure showed no relevant significance ($p > 0.05$) and were excluded from the model. Harrell's C-index (CIH) of the applied multi-marker model was 0.89, which indicates its satisfactory quality. On the other hand, while removing VCAM-1 from the model, it presented lower Harrell's C-index (CIH) of 0.814 with measure of explained risk of 0.83. Consequently, based on higher model quality metrics we continued by analyzing the model which included VCAM-1. With respect to the variables age, low SpO_2, GFR and platelets, WBC and procalcitonin, VCAM-1 remained an indicator associated with fatal events, while the highest HR ($3689 *10^{139}$) was revealed for procalcitonin. In low SpO_2, GFR and platelets variables HR was <1, which indicates that the lower range of the indicators increases in-hospital mortality (**Figure 3**).

Post Discharge 1-Year Follow-Up Survival Analysis

Among the remaining 269 patients, FU analysis was performed from discharge to 366 days. Death was registered in 11 patients (4.1%; **Table 4**). The deceased patients were remarkably older: 73 (61; 82, $p = 0.002$) vs. 59 years (49; 66), and more often had arterial hypertension ($p < 0.001$) but had no difference in the clinical presentation as well as lower rates of diabetes mellitus ($p < 0.001$) and obstructive lung disease ($p = 0.011$). With respect to the investigated biomarkers, only ST2 was significantly higher in the deceased group ($p = 0.024$). Additionally, this group more often had cardiovascular (CV) and non-CV hospitalizations ($p < 0.05$, **Table 4**). The respective biomarkers were analyzed in a next step, with respect to the endpoint 1-year post-discharge mortality, where age was the control variable. **Table 5** presents coefficients of Cox univariate regression proportional hazards for investigated mortality biomarkers. According to the univariant Cox regression models, the most accurate mortality risk predictors were ST2 (HR 1.004, $p < 0.001$) and TnI (HR 1.28, $p = 0.011$).

Using the Univariate Cox regression, we also analyzed the differences in survival rates of 1-year FU mortality in groups divided according to the presence / absence of risk factor based on the normal / out of range laboratory and clinical parameters. The following variables were shown to be associated with mortality with $p < 0.1$: procalcitonin, SpO2, urea, WBC, and arterial hypertension (**Supplementary Table 4**). The Gsslasso Cox Bayesian hierarchical model was constructed based on identified univariate risk factors to assess their combined impact on survival using a multi-marker model. The biomarkers ST2 and TnI as well as age and gender as a control variable were also added to the pool of risk factors to create a multi-marker model for survival. When using a preliminary multifactor model, the risk factors low SpO_2, Urea, WBC, and arterial hypertension were not found to be significant ($p > 0.1$) and were thus excluded from the model. The Harrell's C-index (CIH) of the applied model was 0.856 with a measure of explained

TABLE 2 | Comparison of COVID-19 in-hospital deceased vs. in hospital survivors.

Parameter	Hospital survivals, (Q1; Q3) or %	Hospital deceased, (Q1; Q3) or %	*p*
N, %	269 (96.1%)	11 (3.9%)	
Gender, m/f	114/155 (42.4%/57.6%)	5/6 (45%/55%)	0.820
Age, years	**59 (50; 66)**	**71 (69.5; 75)**	**<0.001**
BMI, kg/m^2	27.83 (25.3; 32.0)	32.05 (27.1; 32.5)	0.235
Clinical presentation at admission			
SpO_2, %	**97 (95; 98)**	**95 (93.25; 96.75)**	**0.003**
Temperature at admission, °C	36.7 (36.5; 37.5)	36,65 (36.6; 36.85)	0.695
SAP, mm Hg	130 (120; 140)	144 (137.75; 148.75)	0.143
DAP, mm Hg	83 (79; 90)	81 (80; 88)	0.523
HR, beats / min	91 (76, 102)	83.5 (80, 104.25)	0.691
BR, breaths /min	19 (18, 20)	19 (18; 20)	0.573
Lung tissue damage on CT, %	36 (22; 52)	38 (27, 43)	0.884
Relevant concomitant disease			
AH, % (*n*)	38.7 (104)	45 (5)	0.447
DM, % (*n*)	7.4 (20)	9 (1)	0.877
CKD, % (*n*)	**1.11 (3)**	**9 (1)**	**0.027**
CHD, % (*n*)	**5.2 (14)**	**36.4 (4)**	**<0.001**
CHF, % (*n*)	1.9 (5)	9 (1)	0.057
History of MI, % (*n*)	0	0	-
History of Stroke, % (*n*)	0	0	-
Obstructive lung disease, % (*n*)	**7.8 (21)**	**0**	**0.013**
AF, % (*n*), % (*n*)	0	0	-
Laboratory parameters			
Hb, dg/l	129 (119; 127)	13.8 (129.5; 144.75)	0.217
WBC, *10^9/l	**4.5 (3.6; 6.6)**	**6.3 (5.6; 9.8)**	**0.035**
Platelets, *10^9/l	**226.5 (173; 277.3)**	**169 (129.5; 144.75)**	**0.011**
ESR, mm/sec	29 (18; 41)	30.5 (19; 36.75)	0.394
CRP, mmol/l	41.6 (18; 77.9)	26.5 (23.1; 51)	0.433
Procalcitonin, ng/ml	**0.09 (0.05; 0.16)**	**0.15 (0.11; 0.26)**	**0.005**
Albumin, g/l	40.3 (37.8; 42.5)	40.4 (37.8; 42.6)	0.529
CK, mmol/l	124 (72; 213)	99 (82.25; 155.5)	0.752
Urea, mmol/l	**5.33 (4.38; 6.4)**	**8.57 (8.5; 8.8)**	**<0.001**
Creatinine, mmol/l	**85.6 (76.9; 98.5)**	**104.5 (97.3; 116.65)**	**0.002**
GFR, ml/min/m^2	**66.34 (57.5; 78.3)**	**48.2 (44.2; 50.9)**	**<0.001**
D-Dimer, ng/ml	705.1 (505; 824)	490 (460; 557)	0.082
Sodium, mmol/l	143 (141; 145)	142 (140.25; 143)	**0.022**
Potassium, mmol/l	4.2 (3.9; 4.4)	4.14 (3.93; 4.7)	0.926
Serum cardiovascular biomarkers			
ST2, ng/mL	52.26 (31.6; 77.64)	72.35 (45.4; 72.4)	0.762
VCAM-1, pg/mL	**13.75 (9.57; 16.98)**	**24.12 (17.7; 33.2)**	**<0.001**
TnI, ng/mL	0.03 (0.01; 0.03)	0.01 (0; 0.105)	0.050
Events during hospitalization			
Oxygen therapy, % (*n*)	62.8% (169)	100% (11)	**0.012**
NIV, % (*n*)	4.8 (13)	45% (5)	**<0.001**
ET, % (*n*)	0.7 (2)	55% (6)	**<0.001**
Hospital stay, days	11 (10; 13)	13 (12; 19)	0.828

AH, arterial hypertension; BA, bronchial asthma; CK, creatine kinase; CHD, coronary heart disease; CHF, congestive heart failure; CKD, chronic kidney disease; CRP, C-reactive protein; CT, computer tomography; DBP, diastolic blood pressure; DM, Diabetes Mellitus; ET, endotracheal intubation; ESR, erythrocytes sedimentation rate; Hb, hemoglobin; HR, heart rate; MI, myocardial infarction; NIV-non-invasive mechanical ventilation; SBP, systolic blood pressure; CK, creatine kinase; ST2 - suppression of tumorigenicity 2; TnI, highly sensitive Troponin I; VCAM-1, vascular cells adhesion molecule-1; WBC, white blood count. The $p < 0.05$ is marked bold.

risk of 0.81, which indicates its satisfactory quality. While removing TnI and ST2 biomarkers from the model, Harrell's C-index (CIH) was 0.812 with the measure of explained risk of 0.730. Consequently, based on higher model quality metrics we continued by analyzing the model which included ST2 and TnI.

Figure 4 presents the results of coefficients of the multivariate Bayesian Hierarchical Cox model for post-discharge all-cause mortality during 1-year FU. Age, TnI, and ST2 remained the indicators associated with post-discharge mortality during 1-year FU (**Figure 4**).

TABLE 3 | Univariate Cox regression for biomarkers, associated with COVID-19 hospital mortality.

Biomarker	Coefficient ± SE	Hazard ratio	CIH	CI	*P*
ST2	−0.0003 ± 0.003	0.999	0.86	0.99–1.005	0.886
VCAM-1	**0.08 ± 0.02**	**1.086**	**0.917**	**1.05–1.13**	**<0.001**
TnI	−0.16 ± 1.12	0.85	0.84	0.09–7.71	0.888

CIH, Harrell concordance index; CI, confidence interval for HR; SE, standard error; ST2, soluble suppression of tumorigenicity 2; VCAM-1, vascular cells adhesion molecule; TnI, highly sensitive troponin I. The p < 0.05 is marked bold.

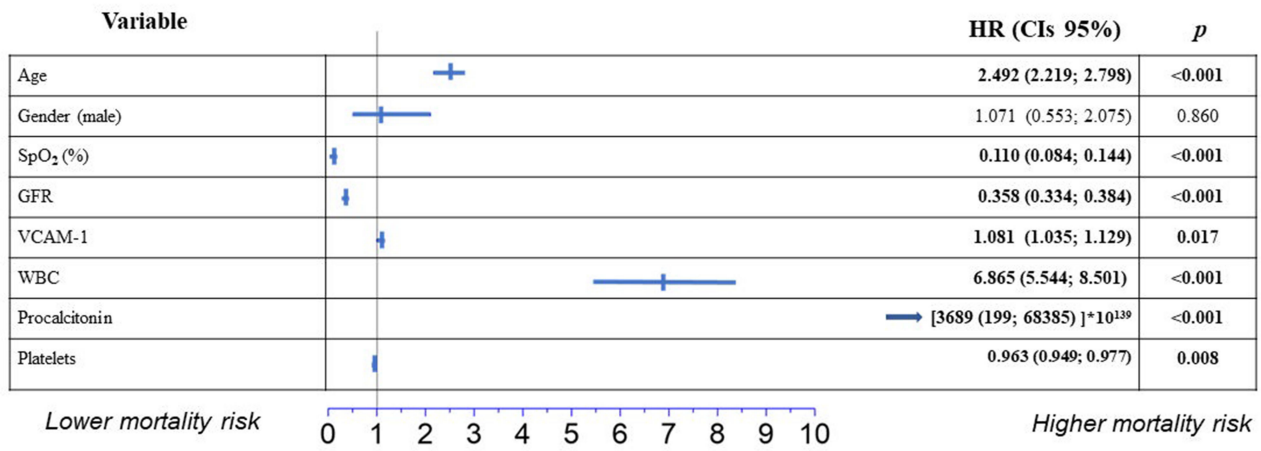

FIGURE 3 | Independent predictors of hospital mortality from COVID-19 in multivariable survival regression (Bayesian Hierarchical Cox model) in a multi-marker model. Results are reported as hazard ratio (HR) and 95% confidence intervals (CIs).

DISCUSSION

The emergence of COVID-19 has posed an unprecedented challenge to clinicians around the world. COVID-19 exhibits a wide clinical spectrum ranging from asymptomatic or mild respiratory tract symptoms to the development of acute respiratory distress syndrome and death. COVID-19 places a significant strain on healthcare systems, and diagnostic tools to guide decision-making to allocate potentially limited resources are still urgently needed. The disease was shown to be correlated to a high inflammatory burden, in part resulting in multi-organ damage and respiratory failure (25, 26). This systemic inflammatory response generates a "cytokine storm" (27), also affecting endothelial function, emphasized also by histological analyses (28, 29). Thus, a stratification of disease severity through vascular biomarkers seems plausible.

In COVID-19, several clinical parameters including laboratory parameters and radiographic findings were shown to help identify high-risk patients (1). Similarly, several clinical scores have been developed to predict the disease course of COVID-19 patients (30–32). The biomarkers most frequently included in these predictive models are typically indicators of cell damage (LDH, TnT/I) and inflammatory parameters (IL-6, ferritin, or lymphocytes count) (33, 34). Nevertheless, despite promising results, the suitability of biomarkers for the assessment of outcome in COVID-19 patients remains a matter of debate. Furthermore, to maximize diagnostic power, a multi-marker approach has been promoted and also shown to enhance the sensitivity and specificity of prognostic assessments (35).

With these previous studies in mind, we therefore aimed to assess the prognostic impact of the cardiac biomarker high-sensitive TnI, along with sST2 and VCAM-1, on in-hospital mortality as well as on 1-year post discharge survival after a hospitalization due to COVID-19 pneumonia. In-hospital mortality of COVID-19 patients was indeed associated with higher levels of VCAM-1 at hospital admission, while no correlation was evident for sST2 and high-sensitive TnI. Along with VCAM-1, typical risk factors such as old age, low SpO_2, GFR and platelet count, high WBC, and high levels of procalcitonin were independent indicators of mortality. Previous studies suggested that VCAM-1, and intracellular cell adhesion molecule-1 (ICAM-1) might promote the interaction between leukocytes and endothelial cells, by serving as ligands for integrins, and thus may play an important role in COVID-19 pathogenesis (36, 37). Impaired endothelial activation can lead to high accumulation of leukocytes and enhanced transmission of intracellular signals, which can result in persistent systemic inflammation and viral-induced endothelial dysfunction. This may be an underlying, unifying mechanism responsible for the widespread systemic manifestations seen with SARSCoV-2 infection (38). On this regard, also term "Acute Vascular Distress Syndrome" was introduced, to

TABLE 4 | Comparison of deceased and surviving patients at 1-year FU.

Parameter	Survivors in 1-year FU, (Q1; Q3) or %	Deceased patients during 1-year FU (Q1; Q3) or %	*P*
n, %	258 (95.9%)	11 (4.1%)	-
FU, days	**354.5 (342; 361)**	**50 (2; 146)**	**<0.001**
Gender, m/f	108/150 (41.9%/58.1%)	6/11 (55%/45%)	0.087
Age, years	**59 (49; 66)**	**73 (61; 82)**	**0.002**
BMI, kg/m^2	27.9 (25.2; 32.3)	27.5 (26.9; 29.3)	0.854
Clinical presentation at admission			
SpO_2, %	97 (95; 98)	98 (96; 98.5)	0.313
Temperature at admission, ◦C	36.5 (36.5; 37.5)	36.7 (36.5; 36.8)	0.315
SAP, mm Hg	130 (140/120)	140 (156.5; 120)	0.240
DAP, mm Hg	82 (72; 90)	88 (82.5; 91)	0.217
HR, beats / min	91 (75.6; 102)	92.5 (79; 109)	0.772
BR, breaths / min	19 (18; 20)	20 (18; 20)	0.645
Lung tissue damage on CT, %	36 (22; 52)	40 (22.5; 50)	0.662
Relevant concomitant disease			
AH, % (*n*)	**37.2 (96)**	**80 (72.7)**	**< 0.001**
DM, % (*n*)	**77.5 (20)**	**0**	**< 0.001**
CKD, % (*n*)	1.2 (3)	0	0.855
CHD, % (*n*)	5.0 (13)	9.1 (1)	0.392
CHF, % (*n*)	1.9 (5)	0	0.512
History of MI, % (*n*)	0	0	-
History of Stroke, % (*n*)	0	0	-
Obstructive lung disease, % (*n*)	**8.1 (21)**	**0**	**0.011**
AF, % (*n*)	0	0	-
Laboratory parameters			
Hb, dg/l	129 (119; 137)	134 (123.5; 138)	0.448
WBC, *10^9	4.54 (3.6; 6.4)	5.26 (4.3; 8.3)	0.154
Platelets, *10^9	226 (173; 277)	234 (165.5; 306)	0.819
ESR, mm/sec	29 (18; 40)	40 (16.5; 47.5)	0.442
CRP, mmol/l	41.8 (18.4; 77.9)	53.7 (25.6; 72.4)	0.658
Procalcitonin, ng/ml	0.09 (0.05; 0.15)	0.226 (0.108; 0.263)	0.032
Albumin, g/l	40.3 (37.5; 42.4)	39.75 (38.1; 42.3)	0.793
CK, *n* (%)	120 (72; 213)	190.5 (95.25; 294)	0.201
Urea, mmol/l	**5.33 (4.29; 6.17)**	**6.88 (6.2; 8.1)**	**0.011**
Creatinine, mmol/l	85.6 (76.9; 96.3)	99.25 (83; 106.9)	0.098
GFR, ml/min/m^2	66.5 (57.6; 78.4)	57.7 (56.5; 67.2)	0.217
D-Dimer, ng/ml	505 (437; 573)	525 (0; 712.5)	0.459
Sodium, mmol/l	143 (141; 145)	142.5 (142; 144.75)	0.865
Potassium, mmol/l	4.2 (3.9; 4.4)	4.15 (3.93; 4.45)	0.805
Serum cardiovascular biomarkers			
ST2, ng/mL	**51.38 (31.4; 76.8)**	**66.41 (57.0; 293.8)**	**0.024**
VCAM-1, pg/mL	13.7 (9.4; 16.7)	18.4 (10.3; 26.9) 0.03	0.148
TnI, ng/mL	0.03 (0.01; 0.07)	(0.01; 0.165)	0.225
FU events			
All FU events (except death):	**22.5 (58)**	**72.3 (8)**	**<0.001**
Non-CV hospitalization, % (*n*)	**14.7 (38)**	**36.4 (4)**	**0.001**
CV hospitalization	**6.6 (17)**	**18.2 (2)**	**0.023**
Myocardial infarction	0.3 (1)	0	>0.999
Stroke	0.3 (1)	18.2 (2)	**< 0.001**
Pulmonary embolism	0.3 (1)	0	>0.999

AH, arterial hypertension; BA, bronchial asthma; CK, creatine kinase; CHD, coronary heart disease; CHF, congestive heart failure; CKD, chronic kidney disease; CRP, C-reactive protein; CT computer tomography; CV, cardiovascular; DBP, diastolic blood pressure; DM, Diabetes Mellitus type 2; ESR, erythrocytes sedimentation rate; Hb, hemoglobin, HR, heart rate; SBP, systolic blood pressure; WBC, white blood count; CK,creatine kinase; VCAM-1-vascular cells adhesion molecule-1; ST2, suppression of tumorigenicity 2; TnI-highly sensitive Troponin I. The p < 0.05 is marked bold.

account for the quite unique vascular pathophysiology in COVID-19 pneumonia (17, 18). A key feature reported is a low ventilation-to-perfusion ratio, leading to an increased pulmonary blood flow with intrapulmonary right to left shunt (18). This mechanism might also account for the incoherence of clinical and radiographic findings and the in

TABLE 5 | Univariate Cox regression for biomarkers associated with post-hospital 1-year FU mortality.

Biomarker	Coefficient ± SE	Hazard ratio	CIH	CI	*P*
ST2	**0.004 ± 0.001**	**1.004**	**0.818**	**1.002–1.006**	**<0.001**
VCAM-1	0.04 ± 0.03	1.042	0.830	0.98–1.11	0.169
TnI	**0.25 ± 0.09**	**1.28**	**0.808**	**1.06–1.56**	**0.011**

CIH, Harrell concordance index; CI, confidential interval for HR; SE, standard error; ST2, soluble suppression of tumorigenicity 2; VCAM-1, vascular cells adhesion molecule-1; TnI, highly sensitive troponin I. The p < 0.05 is marked bold.

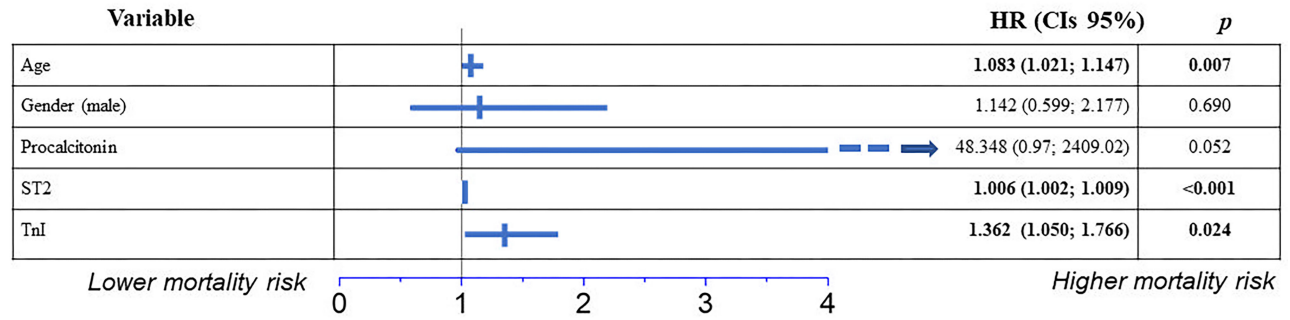

FIGURE 4 | Independent predictors of post-hospital 1-year FU mortality in patients hospitalized with COVID-19, in a multivariate survival analysis using Cox's regression model. Results are reported as hazard ratios (HR) and 95% confidence intervals (CIs).

part atypical clinical presentation of dyspnea in COVID-19 patients (18).

Similar to our findings, a recent meta-analysis comprising 349 critically ill and 337 non-critically ill patients described significantly higher rates of VCAM-1 levels in COVID-19 patients with a proposed cut-off point of 2523.7 ng/ml for critically ill and 1921.1 ng/ml for non-critically ill patients, respectively (21). Moreover, Bauer et al. (39) conducted a comparison of critically ill COVID-19 and non-COVID-19 patients requiring intensive care treatment, which again revealed significantly higher VCAM-1 levels in the COVID-19 group (39). Additionally, a direct correlation between VCAM-1 levels and viral RNA load in plasma was noted (40). Based on these and our findings, it can be speculated that vascular involvement is an important promoter of in-hospital mortality in COVID-19. This is also in line with cardio-embolic events as frequent complications especially in severe COVID-19 (41). Furthermore, the positive results of the Recovery trial along with the reduction of cardio-embolic events through use of dexamethasone therapy further emphasize the relevance of vascular complications in the acute setting of COVID-19 (42).

With regards, to high-sensitive TnI levels, we did not find an impact on prognosis. This finding stands in contrast to previous studies (43, 44). Still, the reasons for our contradictory results might be founded in our study design. On the one hand, the lack of a clear association between high-sensitive TnI and in-hospital mortality may partly be explained by the collection of blood samples at the 1st day of hospitalization. However, virally- induced cardiac injury usually requires 1–2 weeks to develop until clinical manifestations and resultant high-sensitive TnI increases occur (5, 45). This is further emphasized by a study of Zhou et al. (5), in which serum high-sensitive TnI median concentrations increased from 57.6 to 290.6 pg/mL during the period between day 16 and day 22 after the onset of COVID-19 infection in non-survivors (5). Similar effects might be responsible for the findings of sST2. On the other hand, high-sensitive TnI levels showed a strong trend toward an increase in non-survivors, with a *p*-value of 0.050. Accordingly, the lack of prognostic impact might also be attributed to the small sample size of our study, which is a limitation of our study design.

Accordingly, while VCAM-1 had the best prognostic power in the assessment of in-hospital mortality, levels of sST2 were of significant prognostic value with regard to long-term prognosis. This correlates to the results of recent studies which report a significant increase in cardiovascular disease burden over 1-year follow up in COVID-19 survivors (46). Accordingly, the numbers of CV as well as non-CV hospitalizations and stroke were significantly higher in the deceased group ($p < 0.05$). Similar to our findings, a prognostic benefit of sST2 with respect to disease severity and mortality was also shown in a former study of 100 hospitalized COVID-19 patients (47). As soluble ST2 represents a marker of inflammation and cardiac stress, the reasons for this finding may be diverse (9). For one, higher sST2 levels might be triggered by a higher inflammatory burden (16), potentially resulting in ongoing inflammation, or even virus persistence and long-COVID-19 syndrome. Similarly, higher levels of sST2 might be promoted by diverse comorbidities. sST2 was shown to be an effective prognostic tool in long-term risk stratification in patients with heart failure, myocardial infarction, and stable coronary heart disease (48). Thus, by incorporating different pathophysiological processes, higher levels of sST2 might also point toward a more ill patient collective. The higher rates of

CV and non-cardiovascular hospitalizations and stroke in the deceased group during FU ($p < 0.001$) further supports this suggestion. Moreover, the association of high-sensitive TnI with FU mortality matches previous studies, reporting a correlation of higher TnI/T concentrations with subsequent cardiovascular endpoints including heart failure decompensation, myocardial infarction, and viral myocarditis (49, 50).

With regards to the observed differences regarding short- and long-term prognosis, also the pathophysiological mechanisms have to be considered. VCAM-1 and ICAM-1 as well as sST2 represent circulating biomarkers (43, 44). However, circulating levels might still display differences with regards to their cellular, membrane bound forms. Given the fact, that VCAM-1 acts as a cell adhesion molecule in the context of inflammatory processes, a fast effect of an increase in VCAM-1 can be assumed (51, 52). Of note, changes in levels of VCAM-1 were reported in a comparably short timespan of days to hours (51, 52). Thus, VCAM-1 might represent a promising parameter reflecting short term effects in COVID-19, while long-term prognostic impact is limited. On the other hand, expression of sST2 is influenced by numerous comorbidities, thus reflecting an overall health status, not necessarily limited to ongoing inflammatory processes (53–55). While this might limit its impact on short-time prognosis, the incorporation of different pathophysiologic processes makes it a suitable marker for long term prognosis such as in the context of COVID-19 (53–55). From a cardiovascular aspect, sST2 further represents a marker of cardiac fibrosis and was shown to be elevated in heart failure (55). While cardiac injury was reported in the context of COVID-19, cardiac remodeling and cardiac fibrosis itself represent an ongoing process over months and years. Accordingly, worse outcomes due to cardiac fibrosis and remodeling might primarily induce undesirable long-term effects after a COVID-19 infection.

In conclusion, our study demonstrates the potential of novel cardiovascular biomarkers in the context of COVID-19. Based on the pathophysiological processes involved, VCAM-1 represents a promising prognostic marker for the assessment of in-hospital mortality in COVID-19. On the other hand, sST2 as well as high-sensitive Tn I provided prognostic value in the long-term follow-up.

Limitations

The greatest limitation of our study is the single-center design along with a comparably small sample size. This might limit the significance of our results. Thus, the findings of our study have to be considered as primarily hypothesis generating. Furthermore, the rapid evolution of COVID-19 management during the time of biomarker collection (June to August 2020) should be taken into consideration. Cardiac imaging assessments were not routinely performed in our study. Of note, advanced cardiac imaging including echocardiography, would have provided important information about potential correlations between cardiac functional impairments and the investigated biomarkers. Since only hospitalized patients were included, the results cannot be transferred to milder COVID-19 disease. Moreover, biomarkers were measured only at admission, and no FU values were assessed. Hence, no conclusions with regards to the role of tested biomarkers as potential tools for disease and therapy monitoring can be drawn. Accordingly, our data are only representative for their prognostic ability at baseline. Therefore, despite promising results, routine application of the proposed multi-marker approaches may be limited.

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 Ethic committee of the Bashkir State Medical University (N5, 2020). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LM, PJ, DG, PD, RG, IL, AT, RZ, IK, BC, BV, VP, KK, UH, ML, LF, RP, and NZ meet the criteria for authorship and contributorship as defined by the ICMJE. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Prognostic value of acute cor pulmonale in COVID-19-related pneumonia: A prospective study

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Background: It is known that acute cor pulmonale (ACP) worsens the prognosis of non-coronavirus disease 2019 (COVID-19) acute respiratory distress syndrome (NC-ARDS). The ACP risk score evaluates the risk of ACP occurrence in mechanically ventilated patients with NC-ARDS. There is less data on the risk factors and prognosis of ACP induced by COVID-19-related pneumonia.

Objective: The objective of this study was to evaluate the prognostic value of ACP, assessed by transthoracic echocardiography (TTE) and clinical factors associated with ACP in a cohort of patients with COVID-19-related pneumonia.

Materials and methods: Between February 2020 and June 2021, patients admitted to intensive care unit (ICU) at Amiens University Hospital for COVID-19-related pneumonia were assessed by TTE within 48 h of admission. ACP was defined as a right ventricle/left ventricle area ratio of >0.6 associated with septal dyskinesia. The primary outcome was mortality at 30 days.

Results: Among 146 patients included, 36% (n = 52/156) developed ACP of which 38% (n = 20/52) were non-intubated patients. The classical risk factors of ACP (found in NC-ARDS) such as $PaCO_2$ >48 mmHg, driving pressure >18 mmHg, and PaO_2/FiO_2 < 150 mmHg were not associated with ACP (all P-values > 0.1). The primary outcome occurred in 32 (22%) patients. More patients died in the ACP group (n = 20/52 (38%) vs. n = 12/94 (13%), P = 0.001). ACP [hazards ratio (HR) = 3.35, 95%CI [1.56–7.18], P = 0.002] and age >65 years (HR = 2.92, 95%CI [1.50–5.66], P = 0.002) were independent risk factors of 30-day mortality.

Conclusion: ACP was a frequent complication in ICU patients admitted for COVID-19-related pneumonia. The 30-day-mortality was 38% in these patients. In COVID-19-related pneumonia, the classical risk factors of ACP did not seem relevant. These results need confirmation in further studies.

KEYWORDS

acute cor pulmonale (ACP), COVID-19, AVDS, speckle tracking, ARDS

Introduction

Acute cor pulmonale (ACP) is a frequent, well-known complication of non-coronavirus disease 2019 (COVID-19) (NC) acute respiratory distress syndrome (ARDS), requiring protective mechanical ventilation. In NC-ARDS, the prevalence of ACP is 22% despite protective mechanical ventilation and is an independent risk factor for mortality (1). COVID-19-related ARDS seems atypical (2) and needs specific management, such as advanced immune or cell therapies (3). However, data on ACP in COVID-19 are scarce. ACP is defined, using echocardiography, as an acute right ventricular (RV) dilatation (end-diastolic RV/left ventricle ratio of >0.6) associated with septal dyskinesia (4) due to increased RV afterload that may eventually lead to RV failure. In NC-ARDS, several pathophysiological mechanisms, such as hypoxic pulmonary vasoconstriction, hypercapnia, or positive pressure ventilation, induce an elevation of pulmonary vascular resistance (PVR), leading to an increased RV afterload (5).

To assess the risk of ACP under mechanical ventilation, a clinical risk score was previously developed (1). ACP was associated with both right and left ventricular dysfunction due to ventricular interdependence: RV dysfunction leads to RV dilatation and leftward septal shift, restricting the left ventricle and decreasing cardiac output. ACP is reversible, so early diagnosis of ACP is of utmost importance for ventilator setting adaptation and clinical management to avoid hemodynamic instability related to RV dysfunction (6).

The clinical presentation of ARDS related to COVID-19 infection (CARDS) differs from NC-ARDS (7, 8). CARDS presents some "atypical" features (9), including high lung compliance, low recruitability (10), increased cardiac output with low PVR (11), and increased intrapulmonary shunting (12). In this situation of "acute vascular distress syndrome" (AVDS) (13), the increase in pulmonary blood flow and the alteration in PVR may affect RV afterload and promote RV dilation and dysfunction. Several echocardiographic studies have shown that RV dilatation (14) and RV dysfunction (15) were associated with a poor prognosis in COVID-19 infection. However, in these studies, the presence of ACP was rarely reported (14–16) except in cases of pulmonary embolism (PE) (17). Besides, some authors showed that classical factors of the ACP risk score were not associated with ACP, probably due to different pathophysiology (18). There are few data on ACP assessed by transthoracic echocardiography (TTE) in patients with COVID-19-related pneumonia requiring ICU hospitalization.

The aim of this study was to evaluate the incidence, 30-day mortality, and clinical factors associated with ACP evaluated with a TTE in a cohort of patients hospitalized in the ICU for COVID-19-related pneumonia. We hypothesized that ACP is a frequent manifestation of COVID-19-related pneumonia even in non-intubated patients (under high flow oxygen or non-invasive ventilation). Moreover, we also hypothesized that ACP increases 30-day mortality.

Materials and methods

Population

Between 1 March 2020 and 1 June 2021, adult patients (> 18 years of age) were admitted to the ICU at Amiens University Hospital for hypoxemic pneumonia related to SARS-CoV-2 infection, with a TTE performed within 48 h of ICU admission, and were prospectively included in the study. Exclusion criteria were patients with permanent atrial and ventricular pacing, pregnant women, patients under extracorporeal membrane oxygenation (ECMO), those with supraventricular tachycardia during the TTE exam, and those with poor image quality for RV analysis. Patients were included on the day of the TTE examination.

Ethics

This is an ancillary study of a prospective cohort study of patients with COVID-19 infection hospitalized in the ICU at Amiens University Hospital (NCT04354558). This study was approved by the Amiens University Hospital IRB (Comité de Protection des Personnes Nord-Ouest II CHU–Place V. Pauchet, 80054 AMIENS Cedex 1, CNIL Number:

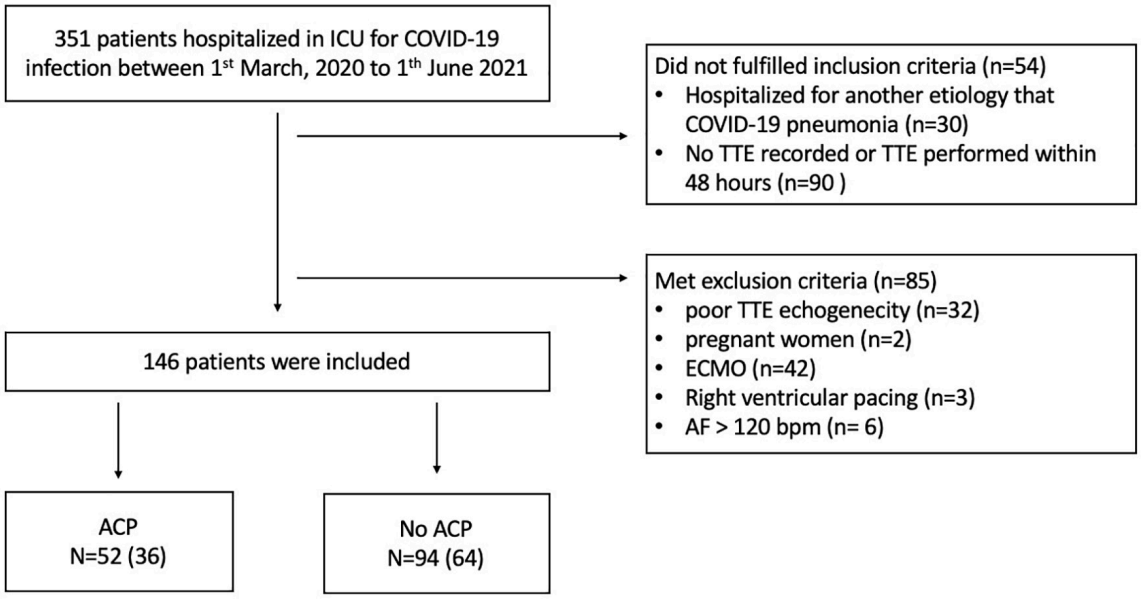

FIGURE 1
Flow diagram of the study group. ACP, acute cor pulmonale; AF, atrial fibrillation; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; TTE, transthoracic echocardiography.

PI2020_843_0026). In accordance with French law on clinical research for non-interventional studies, informed consent was waived but oral and written information was provided whenever possible to the patients and their families, specifying that they could oppose using their data (19).

Data

Electronic data, medical reports, and biological values were collected prospectively. SARS-CoV-2 infection was confirmed by a positive reverse transcription-polymerase chain reaction on a nasopharyngeal swab or bronchoalveolar lavage on ICU admission. The severity of illness at the time of the TTE exam was evaluated by the simplified acute physiology score (SAPS) II (20). The severity of COVID-19-related pneumonia was defined according to the World Health Organization (WHO) case definition (21). The critical group included patients with respiratory failure requiring mechanical ventilation and shock or organ failure (21). Vasopressor use was evaluated by the SOFA cardiovascular (SOFA cv) score (22). The ACP risk score was defined by four variables, namely, pneumonia as cause of ARDS, driving pressure >18 cmH_2O, PaO_2/FiO_2 ratio <150 mmHg, and $PaCO_2$ level > 48 mmHg (1). A chest computed tomography scan assessed radiological lung involvement and PE with intravenous contrast injection before ICU admission. Outcomes during ICU stay and vital status at 30 days were collected. The primary outcome was mortality at day 30. Regarding anticoagulation, all patients received intravenous unfractionated heparin (Heparin Choay®, Sanofi-Aventis, France) for an anti-factor Xa activity target of 0.20–0.40 U/ml to reduce COVID-19-associated risk of thrombosis.

Echocardiography

Trained operators performed TTE in the supine position within 48 h of ICU admission. Standard echocardiography protocol was used according to the American Society of Echocardiography guidelines (23) and the European Society of Cardiology (24). Echocardiographic images were obtained through a high-quality, commercially available ultrasound system (CX50, Philips Healthcare). All operators had a level III competence in general adult TTE (25). Caution was taken for a complete analysis of the RV with the good delimitation of the endocardium border and RV-free wall. Conventional RV systolic parameters such as tricuspid annular plane systolic excursion (TAPSE), tricuspid S wave (RV-S'), and RV fractional area change (RV-FAC) were assessed in apical four-chamber view as recommended (23). RV dilatation was defined when the end-diastolic RV/LV area ratio was >0.6 in a four-chamber or subcostal view (23). In TTE, ACP was defined as RV dilatation (end-diastolic RV/LV area ratio of >0.6) associated with septal dyskinesia (4). RV systolic function was assessed using conventional parameters (TAPSE, RV-S', and RV-FAC) and bidimensional speckle tracking parameters such as tricuspid annular displacement (TAD). TAD parameters were composed of (1) TAD lateral, (2) TAD septal, and (3) RV longitudinal

shortening fraction (RV-LSF). TAD parameters were measured in a focused RV four-chamber view and calculated with a dedicated software described in a previous study (26).

Statistical analysis

Data are expressed as mean ± standard deviation (SD), median [interquartile range], or numbers (percentage), as appropriate. Comparisons between the two groups used the chi-square test or Fisher's exact test for categorical variables and Student's *t*-test or the Mann–Whitney–Wilcoxon test, as appropriate, for continuous variables.

To evaluate independent factors associated with ACP, univariate logistic regression was performed with classical factors, such as PaO_2/FiO_2 <150 mmHg, driving pressure >18, and $PaCO_2$ > 48, which were included in the ACP risk score (1). We also included in the logistic regression variables such as body mass index (BMI), diabetes, PE, and mechanical ventilation reported to be potentially associated with ACP (18).

The multivariate Cox regression model was used to identify the parameters associated with the primary outcome and calculate the hazard ratio (HR) and 95% confidence interval (CI). Variables with a probability of <0.10 were integrated into the multivariate analysis. The Kaplan–Meier method was used to plot the survival curves compared with the log-rank test.

A statistical test was significant when the P-value was less than 0.05. All P-values are the results of 2-tailed tests. Statistical analyses were performed using the SPSS software version 24 (IBM Corp, Armonk, NY).

Results

A total of 351 patients were admitted to the ICU at Amiens University Hospital for COVID-19-related pneumonia during the study period. Notably, 228 (65%) patients had a TEE within 48 h of ICU admission, and 82 (36%) had exclusion criteria (42 (51%) patients received ECMO and 32 (39%) patients had a poor TTE echogenicity). A total of 146 patients were included in the study. Patients were divided into two groups according to the presence or absence of ACP diagnosed by TTE. ACP was diagnosed in 52 out of 146 (36%) patients and was absent in 94 out of 146 (64%) patients (**Figure 1**).

Clinical and demographic characteristics of patients

There was no significant difference between the two groups regarding age, clinical presentation, and biology at inclusion (**Table 1**). Of the 146 patients, 135 (92%) had chest CT angiography before ICU admission. Only 2 (4%) patients had a PE in the ACP group before ICU admission.

Echocardiographic findings (Table 2)

Echocardiographic parameters are presented in **Table 2**. In the non-ACP group, 49 (52) patients had RV dilatation. In the ACP group, RV dilatation was predominant in the middle cavity (39 [35-43] mm vs. 35 [29-42] mm; $P = 0.03$). TAD parameters were more impaired in the ACP group than in the non-ACP group, especially for RV-LSF (20.4 [15.9–23.9]% vs. 22.3 [19.8–26.3]%, $P = 0.004$). There was no significant difference between the two groups for conventional parameters of RV systolic function (TAPSE, S′ wave, and RV-FAC).

Hemodynamic parameters, ventilator settings, and outcomes

A total of 20 (38%) patients in the ACP group were not intubated at TTE examination (**Table 3**). There was no difference between the two groups in the number of variables included in the ACP risk score (all *P*-values > 0.1) and in the ACP risk score itself (2 [2–2.5] vs. 2 [2.2.5], $P = 0.12$). Patients in the ACP group had more noradrenaline than in the non-ACP group ($P = 0.01$). Cardiogenic shock (P = 0.01) and extra renal replacement therapy (P = 0.05) were higher in the ACP group than in the non-ACP group.

Factors associated with acute cor pulmonale

In our study, no predictive factors for ACP were found even in the patients in the mechanical ventilation group. In univariate analysis, factors composing the ACP risk score were not associated with ACP (**Table 4**).

Prognosis of acute cor pulmonale

The primary outcome occurred in 32 (22%) patients and more often in the ACP group ($n = 20/52$ vs. $n = 12/94$, $P = 0.001$). Overall, 40 (27%) patients died during ICU stay, of whom 62% ($n = 25/40$) were in the ACP group (**Table 3**). On Cox univariate analysis, the occurrence of the primary outcome was associated with ACP ($p = 0.001$), age > 65 years ($p = 0.001$), hypertension ($p = 0.075$), and mechanical ventilation ($p = 0.06$). After multivariable adjustment, ACP (HR = 3.35, 95%CI [1.56–7.18], $P = 0.002$) and age >65 years (HR = 2.92, 95% CI [1.50–5.66], $P = 0.002$) remained independently associated with the primary outcome (**Table 5**). The analysis of survival curves

by the Kaplan–Meier curves showed that patients in the ACP group had higher 30-day mortality (P = 0.002), especially in the subgroup of non-intubated patients (log rank P = 0.04, Figure 2).

Discussion

The results of our study evaluating the prognosis of ACP in patients with COVID-19-related pneumonia can be summarized as follows: (1) the incidence of ACP was 36%, (2) ACP was present in 38% of non-intubated patients, (3) classical risk factors of ACP in NC-ARDS were not associated with ACP, (4) ACP increased mortality in patients with COVID-19-related pneumonia admitted to ICU, and (5) RV-LSF could be helpful in RV systolic function assessment in this clinical setting.

Prevalence of acute cor pulmonale in severe COVID-19-related pneumonia

In the era of protective ventilation, the prevalence of ACP in NC-ARDS has been evaluated to be 22% during the first 72 h of mechanical ventilation (1). In our study, ACP occurred in 36% of patients, and 35% (n = 32/90) of patients were under mechanical ventilation. This result was close to a study conducted by Cavaleiro et al., who found a high prevalence of ACP (38%, n = 44/117, 95%CI 0.29–0.47) in a cohort of

TABLE 1 Demographics and clinical data.

Variables	No ACP (n = 94)	ACP (n = 52)	P value
Age (years)	60 [58-68]	59 [58-68]	0.33
BMI (kg.m^{-2})	29.8 [25.7-34.1]	30.7 [26.3-35.7]	0.51
SAPS II score at inclusion	33 [21-57]	38 [24-58]	0.67
Male gender *(n;%)*	67 (71)	37 (71)	0.75
Medical history			
None	12 (13)	9 (17)	0.46
Hypertension	51 (54)	23 (44)	0.3
Diabetes	30 (32)	12 (23)	0.34
Dyslipidemia	27 (29)	17 (33)	0.71
Smoking (former or active)	16 (17)	14 (27)	0.2
Chronic renal disease	8 (9)	5 (10)	1
COPD/asthma	9 (10)	9 (17)	0.19
Coronary or peripheral artery disease	1 (1)	4 (8)	0.77
Chronic treatment			
Statin	29 (31)	12 (23)	0.34
Beta blocker	20 (21)	13 (25)	0.68
ACE inhibitor	19 (20)	11 (21)	1
ARBs	17 (18)	8 (15)	0.82
Time to first symptom to ICU admission (days)	8 [6-11]	7 [4-9]	0.60
CT scan (n = 135/146)			
Frosted glass	84 (89)	51 (98)	0.29
Condensation	55 (59)	29 (56)	0.71
Crazy Paving	24 (26)	11 (21)	0.54
Lung involvement > 50%	43 (46)	23 (44)	0.71
Pulmonary embolism	6 (6)	2 (4)	0.71
Biological investigations at inclusion			
Lymphocyte count, mm^{-3}	700 [500-900]	700 [500-900]	0.93
C reactive protein, $mg\ l^{-1}$	146 [90-201]	145 [89-263]	0.94
Serum creatinine, umol/L	69 [53-88]	80 [58-112]	0.34
Troponine Tc HS, $ng\ ml^{-1}$	19 [7-53]	21 [9-57]	0.95
BNP, $pg\ ml^{-1}$	61 [22-123]	59 [36-142]	0.85
Platelet count x 10^9 l^{-1}	230 [179-391]	256 [174-305]	0.29
Fibrinogen (g l^{-1})	6.0 [4.7-7.3]	5.8 [5.0-7.6]	0.59
PT (%)	76 [70-86]	76 [66-84]	0.67
aPTT	1.1 [0.9-1.2]	1.1 [1.0-1.2]	1

Data are presented as median [interquartile range] and number (percentage). ACE, angiotensin-converting enzyme; aPTT, activated partial thromboplastin time; ARBs, angiotensin II receptor blockers; BMI, body mass index; BNP, brain natriuretic peptide; CT, computerized tomography; COPD, chronic obstructive pulmonary disease; PT, prothrombin time. SAPS, simplified acute physiology score; WBC, white blood cell.

CARDS despite protective mechanical ventilation (18). In a smaller sample size study, Bagate et al. found even a higher prevalence (46%, *n* = 31/67) (27).

Acute cor pulmonale in non-intubated patient and right ventricular dilatation

In our study, 38% (*n* = 20/52) of non-intubated patients with ACP were diagnosed. There are very less data on ACP in non-intubated patients without thrombotic event. Several studies have described RV dilatation and dysfunction (assessed by echocardiography) in COVID-19, but ACP is rarely reported. For example, in a large prospective international survey including 1,272 patients with COVID-19 infection, Dweck et al. reported 33% of RV abnormalities, including 15% of RV dilatation. However, the presence of ACP was not reported (16). In the study by Soulat-Dufour et al., RV dilatation (defined by an RV/LV ratio of >0.6) in non-intubated patients with COVID-19 occurred in 12% of cases (*n* = 47/407). It was independently associated with death or ICU transfer (14). Unfortunately, the presence of septal dyskinesia was not reported. In our cohort, 69% (*n* = 101/146) of patients had RV dilatation, defined by the RV/LV area ratio of >0.6. Previous studies have found an incidence of RV dilatation in patients with COVID-19 admitted to ICU between 30 and 74% (28, 29), depending mainly on the definition used to assess RV dilatation.

Acute cor pulmonale and pulmonary embolism

In our study, PE was diagnosed on CT scan, before ICU admission, in 8 (5%) patients and was not associated with ACP (2/52 vs. 6/94, $p = 0.71$). Cavaleiro et al. found similar results (8%) in their study and showed that PE was the only factor

TABLE 2 Echocardiographic data.

Overall population (*n* = 146]	**No ACP (*n* = 94)**	**ACP (*n* = 52)**	***P* value**
LV systolic parameters			
LVEF (%)	63 [53-72]	61 [50-71]	0.43
LV end diastolic volume (ml)	92 [62-114]	101 [74-124]	0.18
LV end systolic volume (ml)	31 [20-47]	37 [26-57]	0.33
Stroke volume index (ml/m^2)	30 [24-39]	30 [24-36]	0.61
CO (l min^{-1})	4.7 [4.0-6.2]	4.7 [3.9-6.7]	0.87
LV diastolic function parameters			
E wave (cm s^{-1})	77 [66-92]	81 [67-102]	0.22
A wave (cm s^{-1})	75 [58-92]	81 [63-104]	0.27
E/A ratio	0.98 [0.72-1.25]	0.87 [0.73-1.41]	0.69
Lateral E/e'	8.5 [6.8-11.0]	8.2 [6.6-10.8]	0.83
E wave deceleration time (ms)	253 [185-344]	245[192-335]	0.77
LA volume (ml)	32 [22-44]	38 [24-51]	0.53
LA volume index (ml/m^2)	16 [9-20]	17 [9-24]	0.41
RV parameters			
RV basal dimension (mm)	44 [38-49]	45 [40-52]	0.98
RV mid-cavity dimension (mm)	35 [29-42]	39 [35-43]	0.03
RV longitudinal dimension (mm)	77 [68-86]	78 [70-84]	0.63
RV EDA (cm^2)	20.0 [16.0-24.3]	22.8 [18.1-26.0]	0.04
RV ESA (cm^2)	11.0 [7.9-14.2]	12.5 [9.2-16.8]	0.03
RV EDA/VG EDA ratio	0.66 [0.53-0.84]	0.86 [0.67-1.13]	0.0001
RA volume indexed to BSA (ml/m^2)	15.1 [11.0-22.6]	19.0 [10.0-25.1]	0.51
RV dilatation, *n (%)*	49 (52)	52 (100)	-
RV Systolic function parameters			
TAPSE (mm)	23.5 [19.7-27]	22.7 [19-26.2]	0.85
RV- S' (cm/s^{-1})	16.1 [13.4-19.1]	16.0 [12.5-19.4]	0.60
RV FAC (%)	44 [36-53]	44 [38-51]	0.68
TAD parameters			
TAD lateral (mm)	21.6 [18.8-25.9]	18.6 [15.9-23.3]	0.009
TAD septal (mm)	12.8 [9.4-14.3]	9.8 [7.85-13.7]	0.014
RV-LSF (%)	22.3 [19.8-26.3]	20.4 [15.9-23.9]	0.004

Continuous variables are expressed as median [interquartile range] and number (percentage). CO, cardiac output; BSA, body surface area. EDA, end diastolic area; ESA, end-systolic area; FAC, fractional area change; LA, left atrial; LV, left ventricle; LVEF: left ventricular ejection fraction; RA, right atrium; RV: right ventricle; RV-LSF, right ventricle longitudinal shortening fraction; TAD, tricuspid annular displacement; TAPSE, tricuspid annular plane systolic excursion.

TABLE 3 Clinical characteristics and outcomes of patients having COVID-19-related pneumonia with and without acute cor pulmonale.

Variables	No ACP ($n = 94$)	ACP ($n = 52$)	*P* value
Hemodynamic parameters at inclusion			
HR, *bpm*	85 [76- 99]	81 [72-90]	0.46
SAP, *mmHg*	128 [113-142]	130 [117-145]	0.63
DAP, *mmHg*	69 [60-83]	67 [59-76]	0.87
MAP, *mmHg*	85 [70-92]	85 [70-92]	0.37
SpO_2,%	93 [90-96	93 [91-95]	0.61
Blood gas values at inclusion			
pH	7.42 [7.35-7.45]	7.42 [7.32-7.46]	0.64
PaO_2, *mmHg*	80 [60-106]	77 [66-87]	0.59
$PaCO_2$, *mmHg*	38 [33-44]	39 [33-47]	0.59
Critical group at inclusion			
Vasopressors use, *n (%)*	20 (21)	21 (40)	0.01
Mechanical ventilation, *n (%)*	58 (62)	32 (62)	0.96
PaO_2/FiO_2 ratio	91 [70-136]	100 [70-128]	0.89
PEEP, *cmH20*	12 [12-15]	13 [11-14]	0.96
Driving pressure, *cmH20*	14 [12-15]	13 [11-15]	0.88
Tidal volume, *ml per kg*	5.8 [5.2-6.1]	6.1 [5.8-6.2]	0.65
Compliance, *ml/cmH20*	30 [26.4-35.2]	31.7 [25.2-38]	0.87
Plateau pressure, *cmH20*	27 [25-29]	28 [24-29]	0.52
ACP risk score for patients under MV	58	32	
(*n*)	58 (100)	32 (100)	-
Pneumonia as cause of ARDS	4 (7)	6 (18)	0.16
Driving pressure > 18 cmH_2O	43 (74)	24 (80)	0.62
PaO_2/FiO_2 < 150 mmHg	9 (15)	10 (30)	0.11
$PaCO_2$ > 48 mmHg	2 [2-2.5]	2 [2-2.5]	0.12
Total ACP risk score (0-4)			
Respiratory evolution			
Pneumothorax, *n (%)*	10 (11)	5 (10)	1
Ventilator associated pneumoniae, *n (%)*	50 (54)	30 (58)	0.72
ECMO, *n (%)*	9 (10)	6 (11)	0.78
Tracheostomy, *n (%)*	8 (9)	5 (10)	1
Time under MV, days	20 [12-31]	19 [5-26]	0.43
Thrombotic complication			
Pulmonary embolism, *n (%)*	8 (9)	6 (11)	0.77
Deep vein thrombosis, *n (%)*	6 (6)	3 (6)	1
Renal replacement therapy	13 (14)	14 (27)	0.05
Cardiogenic shock, *n (%)*	4 (4)	9 (17)	0.01
Outcome			
Mortality at 30-days, *n (%)*	12 (13)	20 (38)	0.001
ICU Mortality, *n (%)*	15 (16)	24 (46)	0.001
ICU length of stay, *days*	13 [7-32]	19 [7-27]	0.71

Data are presented as median [interquartile range] and number (percentage). ACP, acute cor pulmonale; DAP, diastolic arterial pressure; ECMO, extracorporeal membrane oxygenation; HR, heart rate; ICU, intensive care unit; MAP, mean arterial pressure; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; SpO_2, pulse saturation of oxygen.

associated with ACP (18). It is well known that massive PE may induce ACP and require specific medical management (30). However, in the study conducted by Cavaleiro et al., the number of patients with PE in the two groups (2/73 vs. 7/44, $p = 0.007$) is limited, making it challenging to draw any conclusion.

Classical risk factors for acute cor pulmonale

In NC-ARDS, factors increasing pulmonary vasoconstriction (hypercapnia, hypoxemia, and high driving pressure) under mechanical ventilation are included in the ACP risk score. In NC-ARDS, when two or more risk factors were present, the risk of ACP exceeded 20% (1). In our study, ACP risk score and classical factors were not associated with ACP in patients under mechanical ventilation. Our results were in accordance with a previous study by Cavaleiro et al. Cavaleiro et al. found that the ACP risk score and its components were not associated with ACP (18) in CARDS. They concluded that ACP is likely associated with microangiopathy or thrombosis related to COVID-19 infection (18). To date, no clinical score assesses the risk of ACP in non-intubated patients.

TABLE 4 Factors associated with acute cor pulmonale in patients with COVID-19-related pneumonia.

Variables	Overall population	Univariate analysis	
		OR (95%CI)	*P* value
BMI		1.03 [0.98-1.01]	0.21
Diabetes		0.64 [0.29-1.39]	0.26
Chronic renal disease		1.14 [0.35-3.7]	0.82
Mechanical ventilation		1.11 [0.56-2.2]	0.74
Pulmonary embolism		1.33 [0.43-4.01]	0.61
Patients under mechanical ventilation			
PaCo2 > 48 mmHg*		2.23 [0.80-6.17]	0.12
Driving Pressure > 18 cmH_20*		2.61 [0.59-11.4]	0.20
PaO_2/FiO_2 < 150*		1.86 [0.57-6.01]	0.29

BMI, body mass index; CI, confidence interval; OR, odds ratio. *Acute cor pulmonale risk score parameters.

Right ventricular afterload, pulmonary blood flow, and thrombotic complications

Acute cor pulmonale is the most severe presentation of RV dilatation and dysfunction due to an acute increase in RV afterload. Under normal conditions, RV afterload highly depends on the distribution of blood flow in the lung, the degree of hyperinflation, and the alteration of the pulmonary vasomotor tone (6). Physiological studies have shown that RV is more adapted to rest than stress or exercise. During exercise, the increase in cardiac output increases PVR, consistent with the relationship between mean pulmonary artery pressures and blood flow (the so-called P/Q relationship). This phenomenon promotes RV dilatation (31). In CARDS, the increase in pulmonary blood flow is probably due to pulmonary vessel dilatation and pulmonary neoangiogenesis, leading to perfusion abnormalities toward the areas of diseased lungs, resulting in a worsening ventilation-perfusion mismatch and clinical hypoxemia (12). To cope with COVID-19-related increased pulmonary blood flow, the RV increases its end-diastolic volume by dilatation. Such acute dilatation may lead to ACP. This pathophysiological explanation was emphasized by Caravita et al. in their study using pulmonary artery catheters in patients with CARDS. Caravita et al. showed that PVR was not increased and that a mild increase in pulmonary artery pressure was only explained by an increased cardiac output (11). The decrease in PVR induced by COVID-19 infection (compared to other causes of ARDS) may explain the clinical benefit of administering a selective pulmonary artery vasoconstrictor in patients with CARDS (32, 33). These results emphasize that COVID-19 is a vascular disease that primarily affects pulmonary vessels and induces hypoxemia and RV dysfunction (6, 8). In contrast, COVID-19 infection may also promote pulmonary vasoconstriction. Local pulmonary inflammatory response and vascular endothelial dysfunction induce an immune thrombosis, leading to intravascular clot formation in small and large vessels (34). Thrombotic complications may contribute to causing pulmonary vasoconstriction that worsens RV afterload through a complex interaction between humoral factors, endothelial effects, and hypoxia.

Right ventricular afterload and left ventricular filling pressures

The increases in RV afterload can be attributed to a downstream factor. Caravita et al. showed that post-capillary pulmonary hypertension and pulmonary artery wedge pressure were higher in CARDS than in NC-ARDS (11). It has been

TABLE 5 Univariate and multivariate Cox regression *analyses* of predictive variables correlated with 30-day mortality in patients with COVID-19-related pneumonia.

Variables	Mortality at 30-days			
	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Age > 65 years	2.95 [1.59-5.43]	0.001	2.92 [1.50-5.66]	0.002
BMI (for 1 point increase)	0.71 [0.29-1.69]	0.44	-	-
Hypertension	1.75 [0.87-3.65]	0.12	-	-
RV dilatation	0.45 [0.11-1.99]	0.29	-	
ACP	2.85 [1.53-5.31]	0.001	3.35 [1.56-7.18]	0.002
Mechanical ventilation	2.12 [0.91-4.9]	0.06	1.69 [0.72-3.99]	0.22
SOFA CV > 3	1.23 [0.57-2.62]	0.58	-	

ACP, acute cor pulmonale; BMI, body mass index. CV, cardiovascular. HR, hazard ratio. RV, right ventricle; SOFA, sequential organ failure assessment.

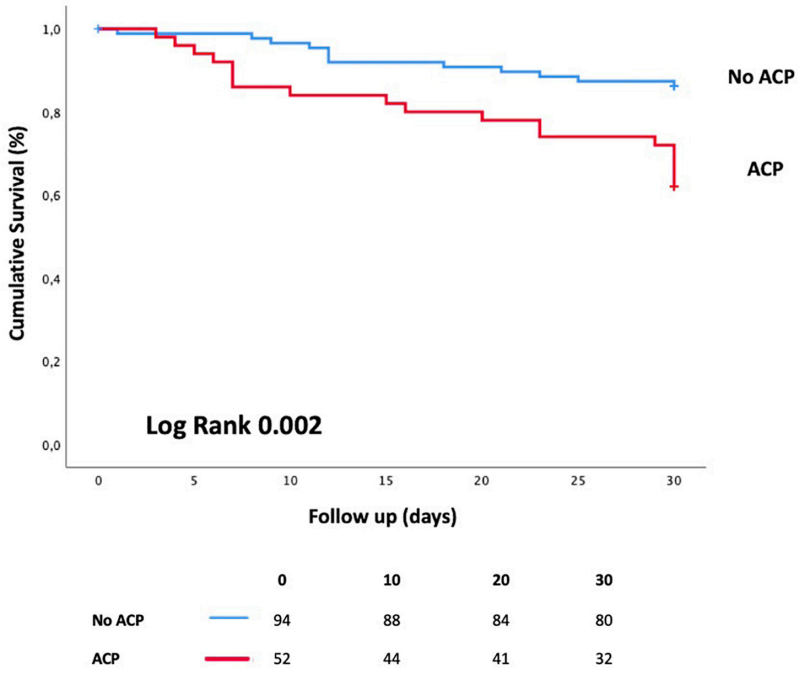

FIGURE 2
Kaplan–Meier curves showing event-free survival according to the presence of acute cor pulmonale. ACP, acute cor pulmonale.

hypothesized that SARS-CoV-2-related myocardial injuries may impair LV diastolic properties (35) and increase left atrial pressures. This increase may be transmitted through the pulmonary circulation to the RV.

Right ventricular injury and COVID-19

Myocardial injury can result from a direct viral lesion of endothelial and myocardial cells, resulting in endothelial dysfunction, local endotheliitis, and myocarditis (36). Besides, myocardial oxygen supply-demand imbalance in hypoxemia, stress-induced cardiomyopathy, and tissular hypoperfusion may lead to RV dilatation due to myocardial injury (34).

In summary, ACP in COVID-19-related pneumonia is probably the result of an increased RV afterload due to a combination of complex physiopathological factors such as low pulmonary resistance (11), intrapulmonary shunting (12), high cardiac output, increased left atrial pressure (8, 13), and direct myocardial injury.

Acute cor pulmonale and mortality

Acute cor pulmonale doubles the mortality risk in NC-ARDS, and an RV protective strategy is necessary to avoid hemodynamic failure. In our study, patients with ACP had more frequently developed cardiogenic shock and renal failure, requiring renal replacement therapy. These complications reflect the low cardiac output and venous congestion due to ACP (37).

In our study, the 30-day mortality of ACP was 38% (n = 20/52), a similar result to that of Cavaleiro's study (34%, n = 15/44) (18). In our research, ACP was associated with 30-day mortality independent of mechanical ventilation. Our study emphasizes previous studies showing a strong association between RV dilatation or RV dysfunction (ACP combines these 2 RV abnormalities) and poor prognosis in COVID-19 (14, 15).

Right ventricular-longitudinal shortening fraction at acute cor pulmonale

In our study, only TAD parameters were impaired in the ACP group. A previous study has shown that RV-LSF, a global RV systolic function parameter, was the most accurate parameter for assessing RV systolic function in ACP (26). ACP is characterized by pressure overload, changes in RV chamber geometry, and myocardial dyssynchrony. These factors may influence the accuracy of conventional parameters such as TAPSE or RV-S' (23). Moreover, the RV-LSF can be a semi-automated and reproducible parameter (26). However, no RV-LSF threshold defines RV dysfunction, even though many studies have found a threshold close to 20% (26, 38, 39).

Contrary to other studies (18), our study provided new echocardiographic data in this particular situation, i.e., ACP.

Limitations

Our study admits several limitations. First, this is a single-center study with a limited sample size. However, it is the first to assess ACP in intubated and non-intubated patients with COVID-19-related pneumonia. Second, we used TTE to assess ACP. The sensitivity of TTE for ACP diagnosis in ARDS under mechanical ventilation is poor compared to transesophageal echocardiography (TEE) (36) and may underestimate the number of ACP. However, in non-intubated patients, TTE is the reference ultrasound method (28) and has good sensitivity and specificity for ACP diagnosis (40). Moreover, TEE may be considered an invasive examination lacking feasibility, especially for hypoxic patients under non-invasive ventilation or high-flow oxygen therapy. Third, we excluded patients under ECMO therapy. Implementing ECMO therapy improves gas exchange and achieves ultra-protective ventilation that may decrease RV afterload and improve ACP. Fourth, in more than 20% of our patients, we could not detect tricuspid regurgitation to evaluate systolic pulmonary artery pressure and arterial-ventricular coupling. Finally, we did not perform pulmonary artery catheters for our patients to accurately measure pulmonary artery pressures and PVR. These data would have been of great interest.

Conclusion

For critically ill patients with COVID-19-related pneumonia, ACP is frequent (36%) even in non-intubated patients and is associated with increased mortality risk. ACP does not seem to be associated with classical risk factors for these patients. These results need confirmation in further studies with a larger sample size.

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 Amiens University Hospital IRB (Comité de Protection des Personnes Nord-Ouest II CHU-Place V. Pauchet, 80054 AMIENS Cedex 1, CNIL Number: PI2020_843_0026). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

CB, OA-A, and YM: concept and design. CB, NM, SB, CD, MC, PH, and CV: data acquisition, analysis, and interpretation. CB: drafting of the manuscript. CB, YM, and HD: critical revision of the manuscript for important intellectual content. CB: statistical analysis. YM: supervision. 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.

Publisher's note

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