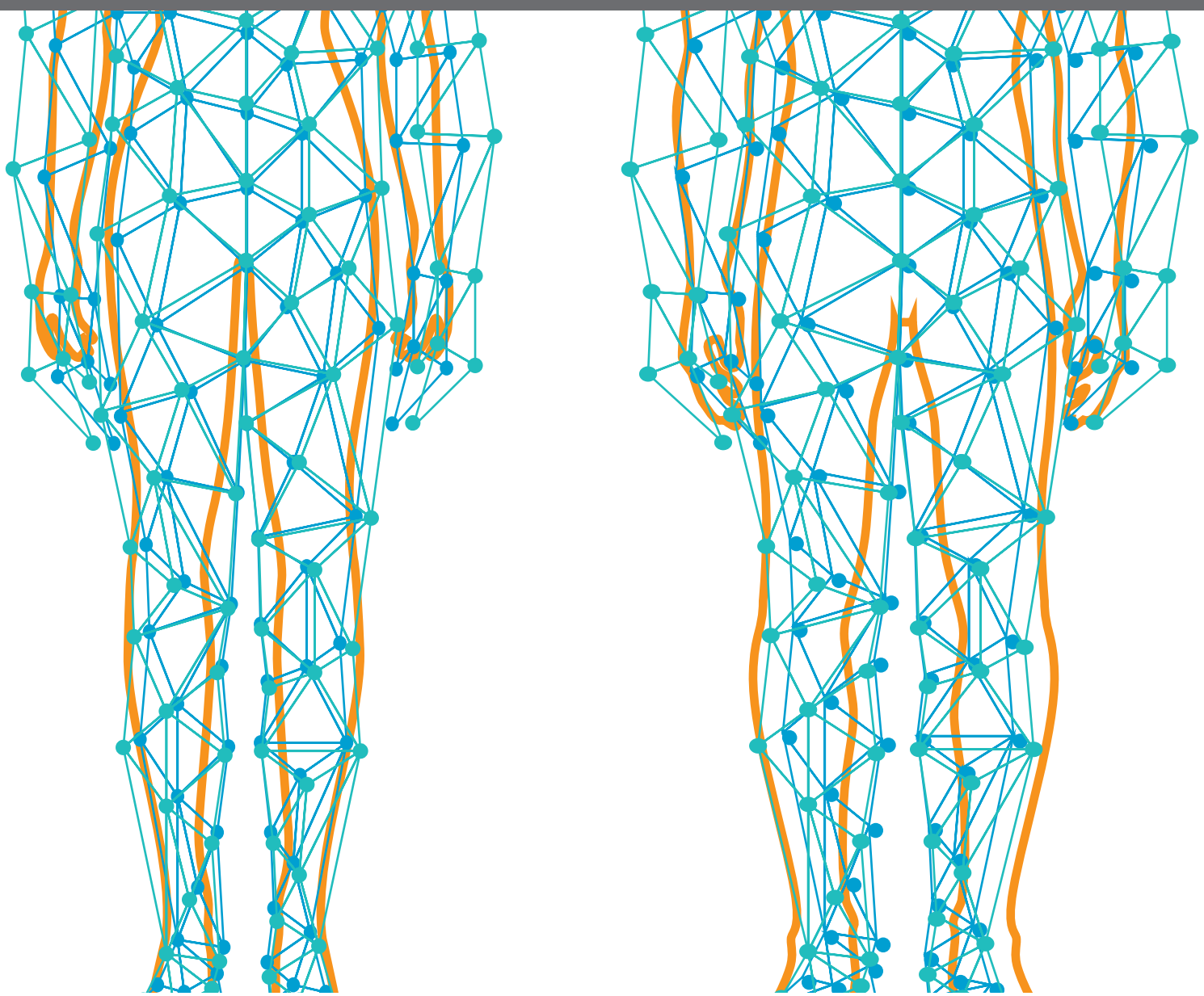
ACUTE RESPIRATORY DISTRESS SYNDROME AND MECHANICAL VENTILATION

EDITED BY: Haibo Qiu, Ling Liu, Claude E. Guérin and Chunbo Chen

PUBLISHED IN: Frontiers in Medicine



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ISSN 1664-8714
ISBN 978-2-88976-798-4
DOI 10.3389/978-2-88976-798-4

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ACUTE RESPIRATORY DISTRESS SYNDROME AND MECHANICAL VENTILATION

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Citation: Qiu, H., Liu, L., Guérin, C. E., Chen, C., eds. (2022). Acute Respiratory Distress Syndrome and Mechanical Ventilation. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-88976-798-4

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frontiers | Frontiers in Medicine

TYPE Editorial
PUBLISHED 20 September 2022
DOI 10.3389/fmed.2022.994611

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

RECEIVED 15 July 2022
ACCEPTED 02 September 2022
PUBLISHED 20 September 2022

CITATION
Hu L, Qiu H, Liu L, Guérin C and Chen C (2022) Editorial: Acute respiratory distress syndrome and mechanical ventilation.
Front. Med. 9:994611.
doi: 10.3389/fmed.2022.994611

Editorial: Acute respiratory distress syndrome and mechanical ventilation

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KEYWORDS

acute respiratory distress syndrome, mechanical ventilation, coronavirus disease 2019, critically ill patients, strategy, intensive care unit

Editorial on the Research Topic
Acute respiratory distress syndrome and mechanical ventilation

Acute respiratory distress syndrome (ARDS) is a life-threatening form of respiratory failure characterized by inflammatory pulmonary edema resulting in hypoxemia (PaO_2/FiO_2 < 300 mmHg) (1). The heterogeneousness of ARDS substantially contributes to the complexity of its management. Mechanical ventilation (MV) is frequently used to sustain life in patients with severe ARDS, especially in the setting of coronavirus disease 2019 (COVID-19). However, a major concern in MV patients is the risk of ventilator-induced lung injury, which leads to but is partially prevented by lung-protective ventilation. However, prospective evidence, definitions, and skills all need to be developed further and shared for better implementation of personalized MV in ARDS patients with or without COVID-19. The aim of the Research Topic of the articles in this issue dedicated to critically ill patients, was to provide an overview of recent advances in ARDS and MV, and seek innovative solutions to resolve the challenges of personalized lung-protective ventilation, starting from titrating positive end-expiratory pressure (PEEP) to adjusting inspiratory trigger to weaning ventilation. Thirteen articles were submitted to this thematic collection, nine of which were original research studies, and four meta-analyses. Eleven articles are associated with COVID-19, ARDS or MV, and two articles focused on the lung physiotherapy of older sepsis patients or drug selection for anesthesia induction.

COVID-19 seriously endangers human health with ARDS and the resultant refractory hypoxemia playing as a common cause of death (2), which generally desired the use of MV with lung protection strategies. First, low tidal volume ventilation (LVTT) is recommended by major guidelines (3, 4). However, gender preference might exist in the implementation of LVTT. To compare and understand differences in the use of

LTVV between females and males with ARDS related to COVID-19, Swart et al. found that in this cohort of patients, females received LTVV less often than males in the first days of invasive ventilation. The difference in the use of LTVV was mainly driven by an anthropometric factor, namely, body height. The authors suggested that use of LTVV may improve by paying attention to correct titration of tidal volume, which should be based on predicted body weight, which is a function of body height and gender.

On the other hand, appropriate PEEP setting is well-acknowledged as one of key roles to lung protection ventilation (5). However, the best way to titrate the PEEP in patients suffering from ARDS is still matter of debate. Gibot et al. conducted a pilot comparison on PEEP values derived from either electrical impedance tomography (EIT) or other techniques when ventilating patients with COVID-19. The authors found that EIT-guided PEEP personalized setting may help to achieve a more homogenous distribution of ventilation. Regarding PEEP setting in ventilated patients without ARDS, Zhou et al. conducted a Bayesian network meta-analysis and systematic review of randomized controlled trials (RCTs) comparing different levels of PEEP based on a novel classification of PEEP level to explore the optimal PEEP. The authors found that higher PEEP was associated with significantly higher PaO_2/FiO_2 ratio and higher incidence of pneumothorax.

When the lung function is improved, getting ventilator weaned off as soon as possible is beneficial to patient outcome (6). Spontaneous breathing trial has been used to predict the optimal time of weaning from ventilator. However, it remains controversial which trial should be preferentially selected. Yi et al. performed a meta-analysis, indicating that automatic tube compensation seems to be the optimal choice of predicting successful weaning from ventilator among critically ill patients. Jhou et al. provided evidence that proportional assist ventilation had a high probability of being the most effective ventilation mode for MV patients, regarding a higher rate of weaning success, a lower proportion of patients requiring reintubation, and a lower mortality rate than other ventilation modes. However, high quality RCTs are needed to further establish these findings.

Despite optimal ventilation and weaning strategies, ARDS is associated with high mortality. A meta-analysis by Wang et al. concluded that the incidence of ARDS in patients with burns was 24% and that mortality was as high as 31%. The incidence rates, which were related to MV, location, and inhalation injury, were significantly higher in patients from western countries than patients from Asian/African countries. To further provide reference data about risk factors for mortality in MV patients with COVID-19, Hernández-Cárdenas et al. described the clinical characteristics of mechanically ventilated COVID-19 patients in Mexico, and, by machine-learning and logistic regression models, identified that the acute kidney injury, uric acid, lactate dehydrogenase, and a longitudinal increase in the ventilatory ratio were risk factors.

Given that ARDS is associated with a high mortality and is a heterogeneous syndrome, early diagnosis that initiates early intervention, is of vital importance to expect a better prognosis. In the absence of specific early warning signals, developing biomarkers may be a way to reach this goal. As we know, ARDS is characterized by dysregulated vascular permeability. Therefore, Tanaka et al. found that plasma 5-hydroxyindoleacetic acid might be a potential biomarker of ARDS severity and highlighted the importance of evaluating vascular leakage magnitude for ARDS treatment. Meanwhile, Cheng et al. found that lower CD8 T cell count was associated with higher severity and early mortality in ARDS patients caused by *Acinetobacter baumannii* pneumonia, which could be valuable for outcome prediction.

In conclusion, the data and reviews published in this Research Topic have shown that ARDS and MV optimization strategies are very active and effective in critically ill patient, especially in the COVID-19 pandemic. However, these clinical studies are non-RCTs, and the sample sizes relatively small, making it not possible to set out any kind of recommendation, as the evidence is not yet conclusive on this Research Topic. In addition, these semantic articles do not include hot topics like extracorporeal membrane oxygenation implementation (7), non-invasive ventilation mode (8) or other hybrid approaches being considered tailored to the patients with ARDS related to COVID-19, which may open the door for the content of the next topic.

Author contributions

LH drafted the original version of the editorial. LL, CG, HQ, and CC revised the editorial. All authors have contributed, read, and approved the final version of the 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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frontiers in Medicine

ORIGINAL RESEARCH
published: 27 August 2021
doi: 10.3389/fmed.2021.699607

Clinical Risk Factors for Mortality Among Critically Ill Mexican Patients With COVID-19

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OPEN ACCESS

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Specialty section:
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

Received: 23 April 2021
Accepted: 06 August 2021
Published: 27 August 2021

Citation:
Hernández-Cárdenas CM, Choreño-Parra JA, Torruco-Sotelo C, Jurado F, Serna-Secundino H, Aguilar C, García-Olazarán JG, Hernández-García D, Choreño-Parra EM, Zúñiga J and Lugo-Goytia G (2021) Clinical Risk Factors for Mortality Among Critically Ill Mexican Patients With COVID-19. Front. Med. 8:699607. doi: 10.3389/fmed.2021.699607

Little literature exists about critically ill patients with coronavirus disease 2019 (COVID-19) from Latin America. Here, we aimed to describe the clinical characteristics and mortality risk factors in mechanically ventilated COVID-19 patients from Mexico. For this purpose, we recruited 67 consecutive mechanically ventilated COVID-19 patients which were grouped according to their clinical outcome (survival vs. death). Clinical risk factors for mortality were identified by machine-learning and logistic regression models. The median age of participants was 42 years and 65% were men. The most common comorbidity observed was obesity (49.2%). Fever was the most frequent symptom of illness (88%), followed by dyspnea (84%). Multilobe ground-glass opacities were observed in 76% of patients by thoracic computed tomography (CT) scan. Fifty-two percent of study participants were ventilated in prone position, and 59% required cardiovascular support with norepinephrine. Furthermore, 49% of participants were coinfected with a second pathogen. Two-thirds of COVID-19 patients developed acute kidney injury (AKIN). The mortality of our cohort was 44.7%. AKIN, uric acid, lactate dehydrogenase (LDH), and a longitudinal increase in the ventilatory ratio were associated with mortality. Baseline PaO2/FiO2 values and a longitudinal recovery of lymphocytes were protective factors against mortality. Our study provides reference data about the clinical phenotype and risk factors for mortality in mechanically ventilated Mexican patients with COVID-19.

Keywords: COVID-19, SARS-CoV-2, ARDS, risk factors, mortality

INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of the coronavirus disease 2019 (COVID-19), has rapidly spread worldwide. Although most infected individuals develop mild disease, the spectrum of COVID-19 encompasses severe manifestations that represent up to 5% of cases (1, 2). These forms are characterized by a severe pulmonary inflammation with exudative diffuse alveolar damage and massive capillary congestion accompanied by microthrombi (3, 4). Physiologically, these alterations result in

ventilation-perfusion inequalities and severe acute hypoxemic respiratory failure leading to mechanical ventilation (MV) requirement. The exuberant immune response elicited by SARS-CoV-2, together with endothelial dysfunction (5), coagulation disorders (6), and extrapulmonary viral dissemination (7), also precipitate multiorgan failure in a significant proportion of severe COVID-19 cases.

The global case fatality rate (CFR) of COVID-19 varies from 0.2 to 10.5%, depending on several factors, such as age, comorbidities, and geographical region (8). Of note, mortality rates can be as high as 80% among cases admitted to the intensive care unit (ICU) (1). Several clinical and immunological parameters impact on COVID-19-associated morbidity and mortality (2, 9–15). However, most prognostic factors that are currently being used by clinicians have been identified in heterogeneous cohorts of COVID-19 patients with mild to severe manifestations. To what extent those factors independently associated with poor clinical outcomes in the overall population of COVID-19 patients remain informative among individuals in critical condition is not well understood.

The experience with critically ill COVID-19 patients from China, Europe, and the United States has been widely reported in the literature (1, 16–18). However, there is limited information available from Latin America, one of the larger epicenters of the COVID-19 pandemic. Here, we describe the clinical features and outcomes of critically ill COVID-19 patients admitted to the respiratory intensive care unit (RICU) of a national reference center for respiratory diseases in Mexico City. Using a machine-learning algorithm and traditional logistic regression analyses, we also identified clinical risk factors for severe COVID-19-associated mortality. Our results provide reference data about the clinical phenotype of severe COVID-19 among non-Caucasian Hispanic patients from Latin America. Furthermore, our study contributes to a better understanding of the frequency and importance of specific clinical characteristics that determine the risk of mortality in COVID-19 among populations from different geographic regions.

METHODS

Study Design and Participants

We conducted a prospective cohort study in patients with acute respiratory distress syndrome (ARDS) admitted to the RICU of the Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas (INER) in Mexico City, during the period from March to June of 2020. Individuals that tested positive for SARS-CoV-2 infection in swab samples, bronchial aspirates (BA), or bronchoalveolar lavage (BAL) specimens were eligible. Detection of SARS-CoV-2 was performed by real-time polymerase chain reaction (RT-PCR), as described before (19). None of the participants was coinfected with the human immunodeficiency virus (HIV).

Data Retrieval and Definitions

Microsoft Excel (MS Excel 365) was used for data collection. Clinical and demographic data were retrieved from patients' medical records, including age, gender, anthropometrics, comorbidities, symptoms, thoracic computed tomography (CT) scan findings, and initial laboratory tests. Initial laboratory tests were defined as the first test results available, typically within 24 h of hospital admission, and included white blood cell counts, liver and kidney function, serum electrolytes, metabolic panel, gasometrical and ventilatory parameters, tissue-injury biomarkers, coagulation parameters, and the severity of disease scores Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health disease Classification System II (APACHE-II). Some laboratory parameters, including lymphocyte counts and ventilatory ratio (VR), were monitored continuously, and the last available test results were retrieved for analysis. The primary endpoint of the study was mortality.

ARDS was diagnosed in accordance with the Berlin definition (20). Acute kidney injury (AKIN) was diagnosed in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines (21). Body mass index (BMI) was calculated as follows: weight (kg)/height $(m)^2$. Obesity was defined as a BMI $\geq$30 kg/m^2. Bacterial coinfection was defined as a positive culture and consistent clinical data. In cases where the cultures were negative, coinfection was defined based on the presence of persistent fever, leukocytosis, neutrophilia, increased procalcitonin levels, and hemodynamic instability for more than 48 h. Static respiratory-system compliance (Cstat) was calculated as the ratio of the tidal volume to the difference between inspiratory plateau pressure (Pplat) and the positive end-expiratory pressure (PEEP). Driving pressure was calculated as the difference between the Pplat and PEEP. VR was calculated as follows: VR = [minute ventilation (mL/min) × PCO2 (mmHg)]/[predicted body weight × 100 (mL/min) × 37.5 (mmHg)]. Fold changes in variables that were continuously monitored (lymphocyte counts and VR, hereinafter referred to as follow-up parameters) were calculated as the ratio of the difference between values at discharge/death and admission divided by the values of the variables of interest at admission.

Study Approval

The Institutional Review Board of the INER in Mexico City approved the study. All participants or their legal guardians provided written informed consent in accordance with the Declaration of Helsinki for Human Research. Clinical data were managed according to the Mexican Constitution law NOM-012-SSA3-2012, which establishes the criteria for the execution of clinical investigations in humans.

Statistical Analysis

Descriptive statistics were used to characterize the study population clinically. Frequencies and proportions were calculated for categorical data. Means, medians, standard deviations (SD), interquartile ranges (IQR), and 95% confidence intervals were used for continuous variables. Differences in categorical variables between groups were assessed by the Fisher exact or Chi-square test. For comparisons of continuous variables, we used the Student T-test or the Mann-Whitney *U*-test, as appropriate. The *K*-means algorithm was used for clustering study participant characteristics according to their clinical outcome (survival or fatality). Before data

TABLE 1 | Cumulative survival rates in patients with severe COVID-19.

Time after hospital admission	Survival (%)	95% CI
7 days	82.0	70.6–89.4
14 days	56.2	41.6–68.5
21 days	47.6	31.1–62.3
28 days	42.3	25.1–58.5

Survival rates and their 95% confidence interval (95% CI) were estimated using the Kaplan-Meyer method and the log-rank test.

visualization, clinical features and laboratory parameters were scaled and centered.

All clinical variables were included in a random forest analysis. For this purpose, and considering that the small sample size of the study could impact the performance of the model, 1,000 classification and regression trees (CARTs) were conducted to minimize the prediction error of the analysis measured in terms of Out-of-bag (OOB) error (22). The variables with the highest mean Gini decrease values were considered as having the highest impact on mortality and used as covariates for binomial logistic regression analyses. The accuracy of the selected mortality risk factors identified by random forest and logistic regression models was further evaluated with the area under the Receiver Operating Characteristic (ROC) curve (AUC). In addition, Kaplan–Meier curves were constructed to look for differences in survival according to these variables dichotomized by the ROC curve threshold with the highest diagnostic accuracy estimated using the Youden index. For random forest and logistic regression analyses, patients with any missing value in the variables of interest were excluded. All analyses were conducted using GraphPad Prism 8 (La Jolla, CA) and R Statistical Software (Foundation for Statistical Computing, Vienna, Austria). Specific tests are also mentioned in figure legends. Two-sided p-values $\leq$0.05 were considered as significant: $^{*}p \leq 0.05$, $^{**}p \leq 0.01$, $^{***}p \leq 0.001$, $^{****}p \leq 0.0001$.

RESULTS

Clinical Characteristics of Participants

Data from 67 consecutive COVID-19 patients admitted to the RICU were analyzed. Thirty-seven patients survived, and 30 died (44.7%). Survival rates at different time points after admission are shown in **Table 1**. Most fatality cases occurred during the second week after RICU admission. The median age of study participants was 42 years (range 23–73), with no differences between survivors and deceased patients (**Table 2**). Sixty-five percent of participants were men, and the proportion of males was significantly higher in the group of dead patients compared to survivors (80 vs. 54%, $p < 0.05$). Also, the BMI of deceased patients tended to be higher than in survivors. The main comorbidity observed in our study was obesity (49.2%), followed by diabetes (20.8%), and systemic arterial hypertension (SAH; 11.9%). These conditions were similarly distributed across participant groups. Fever was the most frequent manifestation of illness (88%), followed by dyspnea (84%), cough (62%), myalgia (50%), and headache (46%). Only 20% of patients reported diarrhea. The frequency of dyspnea was significantly higher among patients that died.

Thorax CT scan revealed multilobe ground-glass opacities in 76% of COVID-19 patients, whereas focal consolidations and a crazing-paving pattern were observed in 44% and 4% of participants, respectively. The overall median of days of stay in the RICU was 10 days. All patients required invasive MV, and most of them were intubated within the first 24 h after hospitalization. Fifty-two percent of patients were ventilated in the prone position, and 59% required norepinephrine for cardiovascular support. Of note, a higher proportion of patients that succumbed to COVID-19 required norepinephrine than survivors (76 vs. 45%, $p < 0.05$). Strikingly, up to two-thirds of COVID-19 patients admitted to the RICU developed AKIN, mostly of KDIGO stage 1. However, the percentage of individuals with AKIN was significantly much higher in the group of deceased patients than in survivors (96 vs. 40%, $p < 0.0001$). Furthermore, 49% of participants got coinfected with a second pathogen, and the frequency of coinfection tended to be higher in patients that died of COVID-19 (**Table 2**).

Laboratory Parameters of Severely Ill COVID-19 Patients

Most laboratory test results and respiratory parameters at hospital admission were similar in the two groups of COVID-19 patients admitted to the RICU (**Table 3**). Indeed, in unsupervised clustering analysis, patients with a similar clinical outcome did not cluster together according to their baseline laboratory parameters (**Supplementary Figure 1**). This finding reflects the high clinical heterogeneity of our entire cohort of severely ill COVID-19 patients admitted to the RICU. Only uric acid, creatinine (Cr), and bilirubin levels, as well as SOFA score, were significantly higher among deceased patients as compared to survivors (**Table 3**). Procalcitonin levels were also higher in patients that succumbed to the infection than in survivors, but the difference did not reach statistical significance ($p = 0.0576$). In contrast, patients who survived differ significantly from deceased individuals with respect to higher PaO_2/FiO_2 values at admission.

We also monitored lymphocyte counts and VR in all COVID-19 patients. Remarkably, the group of survivors showed a significant recuperation of lymphocyte counts at discharge from the RICU with respect to the baseline (**Table 3**). Conversely, deceased patients showed minimal recovery and even displayed depletion of lymphocytes before death. Finally, patients who died showed a significant increase in VR values, whereas survivors were characterized by a decrease in VR at discharge from the RICU. Fold changes in lymphocytes and VR were significantly different between groups (**Table 3**).

Mortality Risk Factors in Patients With Severe COVID-19

We next investigated clinical risk factors for mortality in our cohort of critically ill COVID-19 patients. For this purpose, we performed a random forest analysis using baseline clinical and laboratory characteristics, as well as follow-up parameters

TABLE 2 | Clinical characteristics of critically ill COVID-19 patients.

Characteristic	Total *N* = 67	Survivors *N* = 37	Deceased *N* = 30	*p*-value
Age (years), median (range)	42 (23–73)	37 (23–65)	45 (27–73)	0.2336
Males	44 (65.67)	20 (54.0)	24 (80)	0.0383
BMI	30.5 (26.7–37.5)	29.7 (26.4–34.4)	33.8 (27.4–39.5)	0.0748
Comorbidities				
Obesity	33 (49.2)	16 (43.2)	17 (56.6)	0.3302
Diabetes	14 (20.8)	10 (27.0)	4 (13.3)	0.2314
SAH	8 (11.9)	2 (5.4)	6 (20)	0.1264
Symptoms at onset				
Fever	44/50 (88)	23/27 (85.1)	21/23 (91.3)	0.674
Cough	31/50 (62)	17/27 (62.9)	14/23 (60.8)	>0.9999
Dyspnea	42/50 (84)	19/27 (70.3)	23/23 (100)	0.005
Myalgia	25/50 (50)	15/27 (55.5)	10/23 (43.4)	0.5709
Headache	23/50 (46)	12/27 (44.4)	11/23 (47.8)	>0.9999
Diarrhea	10/50 (20)	6/27 (22.2)	4/23 (17.3)	0.7356
CT scan findings				
Ground glass opacities	38/50 (76)	22/27 (81.4)	16/23 (69.5)	0.5077
Crazing paving pattern	2/50 (4)	2/27 (7.4)	0/23 (0)	0.4931
Consolidation	22/50 (44)	9/27 (33.3)	13/23 (56.5)	0.1532
RICU stay (days)	10 (8–17)	13 (9–18)	8 (6–13)	0.003
Supportive interventions				
MV	67 (100)	37 (100)	30 (100)	>0.9999
Prone position	35 (52.2)	17 (45.9)	18 (60)	0.3271
Norepinephrine	40 (59.7)	17 (45.9)	23 (76.6)	0.0133
Complications				
AKIN	44 (65.6)	15 (40.5)	29 (96.6)	<0.0001
Stage 1	20 (29.8)	10 (27.0)	10 (33.3)	0.6019
Stage 2	12 (17.9)	1 (2.7)	11 (36.6)	0.0007
Stage 3	12 (17.9)	4 (10.8)	8 (26.6)	0.1165
Coinfection	33 (49.2)	14 (37.8)	19 (63.3)	0.0506

Data are displayed as n (%), n/N (%), or median (IQR). N is the total number of patients with available data. AKIN, acute kidney injury; BMI, body mass index; CT, computed tomography; IQR, interquartile range; MV, mechanical ventilation; RICU, respiratory intensive care unit; SAH, systemic arterial hypertension. Differences in continuous variables were estimated using the Student T-test or the Mann Whitney U-test. Differences in categorical variables were calculated using the Fisher's exact or the Chi-square test as appropriate.

of study participants. This is a machine-learning algorithm that accurately estimates the importance of each variable from a dataset for the occurrence of a dichotomous variable (i.e., mortality) (22). The results showed that fold change in VR, fold change in lymphocytes, AKIN, uric acid, bilirubin, Cr, activated partial thromboplastin time (aPTT), BMI, lactate dehydrogenase (LDH), age, and PaO_2/FiO_2 were the most explicative variables for mortality, all of them with importance above the overall mean importance of the model (**Figure 1**).

From these variables identified in the random forest analysis, only fold change in VR, AKIN, uric acid, and LDH were independent mortality risk factors in binomial logistic regression analyses. Meanwhile, baseline PaO_2/FiO_2 values and fold change in lymphocytes were protective factors (**Table 4**). In fact, patients with an increase in VR (fold change ≥-0.0351 from baseline), AKIN, high uric acid (≥3.085 mg/dL), and elevated LDH levels (≥528.5 U/L), showed significantly lower survival rates at 28 days after admission to the RICU (**Table 5**; **Figure 2**). In contrast, patients with a longitudinal increase in lymphocyte counts (fold change ≥0.127 from baseline) and higher PaO2/FiO2 (≥157.5) values at admission had lower mortality rates.

Finally, a binomial regression analysis of the variables not identified as important for mortality by random forest analysis showed that male gender, use of norepinephrine, and SOFA score were independently associated with mortality. In contrast, the neutrophil to lymphocyte ratio (NLR) was a protective factor (**Supplementary Table 1**). From these, only norepinephrine usage was associated with significantly lower survival rates in the Kaplan-Meier and log-rank test analysis (**Supplementary Figure 2**). However, in a second random forest model using all the independent mortality risk and protective factors identified only by binomial logistic regression, none of these additional factors showed to be explicative for mortality (**Supplementary Figure 3**).

TABLE 3 | Laboratory parameters of critically ill COVID-19 patients.

Characteristic	Total *N* = 67	Survivors *N* = 37	Deceased *N* = 30	*p*-value
Blood count				
White blood cells (10^9/L)	9.4 (7.3–13.03)	9.3 (7.2–12.4)	10.2 (7.3–14)	0.7857
Neutrophils (10^9/L)	7.9 (5.7–11.4)	7.9 (5.9–10.5)	8.2 (5.3–12.7)	0.9515
Lymphocytes (10^9/L)	0.8 (0.5–1.02)	0.7 (0.5–1.0)	0.9 (0.6–1.2)	0.1188
NLR	11.2 (6.4–16.2)	11.5 (6.7–17.9)	10.2 (5.6–16)	0.3784
Hgb (g/dL)	13.9 (13.1–15.2)	13.8 (12.7–15.1)	14.0 (13.2–15.4)	0.4139
Platelets (10^9/L)	243 (188.8–308.8)	252 (202–326.5)	213 (150.8–307)	0.1473
Metabolic parameters				
Glucose (mg/dL)	141.2 (108–185)	142.6 (114.5–211)	138.9 (106.5–170.5)	0.4729
Uric acid (mg/dL)	4.0 (2.5–5.0)	3.5 (1.6–4.6)	4.6 (3.6–5.6)	0.0069
Na (mmol/L)	141.2(138.2–143.6)	141 (138.5–143)	141.5(137.8–144.5)	0.4553
K (mmol/L)	4.3 (3.9–4.7)	4.2 (3.9–4.6)	4.3 (3.9–4.7)	0.7808
Total proteins (g/dL)	5.9 (5.5–6.4)	5.8 (5.4–6.3)	6.0 (5.6–6.5)	0.1663
Albumin (g/dL)	2.9 (2.6–3.3)	2.9 (2.6–3.5)	2.9 (2.6–3.2)	0.5667
Renal function				
Cr (mg/dL)	0.9 (0.7–1.4)	0.8 (0.6–1.2)	1.2 (0.8–1.8)	0.0105
BUN (mg/dL)	19.6 (13.9–31.5)	19.8 (14.1–28.9)	19.6 (13.7–36.7)	0.3579
Liver function				
Total bilirubin (mg/dL)	0.5 (0.4–0–6)	0.4 (0.3–0.5)	0.5 (0.4–0.6)	0.036
AST (U/L)	47.3 (30–76)	42.5 (26.8–69.7)	49.5 (31.9–108.8)	0.1981
ALT (U/L)	39.6 (27.9–67.4)	45.4 (28.1–68.5)	37.4 (25.6–62.6)	0.5368
Coagulation parameters				
D dimer (mg/L)	1.0 (0.7–2.1)	1.0 (0.7–2.4)	1.1 (0.7–2.2)	0.6052
INR	1.0 (1.0–1.1)	1.0 (1.0–1.0)	1.0 (0.9–1.1)	0.5146
PT (sec)	15.1 (14.5–16.5)	14.9 (14.6–16.5)	15.4 (14.2–16.5)	0.8317
aPTT (sec)	38.4 (34.6–44.8)	38.5 (35.9–42.1)	37.6 (33.5–49.5)	0.7963
Other biomarkers				
LDH (U/L)	494 (357–711)	450 (356.5–589)	566.5 (358.8–738.3)	0.2009
ALP (U/L)	81.6 (64–96.8)	81.8 (59.1–94)	81.6 (66.3–128.6)	0.3252
CPK (U/L)	152.5 (62.3–900)	180.4 (52.2–964)	146.2 (72.5–1016)	0.694
Procalcitonin (ng/mL)	0.16 (0.1–0.37)	0.12 (0.07–0.2)	0.2 (0.1–0.69)	0.0576
Respiratory parameters				
SO_2%	73 (50–85)	73 (41.5–84.5)	71.5 (57.5–85)	0.8582
PCO_2 (mmHg)	47 (38–56)	49 (41–58)	46 (37.5–52.2)	0.1853
PaO_2/FiO_2 (mmHg)	141 (96–177)	158 (110.5–188.5)	121 (88–157.3)	0.0109
DP (cm H2O)	12 (10–14)	12 (10–14.5)	12 (10.6–14.2)	0.4978
Cstat (ml/cm H2O)	33.6 (27–40.9)	33.3 (26.2–40.9)	35.0 (29.6–40.9)	0.4424
VR	2.0 (1.6–2.4)	2.0 (1.7–2.6)	2.0 (1.6–2.3)	0.3483
Severity of disease				
SOFA score	5 (4–7)	4 (3–7)	6 (4–8)	0.0155
APACHE-II score	10 (6–17)	9 (5–14)	12 (6–17)	0.2706
Follow-up parameters				
Fold change in lymphocytes	0.32 (−0.23–1.12)	0.87 (0.21–1.83)	−0.11 (−0.41–0.68)	<0.0001
Fold change in VR	−0.22 (−0.40–0.22)	−0.35 (−0.45–0.19)	0.15 (−0.23–0.59)	<0.0001

Data are displayed as n (%) or median (IQR). N is the total number of patients with available data. ALP, alkaline phosphatase; ALT, alanine aminotransferase; APACHE-II, Acute Physiology and Chronic Health disease Classification System II; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; Cstat, static compliance; BUN, blood ureic nitrogen; CPK, creatine phosphokinase; Cr, creatinine; DP, driving pressure; FiO2, fraction of inspired oxygen; Hgb, hemoglobin; INR, international normalized ratio; IQR, interquartile range; K, potassium; LDH, lactate dehydrogenase; Na, sodium; NLR, neutrophil/lymphocyte ratio; PaO2, partial pressure of oxygen in arterial blood; PCO_2, partial pressure of carbon dioxide in the blood; PT, prothrombin time; SO_2%, oxygen saturation; SOFA, Sequential Organ Failure Assessment; VR, ventilatory ratio. Differences in continuous variables were estimated using the Student T-test or the Mann Whitney U-test. Differences in categorical variables were calculated using the Fisher's exact or the Chi-square test as appropriate. Fold changes were calculated as the ratio of the difference between values at discharge/death and values at admission divided by the initial values of the variables of interest (lymphocyte counts and VR).

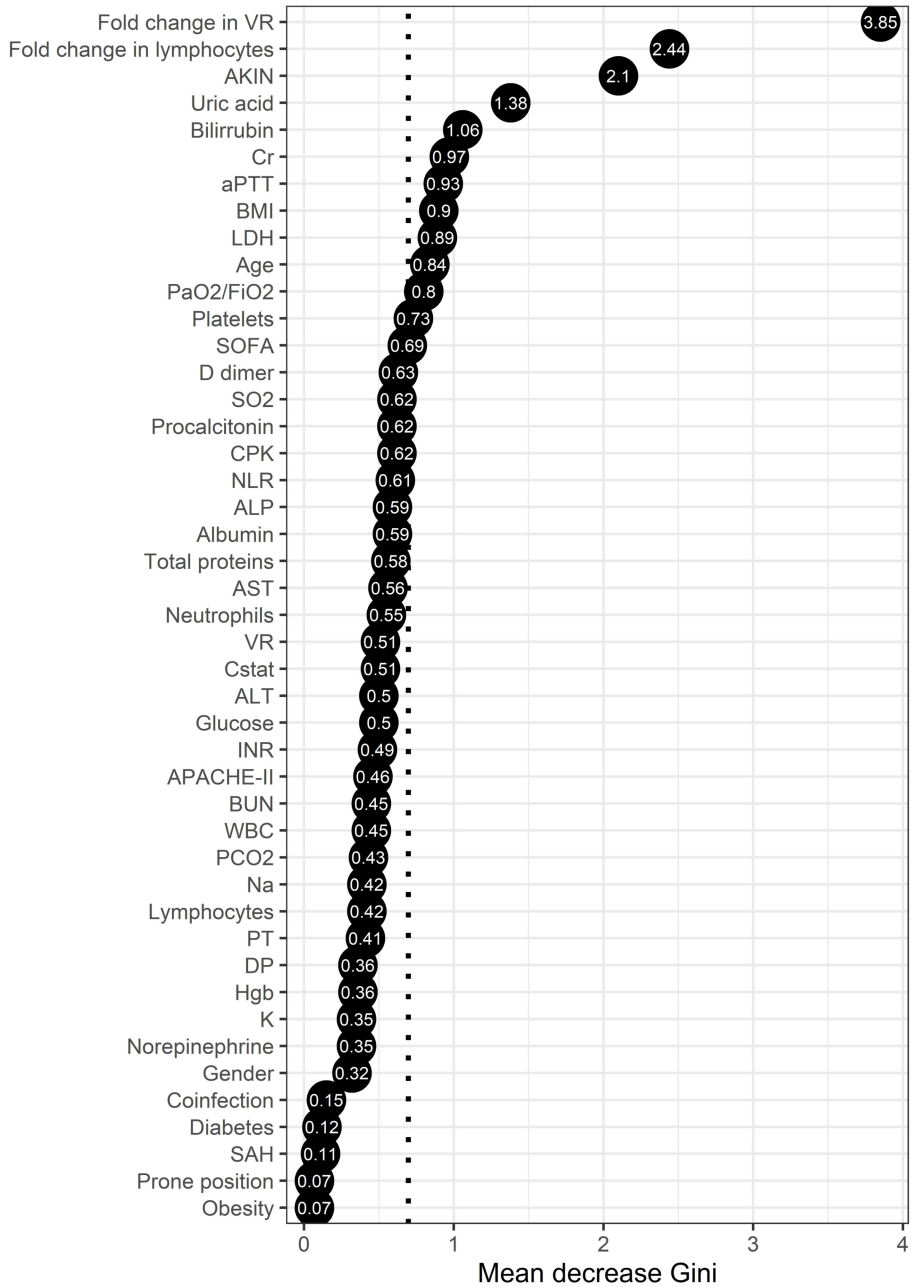

FIGURE 1 | Random forest analysis of the clinical characteristics associated with mortality in critically ill COVID-19 patients. The points represent the mean decrease Gini values, indicative of the importance of each variable to mortality. Variables with mean decease Gini values above the mean importance of the model (discontinuous vertical line) were considered as the most explicative variables of severe COVID-19-associated mortality in our cohort.

DISCUSSION

In the current study, we report the clinical characteristics of a cohort of critically ill patients with COVID-19 that were admitted to the RICU of a national reference center for respiratory diseases in Mexico City. Our analyses showed that most demographic, clinical, radiological, and biochemical characteristics of Mexican patients with severe SARS-CoV-2 infection resemble those reported previously by other groups from China, Europe, and the United States. Furthermore, we determined which factors were independently associated with mortality using a non-conventional statistical approach that included machine-learning algorithms and traditional regression analyses. This strategy of analysis allowed us to identify six variables that had the

TABLE 4 | Logistic regression analysis of risk factors for COVID-19-associated mortality.

Variable	OR	95% CI	*p*-value
Fold change in VR	50.20	8.187–548.3	<0.0001
Fold change in lymphocytes	0.226	0.08815–0.4747	<0.0001
AKIN	36.73	6.631–692.1	<0.0001
Uric acid (mg/dL)	1.237	1.003–1.587	0.0463
Total bilirubin (mg/dL)	3.533	0.3235–45.64	0.3023
Cr (mg/dL)	1.086	0.7491–1.613	0.6568
aPTT (sec)	1.040	0.9702–1.120	0.2696
BMI	1.068	0.9930–1.162	0.0778
LDH (U/L)	1.002	1.000–1.005	0.0360
Age (years)	1.019	0.9778–1.063	0.3768
PaO_2/FiO_2 (mmHg)	0.9872	0.9751–0.9984	0.0241

95% CI, 95% confidence interval; AKIN, acute kidney injury; aPTT, activated partial thromboplastin time; BMI, body mass index; Cr, creatinine; FiO_2, fraction of inspired oxygen; LDH, lactate dehydrogenase; OR, odds ratio; PaO_2, partial pressure of oxygen in arterial blood; VR, ventilatory ratio. Fold changes in lymphocyte counts and VR are defined as the ratio of the difference between values at discharge/death and values at admission divided by the initial values of these variables.

highest impact on the mortality of our cohort: fold change in VR, fold change in lymphocyte counts, AKIN, uric acid, LDH, and PaO^2/FiO^2. From these, fold change in lymphocytes and PaO^2/FiO^2 at admission acted as independent protective factors.

A dramatic depletion of total lymphocytes, as well as of CD8+ and CD4+ T-cells, has been reported in patients with SARS-CoV-2 infection (23–25). This phenomenon is the expression of a dysregulated immune response elicited by the virus that favors immunosuppression and is associated with a high risk of secondary bacterial infection, septic shock, and organ dysfunction (26). Indeed, lymphopenia has been described as a marker of severity and a predictor of mortality in COVID-19 (27). In our cohort, baseline lymphocyte counts were extremely low in all patients, with no differences between survivors and non-survivors. These data may indicate that despite lymphopenia is a readout of severity in the overall population of COVID-19 patients, this marker is not further informative when used only among critically ill individuals. Thus, lymphocyte counts on admission should be used only in the decision-making for patients with mild-to-moderate forms of the disease to predict the progression to severe COVID-19.

Recovery of the adaptive immune system with an increase in the number of circulating T lymphocytes is necessary to eliminate the virus (28). Notably, we also found that longitudinal increases in the number of circulating lymphocytes (here expressed as a fold change in lymphocytes) have a strong protective effect against mortality. In other words, a longitudinal increase in lymphocytes associates with a decreased mortality risk, while a decrease in lymphocytes correlates with a significant increase in the risk of death. This result is consistent with the rapid and dramatic restoration of peripheral T lymphocytes observed in patients who recovered from SARS-CoV-2 infection (28). Hence, our results indicate that changes in the lymphocyte counts could be used as a parameter to guide therapeutic decisions for critically ill COVID-19 patients. For instance, this parameter could determine which patients would benefit from steroids use. These drugs could have both favorable and unfavorable consequences. For example, in patients with an exaggerated inflammatory response, steroids may reduce organ damage. In contrast, in patients with severe immunosuppression, steroids could accentuate this defect, increasing the risk of sepsis and mortality; applying treatments that stimulate the immune system could be useful in these patients (29).

VR is governed by the production of carbon dioxide (CO_2) and the ventilatory efficiency (1-(Vd/Ve)) and can be easily calculated at the patient's bedside using ventilation and blood gas parameters. It correlates with the percentage of dead space and is also associated with an increased risk of mortality (30–32). Previous studies on patients with ARDS and COVID-19 have reported a significant association between the VR at admission and mortality (33). In our patients, we did not observe this association upon admission to the RICU. However, we observed that a longitudinal increase in VR was a marker of poor clinical outcome in our cohort of patients with ARDS due to COVID-19. This result is consistent with other reports that demonstrated that an increase in the fraction of dead space during the first weeks of ARDS is an independent predictor of mortality (30–32). In summary, the worsening of the VR in our cohort was independently associated with an increased risk of mortality. Similar to the tidal volume adjusted for the predicted weight, plateau pressure, DP, and PaO2/FiO2 ratio, the VR should be monitored daily and used to make adjustments to the ventilatory parameters, always taking into account the variables mentioned above.

The most striking mortality risk factor identified in our study population was the incidence of AKIN. The injury of the kidney has been widely reported in patients with sepsis and severe ARDS associated with other respiratory pathogens, such as influenza viruses (34–36). Indeed, AKIN is a well-recognized mortality risk factor in patients with severe pneumonia caused by the pandemic influenza A(H1N1)pdm09 virus (37). Similarly, a high incidence of AKIN has been reported in patients with COVID-19. For instance, Hirsch et al. reported an incidence of 36.6% in a cohort of 5,449 patients with COVID-19 (38). However, in patients with respiratory failure who required invasive MV, the incidence of AKIN was 89.7%, and in those who required hemodialysis the mortality was 55% (38). In our cohort, up to 65% of the patients developed AKIN, and its incidence had a strong effect on mortality. Several mechanisms could contribute to the development of AKIN among patients with severe COVID-19, including direct injury driven by the virus and detrimental effects of the high levels of circulating proinflammatory mediators, endothelial dysfunction, and micro-thrombosis of renal blood vessels. Independently of the causative mechanism, the implementation of the KDIGO supportive care guidelines to avoid AKIN or to prevent progression to more advanced stages must be a priority in critically ill patients with COVID-19 (21).

Uric acid, LDH, and PaO_2/FiO_2 also impacted on mortality of our study population. Interestingly, little evidence exists about

TABLE 5 | Survival rates of severely ill COVID-19 patients according to their clinical characteristics.

Variable	ROC AUC (95% CI)	Sensitivity (%)	Specificity (%)	Survival (%, 95% CI)	*p*-value
Fold change in VR	0.8441 (0.7521–0.9361)	63.33	88.24		<0.0001
≥-0.0351				11.68 (1.09–36.03)	
<-0.0351				61.82 (36.03–79.72)	
Fold change in lymphocytes	0.8039 (0.6981–0-9098)	63.33	85.29		<0.0001
≥0.127				68.51 (48.44–82.09)	
<0.127				8.31 (0.58–29.97)	
AKIN	N/A	96.67	59.46		<0.0001
Yes				22.53 (7.84–41.79)	
No				95.00 (69.47–99.28)	
Uric acid (mg/dL)	0.6971 (0.5682–0.8260)	90	44.12		0.025
≥3.085				32.29 (16.25–49.49)	
<3.085				83.33 (56.76–94.29)	
LDH (U/L)	0.6245 (0.4822–0.7668)	60	73.53		0.0035
≥528.5				19.10 (4.30–41.85)	
<528.5				61.09 (35.88–78.90)	
PaO_2/FiO_2 (mmHg)	0.6569 (0.5232–0.7905)	76.67	50		0.0706
≥157.5				58.18 (27.79–79.53)	
<157.5				32.28 (13.51–52.78)	

95% CI, 95% confidence interval; AKIN, acute kidney injury; AUC, area under the curve; FiO_2, fraction of inspired oxygen; LDH, lactate dehydrogenase; N/A, not applicable; PaO_2, partial pressure of oxygen in arterial blood; ROC, receiver operating characteristic curve; VR, ventilatory ratio. Survival rates at 28 days of admission, and their 95% CI were estimated using the Kaplan-Meyer method and the log-rank test. Best ROC curve thresholds were calculated with the Youden index. Sensitivity and specificity for AKIN were calculated by the Wilson/Brown method. Fold changes in lymphocyte counts, and VR are defined as the ratio of the difference between values at discharge/death and values at admission divided by the initial values of these variables.

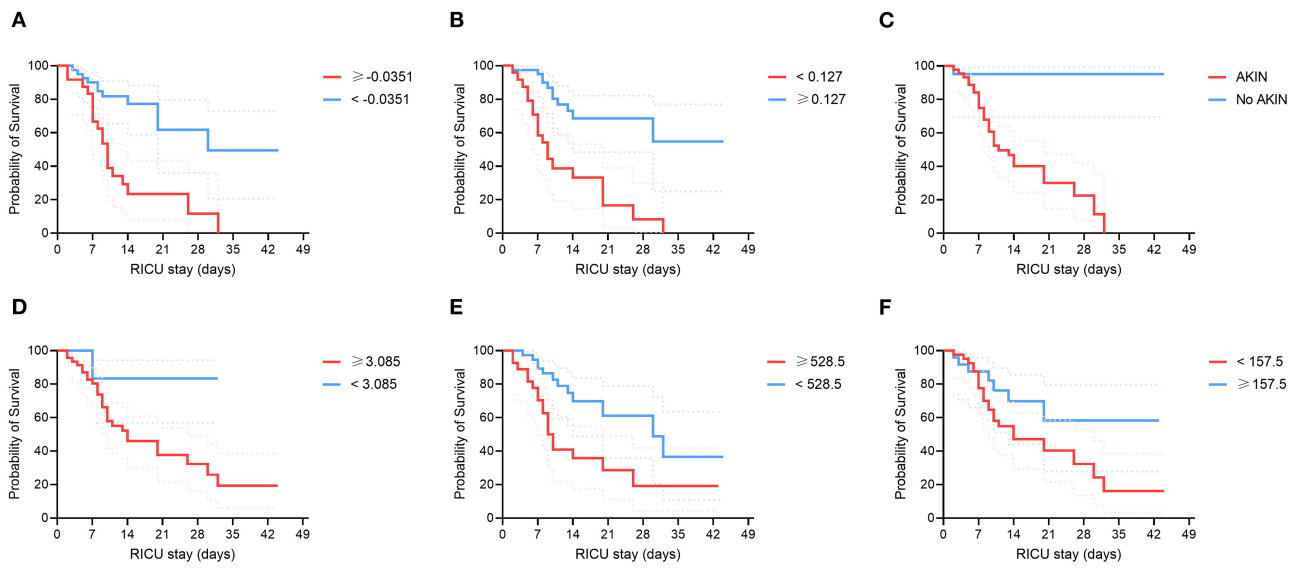

FIGURE 2 | Survival of COVID-19 patients admitted to the RICU according to their clinical characteristics. Critically ill COVID-19 patients were categorized according to different clinical risk factors for mortality identified by random forests and binomial logistic regression analyses. **(A)** Fold change in the ventilatory ratio (VR). **(B)** Fold change in lymphocytes. **(C)** Acute kidney injury (AKIN). **(D)** Uric acid levels. **(E)** Lactate dehydrogenase (LDH) levels. **(F)** PaO_2/FiO_2 index. Survival curves were compared using the Kaplan-Meyer method and the log-rank test. Continuous variables were dichotomized using the best ROC curve threshold determined using the Youden index. Fold changes in lymphocyte counts and VR are defined as the ratio of the difference between values at discharge/death and values at admission divided by the initial values of these variables.

the prognostic value of uric acid in COVID-19. Hence, ours is among the first studies that bring forward this marker for mortality prediction after SARS-CoV-2 infection. As uric acid levels primarily depend on the balance between its production and excretion through the urine, we speculate that the elevated uric acid levels observed among critically ill COVID-19 that died are related to the high incidence of renal dysfunction in these individuals. Notably, other biomarkers of renal function, such as Cr, were not associated with mortality. Collectively, these data indicate that uric acid may be a more useful readout of the renal function status than Cr and blood ureic nitrogen (BUN) among patients with COVID-19 in critical conditions. Regarding LDH, several studies have reported that this is a good marker to predict mortality in patients infected with SARS-CoV-2 (39, 40). Hence, our study reinforces the usage of LDH as a prognostic indicator of mortality that could be useful to guide therapeutic interventions.

Finally, the PaO2/FiO2 ratio showed a significant protective effect against mortality in our analyses. The PaO2/FiO2 ratio is a crucial determinant of the severity of ARDS, according to the Berlin definition (20). The majority of our patients showed ground-glass opacities on chest tomography, without extensive consolidation images. This explains the rapid response of many patients to oxygen administration and the poor response at this stage to recruitment maneuvers because there are no extensive recruitable consolidation areas. Therefore, the primary mechanism of hypoxemia in these patients in the initial phase is an abnormality in the distribution between ventilation and blood flow; the latter is assumed to be abnormal due to endothelial and vascular alterations documented among COVID-19 patients (41). Therefore, the PaO2/FiO2 ratio may be a good physiological biomarker of the amount of pulmonary shunt and lung parenchymal damage in the early phase of ARDS due to COVID-19, which explains why this parameter was a protective factor against mortality in our study. In contrast with our results, other investigations have shown that the PaO2/FiO2 ratio is not a strong predictor of mortality, which may be related to the clinical heterogeneity observed in studies involving patients with moderate-to-severe COVID-19.

One limitation of the study is the small size of the cohort, which originated from a single third-level center in Mexico City. Therefore, although our results are consistent with those reported in China, Europe, and North America, and despite the machine-learning approach used in our study may compensate for this caveat, the predictive value of the mortality risk factors identified here require further external validations in larger cohorts. In summary, we described the clinical characteristics of a cohort of critically ill Mexican patients with COVID-19 and identified independent factors associated with mortality. Based on our results, it is possible to suggest some management recommendations in patients with COVID-19 who require intensive care. These include respiratory management based on low tidal volumes and adjustment of parameters according to the VR. Measures to protect kidney function and adjustment of fluid balance according to volume responsiveness is also recommendable. Furthermore, the avoidance of immunosuppressants in patients who do not show lymphocyte recovery, strict measures to prevent nosocomial infections, early detection, and aggressive treatment of suspected coinfections are crucial interventions. These simple measures could reduce the risk of mortality until an effective therapy against SARS-CoV-2 infection is available.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of the Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas in Mexico City under the approval number B09-20. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CH-C, JC-P, JZ, and GL-G: designed the research study. CH-C, CT-S, FJ, HS-S, CA, JG-O, DH-G, and GL-G: recruited patients. CH-C, JC-P, CT-S, FJ, HS-S, CA, JG-O, DH-G, and GL-G: retrieved clinical data. JC-P and EC-P: performed statistical analyses of the data. JZ: discussed the manuscript. JC-P, JZ, CH-C, and GL-G: drafted the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the Institutional research funds of INER, and also received funding from the National Council of Science and Technology of Mexico (CONACyT) under the research contracts: SECTEI/050/2020, Secretaría de Ciencia, Tecnología e Innovación de la Ciudad de México (SECTEI CDMX); FORDECYT/10SE/2020/05/14-06 and FORDECYT/10SE/2020/05/14-07 from the Fondo Institucional de Fomento Regional para el Desarrollo Científico y Tecnológico y de Innovación (FORDECYT). JC-P was supported by a scholarship (CVU 737347) from CONACyT to his Ph.D. degree. Funders did not play any role in the study design and conduction.

ACKNOWLEDGMENTS

To all study participants and their family members.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.699607/full#supplementary-material

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frontiers in Medicine

SYSTEMATIC REVIEW
published: 01 September 2021
doi: 10.3389/fmed.2021.730018

Optimal Positive End Expiratory Pressure Levels in Ventilated Patients Without Acute Respiratory Distress Syndrome: A Bayesian Network Meta-Analysis and Systematic Review of Randomized Controlled Trials

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Background: To find the optimal positive end expiratory pressure (PEEP) in mechanical ventilated patients without Acute Respiratory Distress Syndrome (ARDS), we conducted a Bayesian network meta-analysis and systematic review of randomized controlled trials (RCTs) comparing different level of PEEP based on a novel classification of PEEP level: ZEEP group (PEEP = 0 cm H2O); lower PEEP group (PEEP = 1–6 cm H2O); intermediate PEEP group (PEEP = 7–10 cm H2O); higher PEEP group (PEEP > 10 cm H2O).

Result: Twenty eight eligible studies with 2,712 patients were included. There were no significant differences in the duration of mechanical ventilation between higher and intermediate PEEP (MD: 0.020, 95% CI: −0.14, 0.28), higher and lower PEEP (MD: −0.010, 95% CI: −0.23, 0.22), higher PEEP and ZEEP (MD: 0.010, 95% CI: −0.40, 0.22), intermediate and lower PEEP (MD: −0.040, 95% CI: −0.18, 0.040), intermediate PEEP and ZEEP (MD: −0.010, 95% CI: −0.42, 0.10), lower PEEP and ZEEP (MD: 0.020, 95% CI: −0.32, 0.13), respectively. Higher PEEP was associated with significantly higher PaO2/FiO2 ratio(PFR) when compared to ZEEP (MD: 73.24, 95% CI: 11.03, 130.7), and higher incidence of pneumothorax when compared to intermediate PEEP, lower PEEP and ZEEP (OR: 2.91e + 12, 95% CI: 40.3, 1.76e + 39; OR: 1.85e + 12, 95% CI: 29.2, 1.18e + 39; and OR: 1.44e + 12, 95% CI: 16.9, 8.70e + 38, respectively). There was no association between PEEP levels and other secondary outcomes.

Conclusion: We identified higher PEEP was associated with significantly higher PFR and higher incidence of pneumothorax. Nonetheless, in terms of other outcomes, no significant differences were detected among four levels of PEEP.

OPEN ACCESS

Edited by:
Ling Liu,
Southeast University, China

Reviewed by:
Burcin Halacli,
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Specialty section:
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

Received: *24 June 2021*
Accepted: *03 August 2021*
Published: *01 September 2021*

Citation:
Zhou J, Lin Z, Deng X, Liu B, Zhang Y, Zheng Y, Zheng H, Wang Y, Lai Y, Huang W, Liu X, He W, Xu Y, Li Y, Huang Y and Sang L (2021) Optimal Positive End Expiratory Pressure Levels in Ventilated Patients Without Acute Respiratory Distress Syndrome: A Bayesian Network Meta-Analysis and Systematic Review of Randomized Controlled Trials. Front. Med. 8:730018. doi: 10.3389/fmed.2021.730018

Systematic Review Registration: The study had registered on an international prospective register of systematic reviews, PROSPERO, on 09 April 2021, identifier: [CRD42021241745].

Keywords: Acute respiratory distress syndrome, Mechanical ventilation, Positive end expiratory pressure, Pneumothorax, Mortality

INTRODUCTION

Although invasive mechanical ventilation is a lifesaving strategy for critically ill patients, previous studies have considered it a potentially harmful intervention (1, 2). Positive end expiratory pressure (PEEP) has shown efficacy in maintaining alveoli opening, improvement of gas exchange and reduction of injurious shear forces in acute respiratory distress syndrome (ARDS) patients since 1960 s (3). To date, however, the optimal PEEP levels remain unclear, owing to occurrence of potential negative effects that cause overdistention of the lungs, exacerbate lung stress as well as strain and impair hemodynamics by reducing venous return and increasing pulmonary vascular resistance. Therefore, PEEP's net benefits or harm are depended on the balance between alveolar recruitment and overdistension, and should be particularly beneficial in disease states with substantial alveolar collapse (4). Nevertheless, this trade-off is often difficult to achieve clinically.

Similarly, the optimal PEEP level for mechanical ventilated patients without ARDS remains unclear. Several studies have demonstrated that higher PEEP levels could improve oxygenation, reduce occurrence of ventilator-associated pneumonia (VAP), prevent ARDS in this population (5). In fact, application of PEEP has increased in clinical practice (6). However, PEEP level in a relatively healthy lung is expected to be lower because of less lung collapse which requires less pressure to open the collapsed lung. In addition, previous research evidences from animal studies have shown that ventilation with higher PEEP levels might worsen existing lung injuries or cause development of new ones (7–9). A recent RELAx trial demonstrated that a higher PEEP strategy generated clinically superior outcomes than lower levels with regards to the number of ventilator-free days (VFD) at day 28 in ventilated patients without ARDS, although there was a possibility of elevated hypoxemia in the lower PEEP group (10).

A previous systematic review and meta-analysis compared efficacy of different PEEP levels in patients without ARDS (11). However, the findings therein should be interpreted with caution, owing to a moderate to high heterogeneity, a low to very low quality of evidences (QoE), and the fact that the included studies could not allow the authors to comprehensively address the effects of moderate PEEP levels. In the present study, we conducted a Bayesian network meta-analysis and systematic review of RCTs to compare efficacy of different PEEP levels in ventilated patients without ARDS, and identify the optimal level for this population. Specifically, we divided the patients into four groups according to their PEEP levels. We chose a novel classification, based on patients' PEEP levels, which is closer to clinical practice, and can allow for reduction of heterogeneity in the analysis as well as precise evaluation of the effects of different PEEP levels.

MATERIALS AND METHODS

This meta-analysis was performed in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension statement for reporting network meta-analyses (PRISMA- NMA) (12). The study was also prospectively registered on PROSPERO database (Registration number: CRD42021241745).

Data Sources and Study Search

We searched PubMed, Web of Science, Embase, Cochrane Library, Embase up to January 2021. Reference lists of relevant articles were also reviewed. The inclusion criteria were as follows: (i) studies were RCTs; (ii) the study population comprised ventilated patients without ARDS; (iii) intervention included higher *vs*. lower PEEP; and (iv) studies were published in English. The exclusion criteria were as follows: (i) studies that analyzed pediatric patients; (ii) patients were not in ICU; (iii) data were unavailable; and (iv) duplicate publications.

Study Selection and Data Extraction

Meta-analysis was performed by two researchers (JZ and ZML), who independently screened the citations and abstracts in duplicate and extracted the data. All references that were judged potentially relevant were evaluated for full-text eligibility. Discrepancies were resolved by consensus with a third author (YBH). In cases where relevant data or information was missing, we attempted to contact the authors of the studies.

Outcome Measures

Primary outcome was the duration of mechanical ventilation, whereas secondary outcomes included PaO_2/FiO_2 ratio (PFR), length of stay (LOS) in ICU, LOS in hospital, hospital mortality, 28-day mortality, ICU mortality, occurrence of ARDS, pneumothorax, atelectasis and hypoxemia.

Assessment of Risk of Bias

Two authors (JZ and ZML) independently assessed the risk of bias (RoB) in individual studies, using the revised Cochrane risk-of-bias tool for randomized trials (13), and classified them as either low or high. Any disagreements between them were resolved by discussion and consensus with a third author (YBH). Low-biased studies were defined as those with no <4 low-risk items, based on the Cochrane risk-of-bias tool.

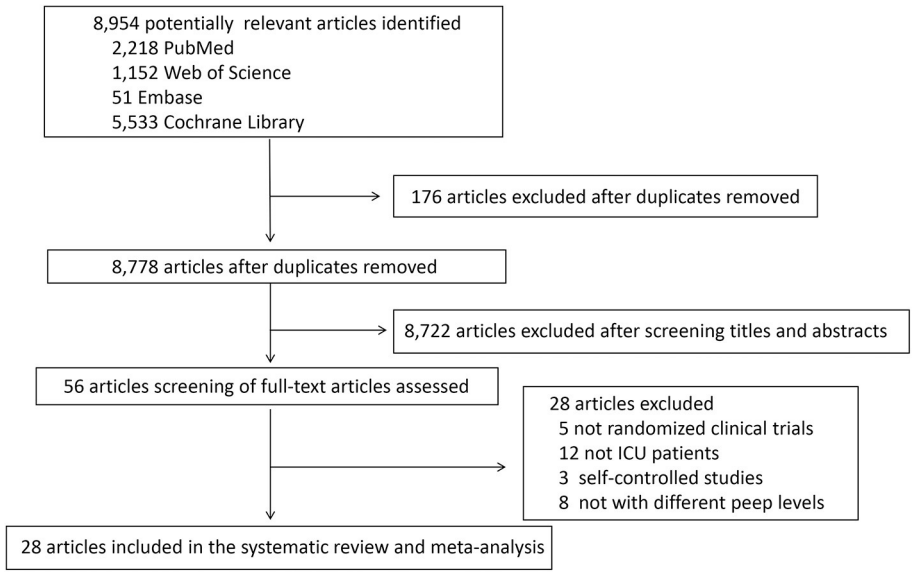

FIGURE 1 | PRISMA Flowchart.

Statistical Analysis

A random effects network meta-analysis was performed using a Bayesian framework. We also calculated mean differences for continuous outcomes and odds ratios (ORs) for dichotomous outcomes, then converted medians and interquartile ranges to means and standard deviations as previously described (14). Network meta-analysis was performed using the "gemtc" package (version 0.8–2) implemented in R version 3.4.4 (https://www.r-project.org/). This package is based on an approach that follows the graph-theoretical methodology. We ranked the treatments using the P-score to reveal the degree of certainty that a specific treatment was better than the others. Based on this, P-scores close to 1 and 0 denoted the best and worst treatments, respectively. Moreover, studies followed by a value of $I^2 \geq 50\%$ were considered to have substantial heterogeneity. To limit the possibility of type I error, we performed a Trial sequential analysis (TSA) using TSA version 0.9.5.10.

RESULTS

Eligible Studies

A total of 8,954 articles were retrieved from the aforementioned databases, of which 56 were considered potentially eligible after reviewing their full texts. Finally, 28 studies (5, 10, 15–40), comprising 2,712 patients, met all our inclusion criteria and were included in the meta-analysis (**Figure 1**).

Among the 28 eligible trials, 1 compared higher PEEP levels with ZEEP, 7 compared intermediate PEEP with ZEEP, 4 compared lower PEEP with ZEEP, 1 compared higher with lower PEEP, 4 compared higher with intermediate PEEP, 8 compared intermediate with lower PEEP, while 3 compared intermediate with lower PEEP and ZEEP. Sample sizes in these trials ranged from 15 to 969 patients. The network geometry is shown in **Figure 2**. With regards to regions, the eligible RCTs were conducted across different countries in the world, with 16 of them focusing on post-cardiac patients. Meanwhile, the year of publication widely varied across the studies, with 12 of them published before 2000 (**Table 1**). RoB was high in 18 (15–17, 20, 23, 24, 27, 28, 30–32, 34–38, 40, 41) and low in 10 (5, 10, 18, 19, 21, 22, 25, 26, 29, 33) trials. The high RoB was

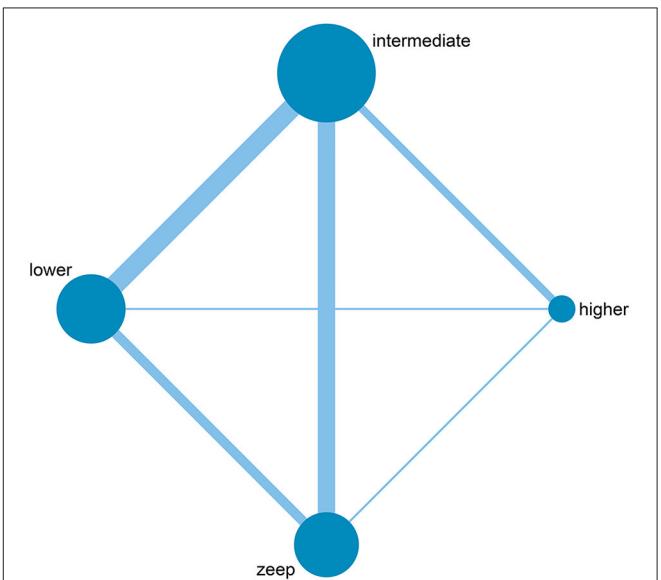

FIGURE 2 | Network geometry of included studies. The size of the nodes is proportional to the number of patients randomized to receive the intervention. The width of the lines is proportional to the number of trials comparing the connected intervention.

TABLE 1 | Characteristics of included studies.

Study; country	Type of patients; Mean age (years)	N	Interventions	Sample Size	TV (ml/kg)	RM	Main findings
Post-Cardiac Surgery Patients							
Borges et al. (15); Brazil	Post-CABG; 60	136	M vs. L	92/44	6∼8	NO	Better pulmonary compliance values, oxygenation indexes, and lower frequency of hypoxemia were found in higher PEEP group
Lago Borges et al. (16); Brazil	Post-CABG; 60	136	M vs. L	92/44	6∼8	NO	Patients in higher PEEP group had shorter duration of mechanical ventilation.
Carroll et al. (17); America	Postoperative; 63	50	H vs. L	22/28	12	YES	Higher incidence of barotrauma and hypotension and death and higher duration of ventilation with higher PEEP.
Celebi et al. (18); Turkey	Post-CABG; 56	40	M vs. L	20/20	7	YES	Higher P/F ratio in the first 4h and less atelectasis in higher PEEP group.
Collier et al. (19); America	Post-cardiac surgery; 66	84	M vs. L	40/44	10	NO	Higher PEEP does not decrease chest-tube output or transfusion requirements but it may increase the fluid requirements.
Cordeiro et al. (20); Brazil	Post-CABG; 61	30	H vs. M	20/10	6∼8	NO	Non-invasive ventilation with PEEP 15cm H2O represented an improvement in oxygenation levels.
Cordeiro et al. (21); Brazil	Post-cardiac surgery; 64	60	H vs. M	41/19	6	NO	Significant improvement in the oxygenation rate with higher peep.
Dyhr et al. (22); Denmark	Post-CABG; 60	15	H vs. Z	7/8	6	YES	Improvement in P/F ratio and end-expiratory lung volume in PEEP group.
Good et al. (23); America	Post-cardiac surgery; 55	24	M vs. Z	10/14	10∼12	NO	Routine PEEP did not prevent atelectasis or improve pulmonary oxygen transport.
Holland et al. (24); Germany	Post-cardiac surgery; 66	28	M vs. L	14/14	6∼8	NO	A PEEP of 10 mbar over 2 h did not compromise liver function and gastric mucosal perfusion
Lima et al. (25); Brazil	Post-CABG; 62	78	M vs. L	46/32	6∼8	NO	No difference in gas exchange in the first 6 h after extubation between groups.
Marvel et al. (26); America	Post-CABG; 59	44	M vs. L vs. Z	12/15/17	NA	NO	No difference in the incidence of atelectasis or duration of hospitalization among groups.
Michalopoulos et al. (27); Greece	Post-CABG; 61	67	M vs. L vs. Z	21/24/22	NA	No	No differences in PaO_2/FiO_2, SvO_2, PvO_2 and in cardiac index among the three groups
Murphy et al. (28); America	Post-cardiac surgery; NA	139	M vs. Z	NA	NA	NO	PEEP reduced mediastinal bleeding after cardiac operations
Setak-Berenjestanaki et al. (29); Iran	Post-cardiac surgery; 56	180	M vs. L	120/60	NA	NO	Higher peep resulted in lower incidence of atelectasis and shorter duration of intubation
Zurick et al. (30); America	Post-cardiac surgery; 57	83	M vs. Z	41/42	NA	NO	PEEP did not reduce the amount of blood loss, the need for reexploration for bleeding, or the blood requirements
Non-Post-Cardiac Surgery Patients							
Cujec et al. (31); Canada	ARF: 59	46	M vs. Z	NA	NA	NO	Higher PEEP reduced alveolar–arterial oxygen difference and shunt fraction
Koutsoukou et al. (32); Greece	Severe brain damage; 41	21	M vs. Z	11/10	8∼10	NO	Five days of mechanical ventilation on ZEEP resulted in higher static elastance and minimal resistance
Lesur et al. (33); Canada	ARF; 64	63	L vs. Z	30/33	6∼9	NO	No difference in the occurrence of hypotension and duration of ventilation and mortality
Ma et al. (31); China	NPE; 64	120	H vs. M	60/60	6∼8	NO	Higher PEEP resulted in lower 28-day morality rate and higher P/F ratio

(Continued)

TABLE 1 | Continued

Study; country	Type of patients; Mean age (years)	N	Interventions	Sample Size	TV (ml/kg)	RM	Main findings
Nelson et al. (35); America	At risk of ARF; 54	38	H vs. M	20/18	NA	NO	No difference in entry PaO2, intubated/ICU/hospitalization days, incidence of barotrauma, ICU/overall mortality between groups.
Pepe et al. (36); America	At risk of ARDS; 44	92	M vs. Z	44/48	12	NO	No difference in the incidence of the ARDS or other associated complications between groups.
Vigil et al. (37); America	Trauma; 34	44	L vs. Z	23/21	12∼15	NO	Significantly less hospitalization days in zeep group whereas higher P/F ratio in the peep group.
Weijelt et al. (38); America	At risk of ARDS; 45	79	L vs. Z	45/34	15	NO	Peep altered the degree of deterioration and incidence of ARDS rather than preventing its occurrence
Miscellaneous Patients							
Algera et al. (10); Netherlands	Receiving IMV; 66	969	M vs. L	493/476	6∼8	NO	With regard to the number of ventilator-free days at day 28, no difference was found between the two groups
Cao et al. (39); China	Hypovolemic patients; 44	30	M vs. L vs. Z	10/10/10	6∼8	NO	Higher levels of PEEP increased CVP and CIVP
Manzano et al. (5); Spain	Without hypoxemia; 45	127	M vs. Z	64/63	8∼9	NO	Application of prophylactic PEEP reduced the number of hypoxemia episodes and the incidence of ventilator-associated pneumonia
Feeley et al. (40); America	ARF; 61	25	L vs. Z	12/13	10	NO	PEEP may be useful in weaning patients who have a low vital capacity and inspiratory force

N means total number of participants in each study; Sample Size means number of participants in each group in study; NA, not available; TV, tidal volume; RM, recruitment maneuvers; PEEP, positive end-expiratory pressure (in cmH2O); P/F ratio: PaO2/FiO2; IMV, invasive mechanical ventilation; CABG, coronary artery bypass grafting; ARF, acute respiratory failure; ARDS, acute respiratory distress syndrome; NPE, neurological pulmonary edema.

H, higher peep (peep level >10 cmH_20); M, intermediate peep (5 < peep level ≤ 10 cmH_20); L, lower peep (0 < peep level ≤ 5 cmH_20); Z, zeep means peep level of zero.

attributed to blinding of participants, personnel and outcome assessors (**Figure 3**).

Primary Outcomes

A total of 11 eligible articles (5, 10, 16, 19, 21, 23, 25, 29, 33, 35, 38), with 1,848 participants, reported duration of mechanical ventilation. Among them, 6 studies (16, 19, 21, 23, 25, 29), with 572 patients (16, 19, 21, 23, 25, 29). A summary of the RoBs is shown in **Figure 3** while the resulting funnel plot is illustrated in **Figure 4**. A direct comparison revealed no significant differences in the duration of mechanical ventilation, between higher and intermediate PEEP levels (MD: 0.024, 95% CI: −0.14, 0.28), intermediate and lower PEEP (MD: −0.034, 95% CI: −0.17, 0.050), intermediate PEEP and ZEEP (MD: −0.62, 95% CI: −1.6, 0.35), as well as lower PEEP and ZEEP (MD: −0.028, 95% CI: −0.26, 0.16). Similarly, a direct comparison among a subpopulation of post-cardiac surgery patients revealed no significant differences in the duration of mechanical ventilation among different PEEP strategies (higher vs. intermediate: MD: 0.02, 95% CI: −0.034, 0.073; intermediate vs. lower: MD: −0.03, 95% CI: −0.078, 0.017; and lower PEEP *vs.* ZEEP: MD: 0.03, 95% CI: 0.015, 0.046) (**Figure 5A**). Results from Network Meta-Analysis, which combined direct and indirect comparison approaches, revealed no significant differences in the duration of mechanical ventilation between higher and intermediate PEEP (MD: 0.020, 95% CI: −0.14, 0.28), higher and lower PEEP (MD: −0.010, 95% CI: −0.23, 0.22), higher PEEP and ZEEP (MD: 0.010, 95% CI: −0.40, 0.22), intermediate and lower PEEP (MD: −0.040, 95% CI: −0.18, 0.040), intermediate PEEP and ZEEP (MD: −0.010, 95% CI: −0.42, 0.10), as well as lower PEEP and ZEEP (MD: 0.020, 95% CI: −0.32, 0.13) groups. Pooled estimates from the network meta-analysis were shown in **Table 2**. Network Meta-Analysis of the subpopulation of post-cardiac surgery patients also revealed no significant differences in their duration of mechanical ventilation among different PEEP strategies (higher vs. intermediate PEEP: MD: 0.02, 95% CI: −0.060, 0.090; higher vs. lower PEEP: MD: −0.010, 95% CI: −0.10, 0.080; higher PEEP vs. ZEEP: MD: 0.02, 95% CI: −0.090, 0.12; intermediate *vs.* lower PEEP: MD: −0.03, 95% CI: −0.080, 0.020; intermediate PEEP vs. ZEEP: MD: 0, 95% CI: −0.070, 0.070; lower PEEP vs. ZEEP: MD: 0.03, 95% CI: −0.030, 0.090) (**Figure 5B**). We also performed node-splitting analysis to assess inconsistency in network meta-analysis, and found no significant differences between intermediate *vs.* lower PEEP ($p = 0.22$), intermediate PEEP vs. ZEEP ($p = 0.26$), and lower PEEP vs. ZEEP ($p = 0.22$), indicating that the results

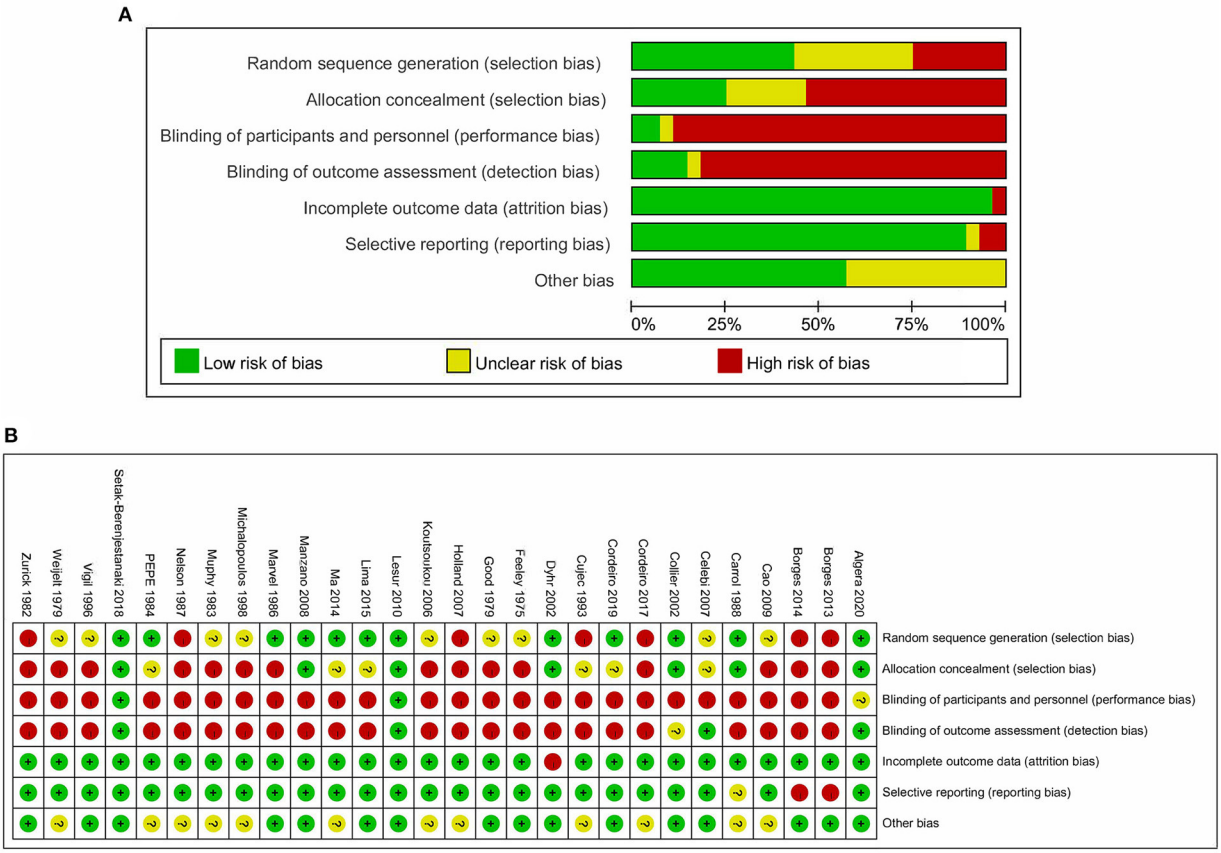

FIGURE 3 | Risk of bias of included studies. **(A)** Risk of bias graph based on the Cochrane Risk of Bias Tool. **(B)** Risk of bias summary based on the Cochrane Risk of Bias Tool.

from both direct and indirect comparisons across the three groups were highly consistent (**Figure 5C**). However, results from ranking analysis showed that intermediate PEEP levels could shorten the duration of mechanical ventilation, followed by ZEEP, higher PEEP and lower PEEP (**Figure 6**). Furthermore, TSA showed that conventional and O'Brien-Fleming significance boundaries were not crossed by the cumulative Z-curve, indicating that the evidence was not sufficient and conclusive. Therefore, further trials are needed to validate these findings. A graphical representation of this analysis is shown in **Figure 7**.

Secondary Outcomes

Eleven eligible studies, with 1,648 patients, reported on PFR (5, 10, 15, 20–22, 24, 25, 32–34), with 6 of them (comprising 347 patients) focusing on post-cardiac surgery patients (5, 10, 21, 22, 24, 33). Results of RoB are shown in **Figure 3** and **Supplementary Figure 1A**. Direct comparison revealed no significant differences in PFR among PEEP levels, in both general or post cardiac surgical patients (**Supplementary Figure 1B**). However, results from Network Meta-Analysis demonstrated that higher PEEP was associated with significantly higher PFR compared to ZEEP in the general population (MD: 73.24, 95% CI: 11.03, 130.7). Meawhile, there were no

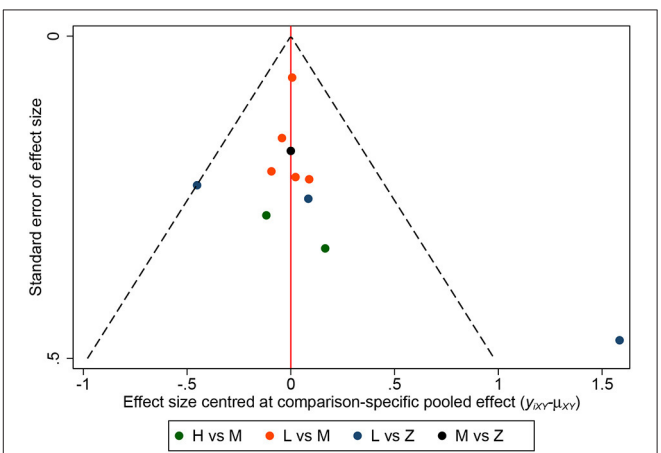

FIGURE 4 | Funnel plot for duration of mechanical ventilation. Funnel plot of association between estimated effect size for each study in terms of duration of mechanical ventilation.

sigificant differences based on the other comparisons (**Figure 8**). Moreover, node-splitting analysis, based on both direct and indirect comparisons in these groups, revealed consistent results

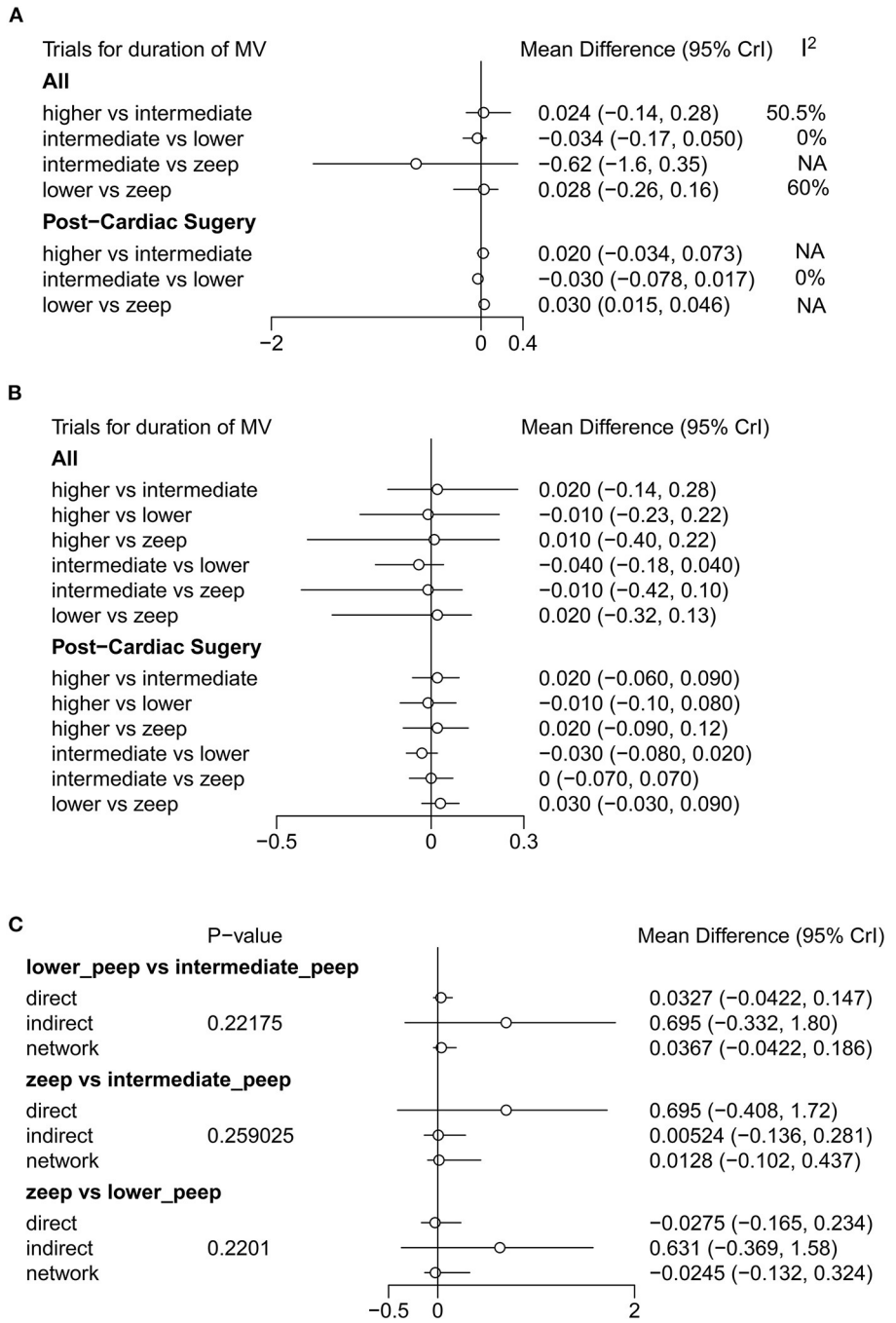

FIGURE 5 | Forest plot of duration of mechanical ventilation. **(A)** Results of direct comparison and heterogeneity test. **(B)** Results of Network Meta-Analysis. **(C)** Node-splitting analysis to assess inconsistency in network meta-analysis. In addition to general population (No statistic difference in inconsistency between direct result and indirect result when *P*-value > 0.05), **(A,B)** also show the results of analysis among post-cardiac surgery patients.

(all $p > 0.05$) (**Supplementary Figure 1C**). Ranking analysis showed that higher PEEP was associated with the best PFR, followed by intermediate and lower PEEP, and lastly ZEEP (**Supplementary Figure 1D**).

A total of 7 studies (5, 10, 18, 19, 26, 29, 35), comprising 1,482 patients, reported LOS of hospital, with 4 (18, 19, 26, 29) of them (that analyzed 348 patients) focusing on post-cardiac surgery patients. Direct comparisons and Network Meta-Analysis revealed no significant differences among all PEEP levels in either the general or post cardiac surgical patients (**Supplementary Figure 2**). Additionally, 6 studies (5, 10, 18, 29, 35, 38) (with 1,433 patients) reported LOS of ICU, with direct

TABLE 2 | Pooled estimates of the network meta-analysis for "duration of MV."

Relative effects	Higher	Intermediate	Lower	Zeep
Higher	–	−0.02 (−0.28, 0.14)	0.01 (−0.22, 0.23)	−0.01 (−0.22, 0.40)
Intermediate	0.02 (−0.14, 0.28)	–	0.04 (−0.04, 0.18)	0.01 (−0.10, 0.43)
Lower	−0.01 (−0.23, 0.22)	−0.04 (−0.18, 0.04)	–	−0.02 (−0.13, 0.32)
Zeep	0.01 (−0.40, 0.22)	−0.01 (−0.43, 0.10)	0.02 (−0.32, 0.13)	–

Results are MDs in the column-defining treatment compared with MDs in the row-defining treatment. Given that "duration of MV" is a negative outcome, MD < 0 favored the column-defining treatment. MD, mean difference; MV, mechanical ventilation.

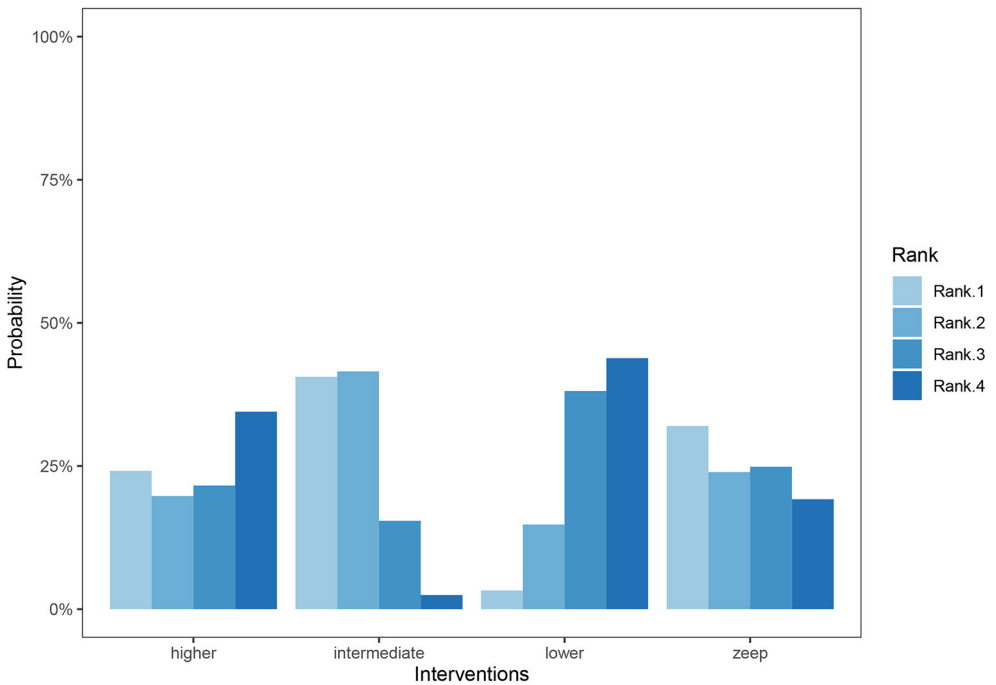

FIGURE 6 | Cumulative ranking bar graph for duration of mechanical ventilation. Ranks represent priority. For each intervention, cumulative ranking bar graph shows the probabilities when they are at Rank1/2/3/4 respectively. To sum up, the probabilities of every 4 columns in each intervention are 100%.

comparison showing that lower PEEP levels were associated with shorter LOS of ICU relative to ZEEP (MD: −6.00, 95% CI: −9.80, −2.20) (**Supplementary Figure 3A**). However, Network Meta-Analysis revealed no significant differences among all PEEP levels (**Supplementary Figure 3B**). Hospital mortality was reported in 9 eligible studies (5, 10, 17, 19, 27, 33, 35, 36, 38), comprising 1,561 patients, 28-days mortality was reported in 3 eligible studies (10, 33, 34), that analyzed 1,152 patients, while ICU mortality was reported in 3 eligible studies (10, 17, 35) (with 1,056 patients). Notably, only direct comparison showed that higher PEEP levels were associated with increased ICU mortality when compared to lower PEEP (OR: 10.1, 95% CI: 1.21, 91.9) (**Supplementary Figure 4A**). Results from Network Meta-Analysis revealed no significant differences among the PEEP levels with regards to hospital, 28 days and ICU mortality (**Supplementary Figure 4B**).

Four eligible studies (5, 10, 36, 38), comprising 1,267 patients, reported incidence of ARDS, 7 (5, 10, 17, 18, 27, 35, 36) (with 1,383 patients) described incidence of pneumothorax, 4 (5, 10, 29, 36) with a total of 1,368 patients reported incidence of atelectasis, while 4 (5, 10, 36) with 1,255 patients described incidence of hypoxemia. Direct comparison revealed no significant differences among PEEP levels in the various complications (**Supplementary Figure 5A**). Similarly, Network Meta-Analysis showed that there were no significant differences among the PEEP levels with regards to occurrence of ARDS,atelectasis and hypoxemia (**Supplementary Figure 5B**), although higher PEEP levels were associated with significantly higher incidence of pneumothorax relative to intermediate and lower PEEP, as well as ZEEP (OR: 2.91e + 12, 95% CI: 40.3, 1.76e + 39; OR: 1.85e + 12, 95% CI: 29.2, 1.18e + 39; and OR: 1.44e + 12, 95% CI: 16.9, 8.70e + 38, respectively) and there was no significant difference among intermediate PEEP, lower PEEP and ZEEP (**Figure 9**). Node-splitting analysis, based on both direct and indirect comparisons among groups, revealed consistent results (all $p > 0.05$) (**Supplementary Figure 6A**).

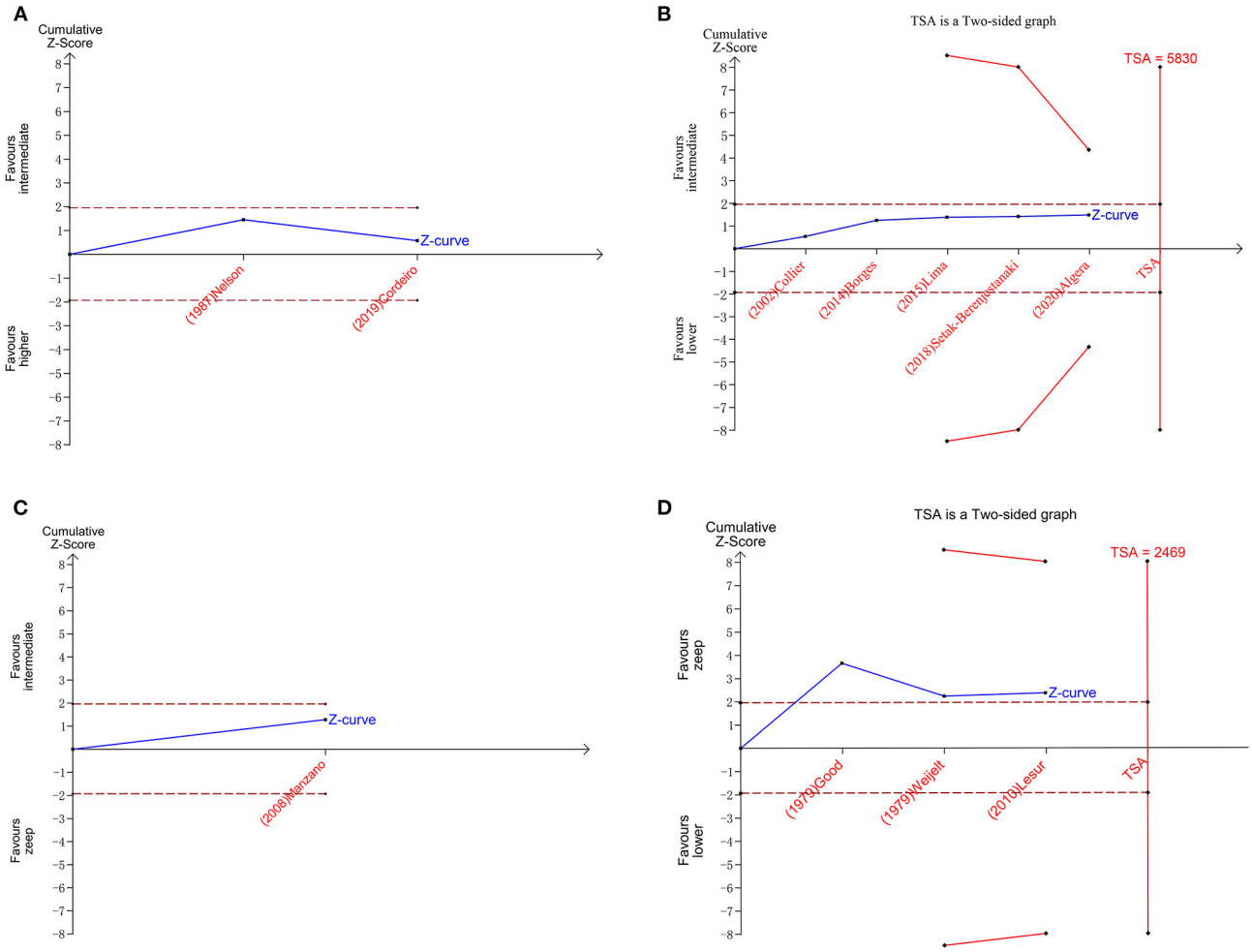

FIGURE 7 | Plots of trial sequential analysis (TSA) for duration of mechanical ventilation. **(A)** TSA for higher peep *vs.* intermediate peep; **(B)** TSA for intermediate peep vs. lower peep; **(C)** TSA for intermediate peep vs. Zeep; **(D)** TSA for lower peep vs. Zeep. TSA boundary is ignored due to too little information use in **A,C**.

Results from ranking analysis showed that high PEEP levels were associated with the highest risk of pneumothorax development, followed by intermediate and lower PEEP, and finally ZEEP (**Supplementary Figure 6B**).

DISCUSSION

We employed a Bayesian network meta-analysis to compare ZEEP levels in 28 RCTs (with 2,709 patients) that focused on ventilated patients without ARDS. Our results revealed that intermediate PEEP levels were associated with the highest decrease in the duration of mechanical ventilation, although there were no significant differences among PEEP levels based on direct and indirect comparisons. Meanwhile, higher PEEP levels were associated with significantly higher PFR and increased incidence of pneumothorax. Notably, we found no significant differences among the PEEP groups with regards to LOS of hospital and ICU, hospital, 28-day and ICU mortalities, occurrence of ARDS, atelectasis and hypoxemia. However, our results should be interpreted cautiously, owing to the TSA outcomes and presence of heterogeneity.

One meta-analysis published in 2016 (11) demonstrated that ventilation with higher PEEP levels in ICU patients without ARDS was not associated with neither reduced in-hospital mortality nor shorter ventilation duration, but with lower incidence of ARDS and hypoxemia, as well as higher PaO_2/FiO_2. Notably, the study had a moderate to high heterogeneity, while its quality of evidence was low to very low. Consequently, the authors could not address the effects of moderate levels of PEEP (11). When compared to the aforementioned meta-analysis, our study had several strengths. Firstly, we included seven recent studies, which included one large RCT describing use of high PEEP in patients without ARDS. The lower and higher PEEP groups in the former study corresponded to low and intermediate PEEP groups, respectively, in our study (10). This could also explain why our results were not completely consistent with previous meta-analyses. Secondly, we employed a novel

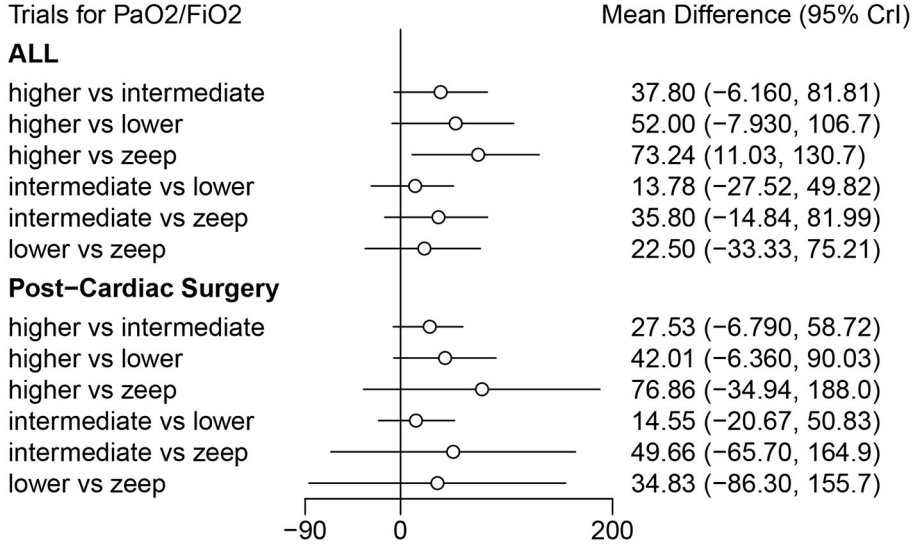

FIGURE 8 | Forest plot of Network Meta-Analysis for PaO_2/FiO_2.

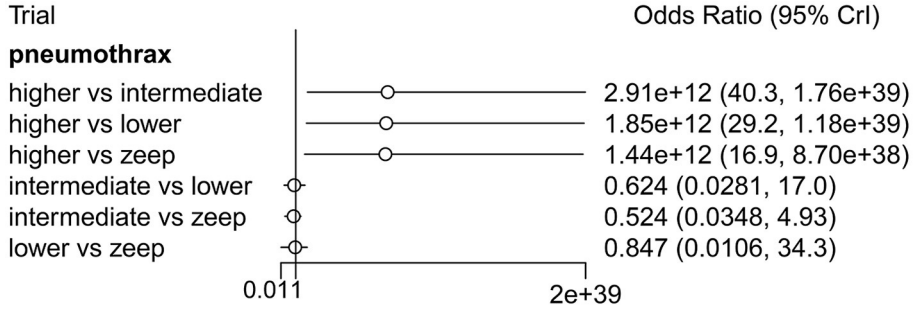

FIGURE 9 | Forest plot of Network Meta-Analysis for the incidence of pneumothorax.

classification, and divided the patients into four groups according to the specific PEEP levels. The ZEEP and very high PEEP (>10 cm H_2O) groups are not routine choices across clinical practice for non-ARDS patients, and these 2 extreme PEEP levels have always been applied in post cardiac surgery patients in our included studies. Moreover, since most of these studies were published 20 years ago, our novel classification allowed us to address the effects of moderate PEEP levels closer to clinical practice. Thirdly, a previous meta-analysis reported PEEP levels that ranged from 0 to10 cm H_2O for the low group, and 5 to 30 cm H_2O for the high group, while the heterogeneity was so large that the authors could not make a definite conclusion. Our novel classification solved this problem to a certain extent, and made the conclusion more credible.

Although previous studies have demonstrated the potential benefits and adverse effects of PEEP in ARDS, selecting appropriate PEEP levels seems to be a complex process in patients without ARDS owing to a huge heterogeneity in this population. Although an increase in PEEP levels has been reported in such population in the real-world, evidence of how to choose an optimal concentration was lacking (6, 41). In our study, Bayesian analysis revealed that intermediate PEEP (PEEP = 7–10 cm H_2O) was associated with shorter duration of mechanical ventilation, whereas network meta-analysis found no significant differences among the studied PEEP levels, which was partially in line with the RELAx trial (10). Interestingly, one study demonstrated that a higher PEEP could reduce the duration of mechanical ventilation (16), was although this corresponded to the intermediate PEEP group in our study. To our knowledge, there were many confounding factors that affected the duration of mechanical ventilation, affirming PEEP's lack of significant impact observed herein.

Our results further showed that PFR was positively correlated with PEEP levels, which was consistent with a previous meta-analysis (11). In ARDS patients, PEEP has been shown to recruit the collapse alveoli, maintain the end expiratory lung volume and improve gas exchange (3). Interestingly, the same principle seems to work in patients without ARDS. On the other hand, inadequate elevated PEEP has been found to cause alveoli overdistension in ARDS patients, thereby causing barotrauma (42, 43). In our opinion, this challenge might be even more pronounced in non-ARDS patients as the collapse alveoli in these patients might be

less than those in ARDS patients. This explains why higher PEEP levels were associated with significantly increased incidence of pneumothorax relative to the other PEEP levels in our study. Although the meta-analysis published in 2016 demonstrated that high PEEP was associated with a lower incidence of ARDS and hypoxemia (11), we found no evidence to support this finding.

Although our findings provide evidence of the potential benefits or harmful effects of different PEEP levels, PEEP should not just be applied according to its height, as many physiologic effects of PEEP could be U-shaped (44, 45), Individualized PEEP regimes should be optimized based on a specific patient's physiology rather than focusing simply on the dosage. To date, however, no trial has attempted to evaluate the efficacy of PEEP in patients without ARDS prior to randomization (4), which necessitates future trials.

CONCLUSION

In summary, results of our Bayesian network meta-analysis and systematic review revealed that intermediate PEEP levels are associated with the highest decrease in duration of mechanical ventilation in patients without ARDS. However, there were no significant differences among studied PEEP level groups based on both direct and indirect comparisons. Meanwhile, it is evident that higher PEEP levels are associated with significantly higher PFR and increased incidence of pneumothorax. Furthermore, the four studied PEEP levels have no significant impact on LOS of hospital, LOS of ICU, hospital mortality, 28-day mortality, ICU mortality, occurrence of ARDS, as well as atelectasis and hypoxemia.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

YH and LS: conceptualization, methodology, and supervision. JZ and ZL: data curation and writing-original draft preparation. XD and BL: software and visualization. YZhang, YZheng, HZ, YW, YLai, and WH: writing-review. XL, WH, YX, and YLi: supervision. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by Emergency Key Program of Guangzhou Laboratory (Grant No. EKPG21-17), National Natural Science Foundation of China (Grant No. 81870069), The Science and Technology Program of Guangzhou, China (202102010366), Self-determined Project of GIRH (2019GIRHQ05) and Natural Science Foundation of Guangdong Province (Grant Nos 2020A1515011459 and 2017A030313781).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.730018/full#supplementary-material

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

frontiers in Medicine

ORIGINAL RESEARCH
published: 04 October 2021
doi: 10.3389/fmed.2021.752984

Methods of Weaning From Mechanical Ventilation in Adult: A Network Meta-Analysis

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OPEN ACCESS

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Specialty section:
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

Received: *04 August 2021*
Accepted: *13 September 2021*
Published: *04 October 2021*

Citation:
Jhou H-J, Chen P-H, Ou-Yang L-J, Lin C, Tang S-E and Lee C-H (2021) Methods of Weaning From Mechanical Ventilation in Adult: A Network Meta-Analysis. Front. Med. 8:752984. doi: 10.3389/fmed.2021.752984

Background/Objective: The aim of study is to assess the efficacy of each ventilator weaning method for ventilated patients in intensive care units (ICUs).

Methods: A systematic search was conducted using PubMed, Embase, and China National Knowledge Infrastructure to identify randomized control studies on ventilated patients regarding extubation associated outcomes (weaning success or failure, proportion requiring re-intubation, or mortality) from inception until April 01, 2020. Commonly used ventilation modes involved pressure support ventilation, synchronized intermittent mandatory ventilation, automatic tube compensation, continuous positive airway pressure, adaptive support ventilation, neurally adjusted ventilatory assist, proportional assisted ventilation, and SmartCare. Pooled estimates regarding extubation associated outcomes were calculated using network meta-analysis.

Results: Thirty-nine randomized controlled trials including 5,953 patients met inclusion criteria. SmartCare and proportional assist ventilation were found to be effective methods in increasing weaning success (odds ratio, 2.72, 95% confidence interval (CI), 1.33–5.58, *P*-score: 0.84; odds ratio, 2.56, 95% CI, 1.60–4.11, *P*-score: 0.83; respectively). Besides, proportional assist ventilation had superior in reducing proportion requiring re-intubation rate (odds ratio, 0.48, 95% CI, 0.25–0.92, *P*-score: 0.89) and mortality (odds ratio, 0.48, 95% CI, 0.26–0.92, *P*-score: 0.91) than others.

Conclusion: In general consideration, our study provided evidence that weaning with proportional assist ventilation has a high probability of being the most effective ventilation mode for patients with mechanical ventilation regarding a higher rate of weaning success, a lower proportion requiring reintubation, and a lower mortality rate than other ventilation modes.

Keywords: systemic review, network meta-analysis, weaning, T-piece, proportional assist ventilation, SmartCare

INTRODUCTION

The most common cause of vital organ failure was acute respiratory failure in critically ill patients. It was estimated that 40–65% of patients in intensive care units (ICUs) needed mechanical ventilation (1), which provided adequate oxygen and reduced the work of breathing for patients with respiratory failure of different etiologies (2). However, there were several complications associated with mechanical ventilation, such as initiating lung injury, ventilator-associated pneumonia (3), and respiratory muscle weakness (4).

Successful and timely weaning of patients from mechanical ventilation could shorten the duration of the ventilation and reduce infection risk, medical costs, and mortality. Some evidence showed that delay weaning might cause unnecessary discomfort, increase complication rates, and result to higher medical costs (5, 6). Even in scheduled extubated patients, up to one-third of patients needed reintubation because of extubation failure (7, 8). Reintubation was associated with high mortality due to new complications (9).

A spontaneous breathing trial (SBT) was the most common method to evaluate the ability of a patient to self-breathing and provided important clinical information for weaning. According to the American Thoracic Society Clinical Practice Guidelines on weaning and extubation (10, 11), an initial SBT was weakly recommended for weaning. PSV and T-piece for SBT in adults were commonly used modes for the liberation process. In a Cochrane review (12), Ladeira et al. found non-significant differences between the pressure support and T-piece modes regarding weaning success, pneumonia, reintubation, ICU mortality, and length of hospital stay.

Closed-loop weaning systems, an automatic system using physiological feedback signal to adjust the process of weaning, may facilitate systematic and early identification of spontaneous breathing ability and the potential for ventilation discontinuation through continuous monitoring and real-time interventions. The concept of closed-loop weaning systems is not new; however, with advanced technology from academia and industry, SmartCare is the first commercial closed-loop systems with intelligent modes in clinical use, and adaptive support ventilation, neurally adjusted ventilatory assist, and proportional assisted ventilation (PAV) have been further developed in recent decades (13). In current studies, closed-loop weaning systems show clinical benefit regarding a reduction of duration of weaning, mechanical ventilation, and length of ICU stay (13, 14).

PAV was first introduced by Younes in 1992 and adjusted the inspiratory pressure in proportion to the flow and volume generated by the patient. New software (PAV+) has been developed based on PAV to adapt to clinical needs through semi-continuous measurements and delivering pressure proportional to the instantaneous inspiratory flow and volume (13, 14). In a meta-analysis (15), PAV+ had benefits of decreasing the rate of weaning failure and the duration of mechanical ventilation in comparison with pressure support ventilation. Another meta-analysis provided the evidence that PAV increases the rate of weaning success, decreases proportion of patients requiring reintubation and the length of ICU stay, but does not reduce the mortality in comparison with pressure support ventilation (16).

Several meta-analyses have evaluated different ventilation modes for weaning; however, no study has presented a head-to-head comparison of the efficacy of different modes for liberation from mechanical ventilation. Therefore, we conducted this network meta-analysis to assess the relative efficacy of each technique with the aim of providing treatment recommendations to physicians in daily clinical practice.

METHODS

We performed this systematic review and network meta-analysis using established guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses (PRISMA-NMA) (17, 18) (**Supplementary Table 1**). The review protocol was registered in the Open Science Framework (OSF, protocol available at https://osf.io/fs8ze).

Data Sources and Search Strategy

We performed a comprehensive search without language restrictions using PubMed, Embase, and China National Knowledge Infrastructure (https://www.cnki.net) from inception until April 01, 2020. The goal was to identify all relevant trials while screening the titles and reviewing the abstracts. To ensure that no randomized controlled trials were missing, gray literature (conference abstracts and doctoral theses) were searched, and the reference lists of included articles were reviewed. Further ongoing trials were searched using Google Scholar, and the US Government Clinical Trials Database (www.ClinicalTrials.gov). The search terms comprised "Ventilation Weaning," "T-piece," "Pressure Support Ventilation," "Synchronized Intermittent Mandatory Ventilation," "Automatic Tube Compensation," "Continuous Positive Airway Pressure," "Adaptive Support Ventilation," "Neurally Adjusted Ventilatory Assist," "Proportional Assisted Ventilation," and "SmartCare," along with a list of all interventions and possibly relevant key words (**Supplementary Table 2**).

Study Selection

We included randomized control studies on mechanically ventilated adults (at least 18 years of age) that reported at least one of extubation associated outcomes (weaning success or failure, proportion requiring re-intubation, or mortality) with respiratory failure of various etiologies and received invasive mechanical ventilation (MV) for at least 24 h. The comparison included two or more ventilation modes for weaning. We excluded trials that evaluated neonatal or pediatrics subjects, enrolled extubated patients directly to non-invasive ventilation for weaning, compared without controls or same ventilation mode but different parameters.

Two authors (HJJ, LJOY) independently selected trials that met the inclusion criteria, and another author (PHC) adjudicated differences. In the case of disagreement, the same authors consulted with another author (CHL) to obtain decisions after group discussion.

Data Extraction and Bias Assessment

Two reviewers (HJJ and PHC) independently assessed the eligibility of identified citations and extracted data. Data extraction was performed with a form to capture information regarding study, participants, and treatment characteristics. We contacted the corresponding authors for missing data (**Supplementary Table 3**).

The same authors independently appraised each study using the Cochrane Risk of Bias (RoB) tool (**Supplementary Figure 1**) (19). We produced RoB graphs using the software Review Manager 5.3 (20). Discrepancies were resolved by consensus in consultation with a third reviewer (CHL) or deliberation through group discussion.

Outcome Measures

1. Weaning success: the absence of the requirement for invasive mechanical ventilation support, without cardiac arrest events, or mortality for 48 h after the extubation (translaryngeal tube) or withdrawal (tracheostomy tube), or as defined by the study authors (**Supplementary Table 4**).
2. The proportion requiring reintubation: the patient requiring reintubation in 48 h after extubation or as defined by the study authors.
3. All-cause mortality: hospital mortality or as defined by the study authors.

Data Synthesis and Statistical Analysis

We performed the network meta-analysis using a frequentist approach and provided a point estimated using a 95% confidence interval (CI) with the frequency distribution. All network meta-analyses were done with the statistical package "netmeta" in R 3.4.2 (R Core Team, Vienna, Austria) and Stata version 16 (Stata Corp, College Station, Texas, USA). We examined the symmetry and geometry of the evidence by producing a network plot with nodes for the number of study subjects and connection size corresponding to the number of studies. The estimation of mixed estimate of the network summary effects was calculated using the combination of the direct and indirect treatment effect and comprised network structure (**Supplementary Figure 2**) (21). For the dichotomous variables, we produced the pooled odds ratio (OR) with 95% CIs to summarize the effects of each comparison tested using a random-effects model (22), allowed for across studies variation.

The probability of a mode being ranked was calculated as its surface under the cumulative ranking curve (SUCRA) in frequentist framework, which is the percentage of efficacy achieved by an approach compared with an imaginary approach that is always the best without uncertainty (i.e., SUCRA = 100%). SUCRA provides a hierarchy of treatments and accounts for the variance of all relative intervention effects (23–25). In the frequentist model, *P*-score is an interpretation analogous to the SUCRA and measures certainty of whether a treatment is better than another treatment. Higher *P*-score scores correspond to a greater weaning success rate, lower proportion requiring reintubation and lower mortality (26).

Forest plots summarized relative mean effects, 95% CIs, and *P*-score for all comparisons together (27). The *P*-score results were summarized in a rank-heat plot (28). We used a multivariate random-effects meta-regression with a consistency model by White et al. (29). We assessed potential inconsistencies by comparing deviance and deviance estimates for each comparison between consistency and inconsistency using a random-effects design-by-treatment interaction model (30, 31) and the node-splitting technique (32, 33). Statistical significance was set at 5% for both analyses.

Network transitivity was examined by visually inspecting tables with study-related characteristics that may modify treatment effects, including differences in patient characteristics, study designs, details of the intervention, and differences in measurements of the outcome. Sensitivity analyses were performed to examine the validity of study findings (34). Subgroup analyses were conducted based on the following effect modifiers: endotracheal prosthesis defined as the methods for attaching to a ventilator such as ventilation through endotracheal tube or tracheostomy, publication year before and after 2008 which was the first published randomized control trial of PAV for weaning, and patients with COPD.

We evaluated whether treatment effects for the outcomes were robust and examined the relationship using random-effect network meta-regression with study characteristics. Comparison-adjusted funnel plots and Egger's test were also used to assess publication bias or other small study effects for available interventions (23). The quality of evidence derived from the GRADE framework. (35, 36) (**Supplementary Table 5**).

RESULTS

Systematic Literature Review

Totally, 39 articles met our inclusion criteria in our study. The studies regarding neurally adjusted ventilatory assist were excluded because of no adequate information. **Figure 1** showed the flowchart. The 39 trials (37–75) investigated a total of 5,953 participants who were randomized into the following interventions: adaptive support ventilation (ASV), automatic tube compensation (ATC), continuous positive airway pressure (CPAP), PAV (including PAV plus mode), pressure support ventilation (PSV), SmartCare, synchronized intermittent mandatory ventilation (SIMV), and the T-piece.

Study characteristics was summarized in **Supplementary Table 3**. The studies were with sample sizes ranging from 23 to 1,153 patients. There were 62.8% males. The mean age of subjects was 62.1 years old (standard deviation (SD): 8.0 years old), and the mean mechanical ventilation duration prior to randomization was 5.4 days (SD: 3.2 days). The mean Acute Physiology and Chronic Health Evaluation II score was 19.8 (SD: 5.6).

Result of Weaning Success

There were 36 studies (5,008 patients; 8 treatment nodes) regarding the weaning success with maintained transitivity (**Figure 2A**). **Figure 3A** presented the results of weaning success, in which the T-piece was used as a comparator. PAV and SmartCare had a significantly better weaning success

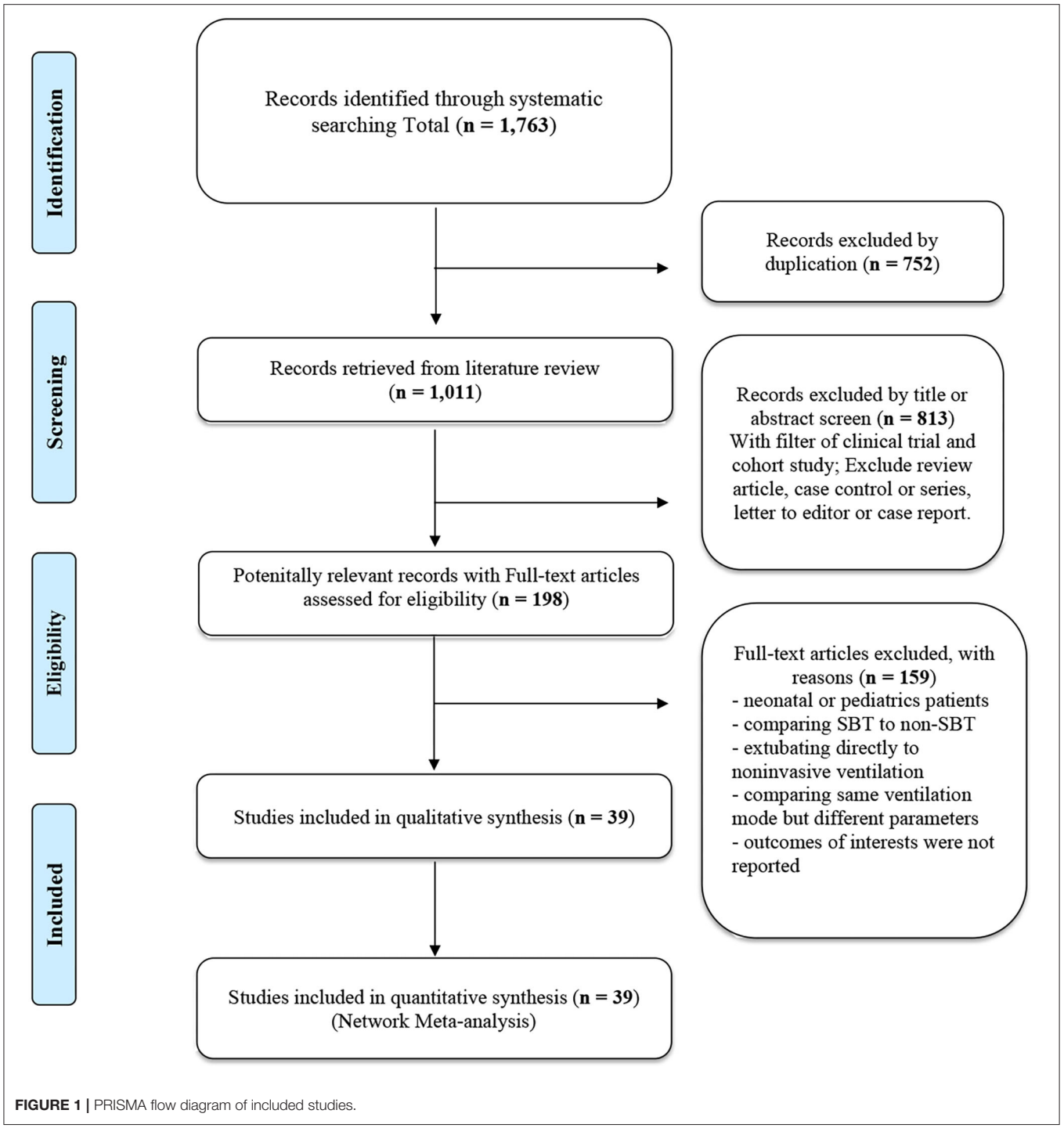

FIGURE 1 | PRISMA flow diagram of included studies.

rate (PAV: OR, 2.56; 95% CI, 1.60–4.11, P-score: 0.83; SmartCare: OR, 2.72; 95% CI, 1.33–5.58, P-score: 0.84; **Figure 4**). **Supplementary Table 6** shows details of the head-to-head comparison of outcomes.

In the sensitivity analyses of, the *P*-score rankings were changed. PAV became the first ranking in weaning success after omitting the small trials (<25th percentiles) or excluding the high risk-of-bias studies (**Supplementary Figure 4**). All the subgroup analyses revealed similar results, favoring PAV, including patients with an endotracheal prosthesis type of translaryngeal tube (PAV: OR, 3.12; 95% CI, 1.67–5.82; *P*-score: 0.91) and patients with COPD (PAV: OR, 5.89; 95% CI, 1.31–26.43; P-score: 0.88). In the subgroup of publication years after 2008, PAV and SmartCare had similar efficacy for weaning success (PAV: OR, 2.69; 95% CI, 1.66–4.37, P-score: 0.84; SmartCare: OR, 2.91; 95% CI, 1.29–6.54, P-score: 0.85; **Supplementary Figure 4**).

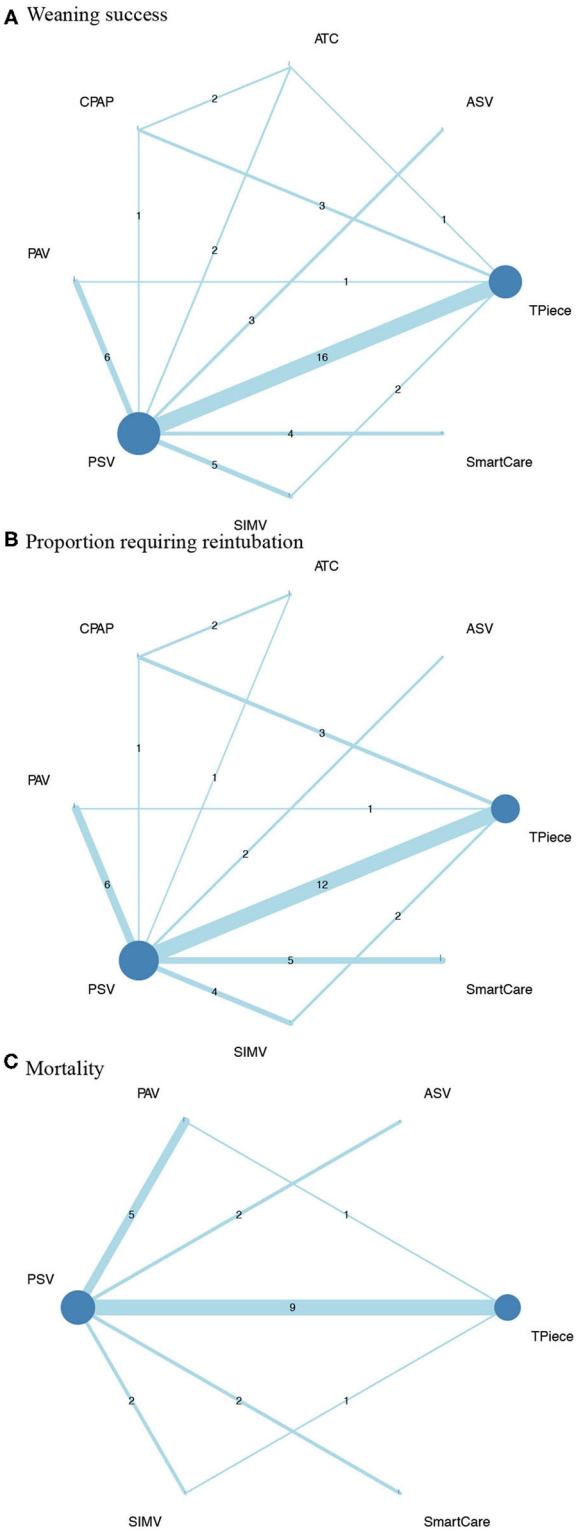

FIGURE 2 | Network plot of comparisons in **(A)**, weaning success **(B)**, proportion requiring reintubation, and mortality among different ventilator modes **(C)**. ASV, Adaptive support ventilation; ATC, Automatic tube compensation; CPAP, Continuous positive airway pressure; PAV, Proportional assist ventilation; PSV, Pressure support ventilation; SIMV, Synchronized intermittent mandatory ventilation.

Result of Proportion Requiring Reintubation

There were 31 studies (4,644 patients; 8 treatment nodes) regarding the proportion requiring reintubation with maintained transitivity (**Figure 2B**). **Figure 3B** presented the results of the proportion requiring reintubation, in which the T-piece was used as a comparator. PAV had a significantly lower proportion of re-intubation (PAV: OR, 0.48; 95% CI, 0.25–0.92; *P*-score: 0.90) (**Figure 4**). The first ranking of PAV was unchanged in sensitivity analyses. Moreover, PAV was the most highly ranked intervention in all subgroups (**Supplementary Figure 4**).

Result of Mortality

There were 18 studies (3,727 patients; 6 treatment nodes) regarding mortality with maintained transitivity (**Figure 2C**). **Figure 3C** presented the results of mortality rate, in which the T-piece was used as a comparator. PAV was significantly beneficial for mortality (PAV: OR, 0.48; 95% CI, 0.26–0.92; P-score: 0.91) (**Figure 4**). The top ranking of PAV was unchanged in sensitivity analyses. Moreover, PAV was the most highly ranked intervention in all subgroups, but no statistical significance (**Supplementary Figure 4**).

Inconsistency, Meta-Regression Analysis, and Publication Bias

In the design-by-treatment interaction model, there was no evidence of global inconsistency in any outcomes (**Supplementary Table 7**). In the node-splitting model, there was no evidence of substantial statistical inconsistency between direct and indirect evidence except for the proportion requiring reintubation. There was local inconsistency between the comparisons of ATC vs. CPAP, ATC vs. PSV, and CPAP vs. the T-piece.

In the meta-regression analysis, there was no relationship between the intervention outcomes and the study characteristics (**Supplementary Table 8**). In all the outcomes, there was no evidence of potential small-study effects or publication bias according to Egger's test and the comparison-adjusted funnel plots, respectively (**Supplementary Figure 5**).

DISCUSSION

We conducted a systematic review and network meta-analysis to compare the efficacy of different modes for weaning in patients with mechanical ventilation. PAV and SmartCare had a higher ratio for weaning success. Furthermore, PAV ranked as the best intervention for the lowest proportion requiring reintubation and mortality rate comparing mechanical ventilator with any other modes for weaning. Therefore, PAV seemed to be the best weaning mode in our analysis.

The difficulty of weaning was associated with two major parameters: the duration of the weaning and the level of support pressure (76–78). In concerned with latest study (65), patients in the 30-min PSV had a higher rate of weaning success and lower hospital mortality than patients in the 2-h T-piece SBT. There was no difference of the proportion

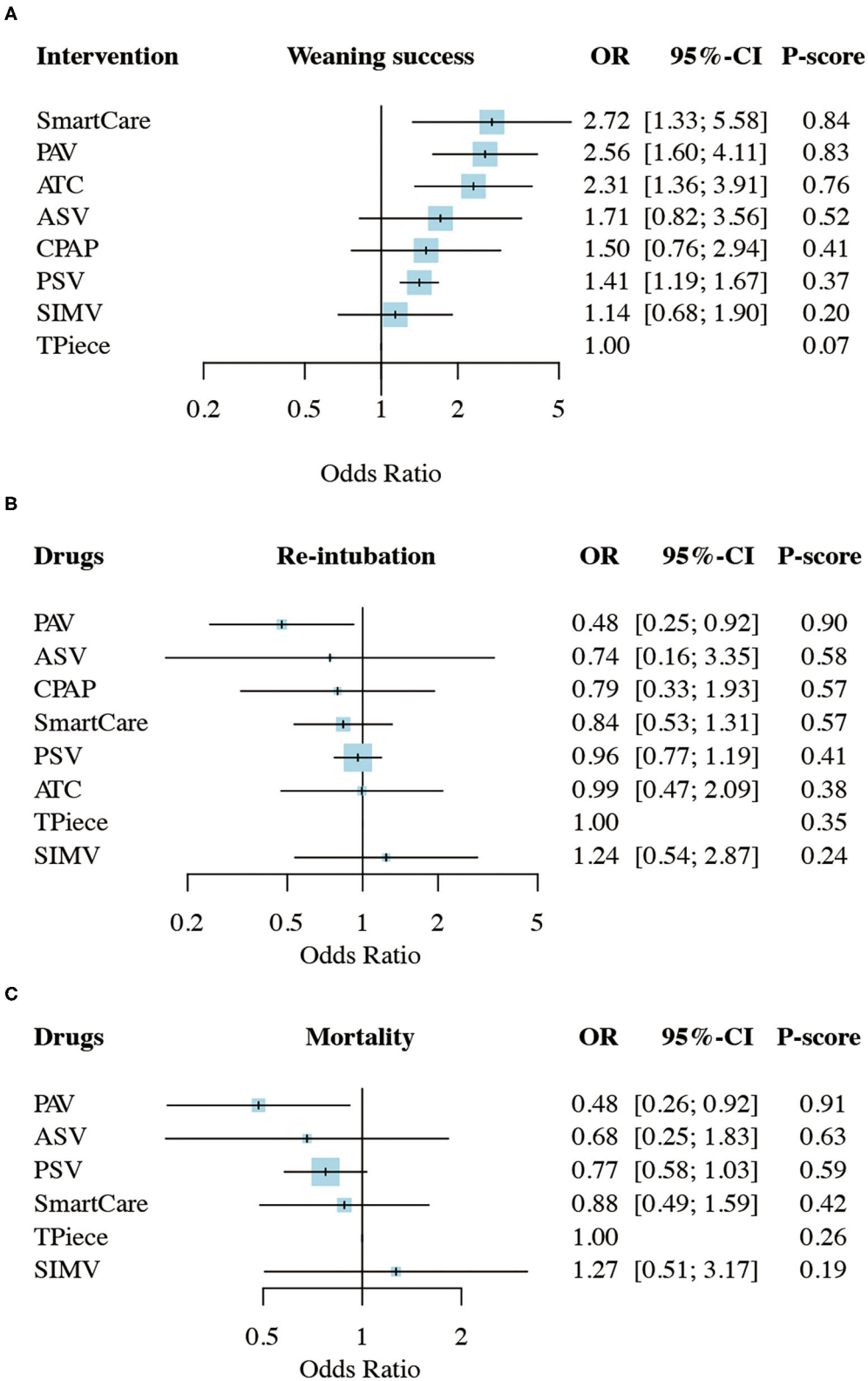

FIGURE 3 | Network meta-analysis results of **(A)**, weaning success **(B)** proportion requiring reintubation, and mortality **(C)**. ASV, Adaptive support ventilation; ATC, Automatic tube compensation; CPAP, Continuous positive airway pressure; PAV, Proportional assist ventilation; PSV, Pressure support ventilation; SIMV, Synchronized intermittent mandatory ventilation; OR, odds ratio; CI, confidence interval.

FIGURE 4 | Rank-heat plot of *P*-score values among different ventilator modes targeting outcomes of weaning success, proportion requiring reintubation and mortality. ASV, Adaptive support ventilation; ATC, Automatic tube compensation; CPAP, Continuous positive airway pressure; PAV, Proportional assist ventilation; PSV, Pressure support ventilation; SIMV, Synchronized intermittent mandatory ventilation; OR, odds ratio; CI, confidence interval.

requiring reintubation and tracheotomy rate between these two groups. Similarly, the comparison between PSV and T-piece in our study, PSV increased the rate of weaning success but did not reduce the rates of reintubation and mortality. The T-piece seemed to be more difficult than the PSV because there was no ventilation support for the T-piece.

Weaning can be accomplished by several methods. PSV or T-piece as a period of SBTs remain common methods for weaning. Automated modes of mechanical ventilation achieve synchrony of interaction between patient and ventilator, thereby improving the patient–ventilator relationship with closed-loop control system. ASV is an automated system that adapts inspiratory pressure to achieve a target tidal volume and a desired minimum

minute ventilation. SmartCare measures selected respiratory variables, adapts ventilator output by an explicit algorithm and automates the conduct of SBTs. PAV automatically adjusts the flow assist and volume assist to represent constant fractions of the measured values resistance and elasticity of the patient's respiratory system instantaneously (13, 14).

Patient–ventilator asynchrony was seen in ∼25–80% of patients with mechanical ventilation and might result in patient distress, prolonged mechanical ventilation, and weaning failure (79, 80). PAV delivered positive pressure ventilation in proportion to instantaneous inspiratory effort, improved patient–ventilator synchrony, and unloaded the respiratory muscles without the risk of over-assistance and periodic breathing (81). In a pilot study, Bosma et al. (55) demonstrated that the weaning protocols of PAV were not inferior to PSV regarding utility, safety, and feasibility. Based on its advantages, PAV might improve quality of life and decreased health care costs (82). In our subgroup analysis of publication years after 2008 when the PAV mode was first applied to weaning, we found that PAV was associated with a higher rate of successful weaning and a lower rate of reintubation, but there was no significant difference in mortality.

COPD was a disease with increasing prevalence and mortality worldwide (83). In severe conditions, mechanical ventilation was used to maintain adequate oxygenation and reduce the work of breathing. In previous studies (84, 85), patients with COPD had a longer weaning phase and a lower success rate of the weaning procedures compared to patients without COPD. However, Elganady et al. (60) showed that PAV was less patient–ventilator asynchrony, reduced period of mechanical ventilation, and shortened ICU and hospital stays. In our study, we found that weaning with PAV in patients with COPD was associated with a higher rate of weaning success.

Despite limited real-world experience about weaning with PAV, our results have demonstrated promising efficacy and a higher weaning success, a lower reintubation rate, and lower mortality than any other ventilation mode. However, due to a paucity of a variety of weaning methods in comparison with PAV, optimization of the weaning strategy was required in further studies.

The strength of this review was that we simultaneously compared seven different ventilation modes for weaning in patients with mechanical ventilation in ICUs using a network meta-analysis. To avoid bias, a comprehensive search, study selection, data extraction, and bias assessment by two reviewers were performed. We produced a rank-heat plot to summarize the results and allowed readers to quickly visualize the highest ranked choice. Besides, inconsistency was properly identified by the node-splitting and design-by-treatment model. Finally, the certainty of evidence was rated by the GRADE approach.

There were several limitations in our study. Firstly, patient population were various cross the studies and it was difficult to separate the individual studies into subgroup analysis to conduct network meta-analysis with more specific aspect. Secondly, the variety of ventilation setting prior to or during weaning might flaw the clinical efficacy; therefore, we summarized the characteristics of included studies in visually inspecting tables to provide more detail information. Lastly, due to the small number of included studies, the results should be interpreted with caution. Despite these limitations, we still hoped our findings provided a rationale for designing future large-scale randomized control trials.

CONCLUSION

According to our network meta-analysis, weaning with PAV and SmartCare results in a higher rate of weaning success. Furthermore, PAV reduce reintubation rate and mortality in comparison with other methods of weaning. We hope that this evidence about the benefits and risks when choosing weaning methods for weaning will help physicians to properly provide the optimal course of actions for patients. However, the further head-to-head randomized control trials are warranted to examine the effects of different ventilation modes for weaning.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

H-JJ and L-JO-Y conceptualized the research goals, planned the analyses, and guided the literature review. H-JJ and P-HC extracted the data from the included studies. P-HC, CL, and C-HL participated in processing the data and doing the statistical analysis. H-JJ and P-HC wrote the first draft of the paper. S-ET and C-HL reviewed and edit. All authors read and approved the final manuscript.

FUNDING

Financial support of this study was from Tri-Service General Hospital/National Defense Medical Centre (Nos. TSGH-D-110141 and TSGH-E-110199).

ACKNOWLEDGMENTS

The authors would like to thank UNIVERSAL LINK CO. (www.service-top1.com) for the English language review.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.752984/full#supplementary-material

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frontiers in Medicine

ORIGINAL RESEARCH
published: 11 October 2021
doi: 10.3389/fmed.2021.762724

Early Alterations of Lymphocyte Subsets in Acute Respiratory Distress Syndrome Caused by *Acinetobacter baumannii* Pneumonia: A Prospective Observational Study

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OPEN ACCESS

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Specialty section:
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

Received: 22 August 2021
Accepted: 13 September 2021
Published: 11 October 2021

Citation:
Cheng W, Zhang J, Li D, Bai G, Han W, Chen J, Wang H and Cui N (2021) Early Alterations of Lymphocyte Subsets in Acute Respiratory Distress Syndrome Caused by Acinetobacter baumannii Pneumonia: A Prospective Observational Study. Front. Med. 8:762724. doi: 10.3389/fmed.2021.762724

Background: To prospectively observe the early alterations of lymphocyte subsets in ARDS caused by Acinetobacter *baumannii*.

Methods: ARDS patients admitted to our ICU between January 1, 2017 and May 30, 2020 were selected. We enrolled all the pulmonary ARDS caused by Acinetobacter *baumannii* pneumonia who required mechanical ventilation or vasopressors. All the available clinical data, follow up information and lymphocyte subsets were recorded.

Results: Eighty-seven of all the 576 ARDS patients were enrolled. The 28-day mortality of the enrolled patients was 20.7% (18/87). The T lymphocyte count (452 vs. 729 cells/ul, $P = 0.004$), especially the $CD8^+$ T lymphocyte count (104 vs. 253 cells/ul, $P = 0.002$) was significantly lower in non-survivors, as were counts of the activated T cell subsets ($CD8^+CD28^+$ and $CD8^+CD38^+$). The $CD8^+$ T cell count was an independent risk factor for 28-day mortality, and a cutoff value of 123 cells/ul was a good indicator to predict the prognosis of ARDS caused by Acinetobacter *baumannii* pneumonia, with sensitivity of 74.6% and specificity of 83.3% (AUC 0.812, $P < 0.0001$).

Conclusions: Lower $CD8^+$ T cell count was associated with higher severity and early mortality in ARDS patients caused by Acinetobacter *baumannii* pneumonia, which could be valuable for outcome prediction.

Keywords: Acinetobacter *baumannii*, lymphocyte subset counts, acute respiratory distress syndrome, prognosis, ARDS

BACKGROUND

Acinetobacter baumannii (A. baumannii) is an opportunistic pathogen and one of the most common causes of hospital-acquired pneumonia, resulting from the increasingly serious occurrence of antibiotic resistance (1). Acute respiratory distress syndrome (ARDS) caused by *A. baumannii* pneumonia has significantly high mortality (2). It follows that there has been

growing interest in identifying biological sub-phenotypes of ARDS patients (3). Measuring plasma biomarkers in ARDS can help find subgroups of patients those share important host-response features and/or those have worse clinical outcomes. Li et al. (4) found that neutrophil to lymphocyte ratio (NLR) was significantly associated with 28-day mortality in patients with ARDS, and NLR was related to the severity of ARDS. However, how the lymphocyte counts changed in NLR and their correlation with prognosis were not clearly illustrated.

Traditionally, *A. baumannii* was thought to cause extracellular infection, and innate immunity played a vital role in the defense against *A. baumannii* infection. Monocytes release tumor necrosis factor (TNF) to recruit granulocytes, which phagocytize bacteria or produce reactive oxygen species. Immature dendritic cells (DCs) capture and process antigens with high efficiency. $CD4^+$ T cells differentiate toward a Th_1-polarizing phenotype through the activation of DCs (5). However, A. baumannii has been shown to cause facultative intracellular infection recently, and many studies have confirmed its ability to invade lung epithelial cells and macrophages (1, 6–8). Therefore, many immune cells and cytokines that act against intracellular and extracellular infection might be involved in the immune response against *A. baumannii* infection, which is worth of further study. There have been few clinical studies on the changes and specific roles of lymphocyte subsets in the pathogenesis of ARDS caused by *A. baumannii* pneumonia. In this study we aimed to explore the role of lymphocyte subsets in ARDS caused by *A. baumannii* and its correlation with prognosis.

METHODS

We screened all the ARDS patients according to the 2012 Berlin definition (9) admitted to the intensive care unit (ICU) of Peking Union Medical College Hospital (PUMCH) between January 1, 2017 and May 30, 2020. Pulmonary ARDS caused by *A. baumannii* pneumonia and required mechanical ventilation or vasopressors were enrolled in our study. All eligible patients needed to be over 18 years old, ICU stays for 48 h and met none of the exclusion criteria. Exclusion criteria were: (1) any condition causing neutropenia as receiving corticosteroids or immunosuppression; (2) pregnancy or lactation; (3) any condition causing primary or acquired immunodeficiency, such as HIV infection, active autoimmune disease, hematopathy, or malignant tumors receiving chemotherapy within the previous 3 months; and (4) life expectancy <48 h. This study was approved by the Institutional Review Board of PUMCH (approval number: JS-1170), and all methods were performed in accordance with the relevant guidelines and regulations. Informed consent was obtained from all patients, and the study was registered at chictr.org.cn (identifier ChiCTR-ROC-17010750).

The Berlin definition of ARDS included 4 aspects (9): (1) Timing: newly onset or worsening respiratory syndrome within 1 week of known clinical insults; (2) Chest imaging: Bilateral opacities—not fully explained by effusion, lobar/lung collapse, or nodules; (3) Origin of edeme: respiratory failure that can not be fully explained by cardiac failure or fluid overload and need objective assessment to exclude hydrostatic edema if no risk factors present, such as echocardiography; (4) Oxygenation: Mild ARDS 200 mm Hg $<$ PaO_2/FIO_2 $\leq$300 mm Hg with PEEP or CPAP $\geq$5 cm H_2O, Moderate ARDS 100 mm Hg $<$ PaO_2/FIO_2 $\leq$200 mm Hg with PEEP$\geq$5 cm H_2O, Severe ARDS PaO_2/FIO_2 $\leq$100 mm Hg with PEEP $\geq$5 cm H_2O.

Clinical diagnostic criteria of pneumonia (10–12): Pneumonia was diagnosed pulmonary infiltrates caused by infection, and at least two of the following findings: fever with a body temperature >38°C or hypothermia with a temperature <36°C; leukocytosis (>12,000 cells/mm^3) or leukopenia (<4,000 cells/mm^3); presence of newly purulent tracheal secretions; and a decrease in oxygenation.

Microbiological methods to diagnose pneumonia (12): lower respiratory tract specimens were obtained immediately after ICU admission and were sent to the PUMCH Clinical Microbiology Laboratory. Samples were obtained using non-invasive sampling and cultured semi-quantitatively. Endotracheal aspirates with >25 neutrophils on Gram's stain with <10 epithelial cells per high-power field were required for culture. If qualified samples of suputum were difficult to obtain or diagnose pneumonia, invasive respiratory sampling with bronchoalveolar lavage, protected specimen brush and blind bronchial sampling could be used. The Clinical Microbiology Laboratory determined antimicrobial susceptibility of isolated bacteria by means of the microdilution method (MicroScan System; Baxter health Care, West Sacramento, CA, USA). Results were interpreted according to breakpoints defined by the National Committee for Clinical Laboratory Standards (13). *A. baumannii* had to be the only pathogenic bacterium isolated from the enrolled patients. Bacterial colonization and ventilator-associated tracheobronchitis was carefully excluded by more than two intensivists, and other infections were cautiously excluded.

After enrollment, the following baseline information was collected: age, sex, comorbidities, treatment strategies, ventilator parameters, antibiotics, lymphocyte subsets, cytokines, and other laboratory data. SOFA score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Clinical Pulmonary Infection Score (CPIS) within 24 h of admission were calculated, as well as the duration of mechanical ventilation, ICU stay and hospital stay, and 28-day mortality.

Lymphocyte subsets were evaluated in the Infection Laboratory. Peripheral blood mononuclear cells were stained with fluorescent monoclonal antibodies, then subjected to flow cytometric analysis (3-Color EPICS-XL Flow Cytometer; Beckman Coulter, Brea, CA, USA) to detect T cells ($CD3^+$),

Abbreviations: ARDS, acute respiratory distress syndrome; *A. baumannii*, Acinetobacter *baumannii*; ICU, intensive care unit; NLR, neutrophil to lymphocyte ratio; TNF, tumor necrosis factor; DCs, dendritic cells; NK, natural killer cells; SOFA, sequential organ failure assessment score; CPIS, clinical pulmonary infection score; Ig, immunoglobulin; IQR, interquartile range; ROC, Receiver operating characteristic curve; OR, odds ratio; AUC, area under the curve; P/F, ratio PaO_a: FiO_2; BALF, bronchoalveolar lavage fluid.

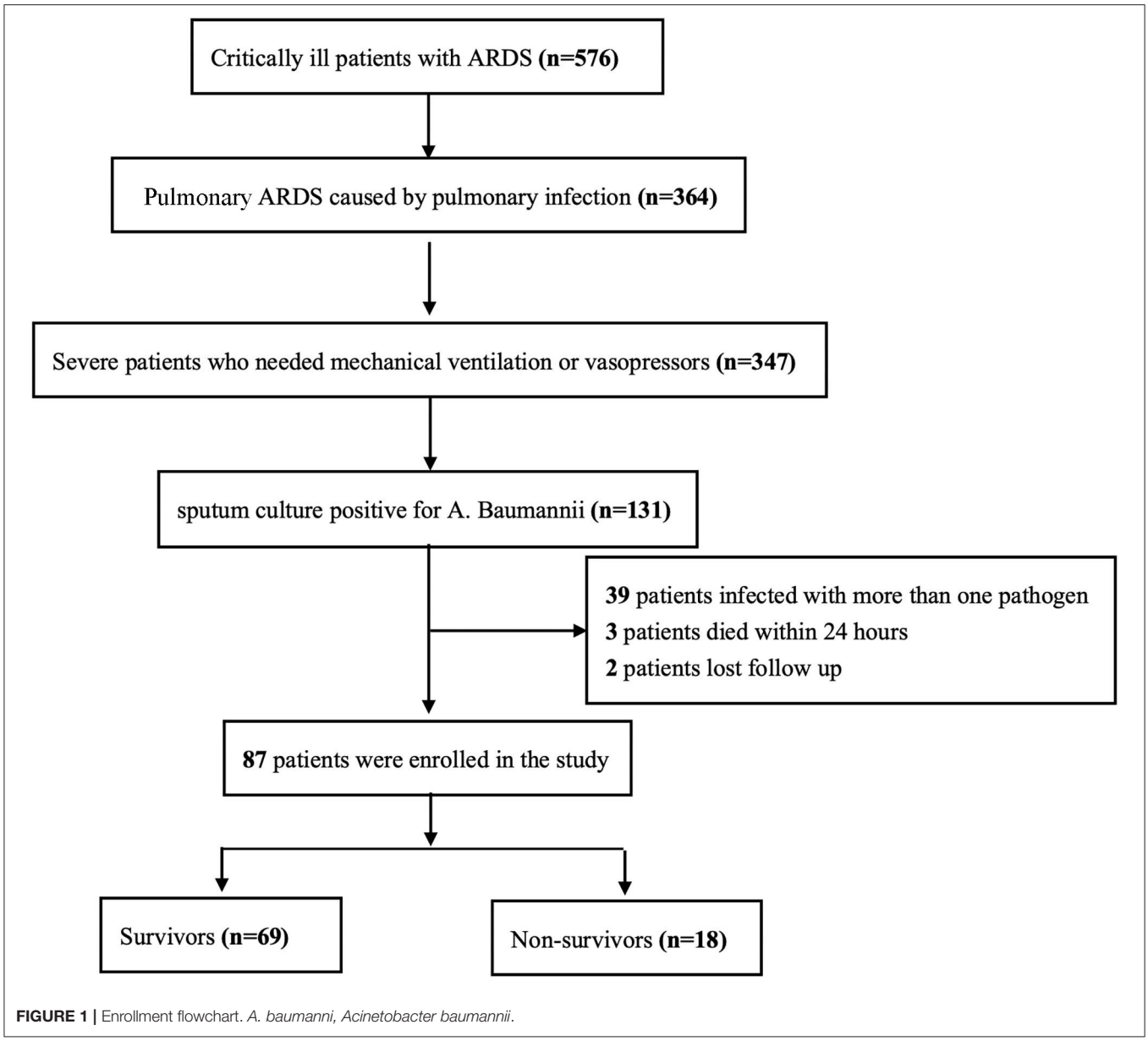

FIGURE 1 | Enrollment flowchart. *A. baumanni, Acinetobacter baumannii*.

$CD4^+$ T cell subgroups, $CD8^+$ T cell subgroups, B cells ($CD19^+$), and NK cells ($CD3^+CD16^+CD56^+$). Rate nephelometry (Array 360; Beckman Coulter) was used to measure serum levels of IgA, IgG, and IgM and complement factors C3 and C4.

Initial and targeted antibiotics: initial antibiotics were those given empirically at admission. Targeted antibiotics were those sensitive to *A. baumannii* in *in vitro* sensitivity tests, commonly including ampicillin/sulbactam, cefoperazone sulbactam, amikacin, ceftazidime averbatan, minocycline, carbapenems, tigecycline, and polymyxins.

The study protocol did not call for a standardized approach to critical care, and all treatment measures and drug selections were decided by the intensivists. As circulatory failure happened in most of patients, ECMO was not commonly used in this group.

Statistical Analysis

Normally distributed data were expressed as the mean and standard deviation and were compared using Students' *t*-test. Non-normally distributed data were presented as median and interquartile range (IQR) and were analyzed using the non-parametric Mann–Whitney *U*-test. Categorical variables were expressed as number and percentage and were compared with the chi-square or Fisher's exact test. A Cox proportional hazards model were performed successively to determine the association between lymphocyte subsets and outcome. Receiver operating characteristic (ROC) curve analysis was performed to determine the discriminatory ability of parameters for predicting 28-day mortality. Youden's index was defined for points along the ROC curve, and the reliability was assessed by sensitivity and

TABLE 1 | Baseline characters of ARDS patients caused by *A. baumannii* pneumonia.

	All ($n = 87$)	Survivors ($N = 69$)	Non-survivors ($N = 18$)	*P*-value
Baseline characteristics				
Sex (male%)	61 (70.1%)	51 (73.9%)	10 (55.6%)	0.13
Age (years) (M, IQR)	66 (57, 71)	66 (57, 71)	64.5 (58, 73)	0.846
Comorbidities				
Chronic pulmonary disease	3 (3.4%)	2 (2.9%)	1 (5.6%)	0.582
Diabetes mellitus	33 (37.9%)	23 (33.3%)	10 (55.6%)	0.084
Cardiovascular disease	45 (51.7%)	38 (55.1%)	7 (38.9%)	0.241
Chronic kidney disease	6 (6.9%)	5 (7.2%)	1 (5.6%)	0.801
Autoimmune disease	4 (4.6%)	3 (4.3%)	1 (5.6%)	0.828
Hepatopathy	2 (2.3%)	2 (2.9%)	0	0.465
Malignant tumor	10 (11.5%)	8 (11.6%)	2 (11.1%)	0.954
SOFA score	11.5 (9.75, 14)	11 (9, 14)	12 (10, 15.5)	0.339
Apache II score	19 (15, 22)	19 (15, 22)	21 (13.5, 26)	0.815
CPIS score	6 (5, 8)	6 (5, 8)	7 (5.5, 9)	0.345
Prognosis related parameters				
Ventilation day (days)	6.1 (2.6, 10.6)	7 (2.5, 10.5)	4.2 (3.8, 11)	0.797
ICU stay (days)	16 (10, 27)	20 (11, 29)	10 (4, 17.3)	0.004
Hospital stay (days)	20 (10, 28.5)	21 (12, 32)	11.5 (4, 21.3)	0.005

ARDS, acute respiratory distress syndrome; A. baumannii, Acinetobacter baumannii; M, Median; IQR, inter quartile range; SOFA, sequential organ failure assessment; Apache II Score, acute physiology and chronic health evaluation II score; CPIS, clinical pulmonary infection score; ICU, intensive care unit.
P-value for the comparison of survivors and non-survivors according to 28-day mortality.

specificity. $P < 0.05$ was considered statistically significant. The results were expressed as *P*-value and hazard ratio (OR) with 95% confidence interval (CI). IBM SPSS 23.0 software was used for all statistical analyses (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 576 ARDS patients based on the Berlin definition were admitted to our ICU during the study period. There were 364 ARDS patients caused by pulmonary infection; 347 of which were severe enough to receive mechanical ventilation or vasopressor treatment. Cultures from the lower respiratory tract of 131 patients were positive for *A. baumannii*. Among the 131 patients with pulmonary ARDS, 39 were infected with more than one pathogen, three died within 24 h after admission, and two were lost to follow-up. Finally, 87 pulmonary ARDS patients caused by *A. baumannii* pneumonia were enrolled in the study (**Figure 1**).

Baseline Characteristics of Pulmonary ARDS Patients Caused by *A. baumannii*

The median age of these ARDS patients caused by *A. baumannii* was 66 years (IQR 57–71 years), with males accounting for 70.1% (61/87). The 28-day mortality of these patients was 20.7% (18/87), and there were no significant differences in sex, age, and comorbidities between survivors and non-survivors. According to the 28-day mortality, the severity of the disease was slightly higher in non-survival group than that of survival group, as the differences in SOFA core, APACHE II score, and CPIS score at admission were not significant. The ICU and hospital stays were significantly longer in the survivors (20 vs. 10 days, $P = 0.004$, and 21 vs. 11.5 days, $P = 0.005$, respectively) (**Table 1**).

Clinical Characteristics of ARDS Patients Caused by *A. baumannii* Pneumonia

According to the 28-day mortality, there were no significant differences in vital signs and laboratory results between survivors and non-survivors. In terms of respiratory parameters, the PaO_2: FiO_2 (P/F) ratio (198 vs. 178, $P = 0.173$) was lower, the driving pressure (12 vs. 13 cmH_2O, $P = 0.083$) was higher, and the peak airway pressure (21 vs. 24 cmH_2O, $P = 0.016$) was significantly higher in the non-survivor group. As for treatment, the non-survivors received more renal replacement therapy and glucocorticoids (23.2 vs. 55.6%, $P = 0.008$ and 11.6 vs. 33.3%, $P = 0.025$, respectively). There was no significant difference between the two groups in the initial empirical antibiotic treatment, including the use of effective antibiotics against *A. baumannii* and the subsequent targeted anti-infective treatment. There was also no significant difference in the time interval from the empirical treatment to the targeted treatment. One patient in each group changed antibiotics because of adverse effects, which had no effect on the final statistical analysis (**Table 2**).

Comparison of Inflammatory and Immune Parameters in ARDS Caused by *A. baumannii* Pneumonia

According to the 28-day mortality, there was no significant differences in procalcitonin, (1,3)-β-D Glucan, interleukin, Tumor necrosis factor-α and other inflammatory markers, as well as complement and immunoglobulin between the two groups.

TABLE 2 | Clinical characteristics of ARDS caused by *A. baumannii* pneumonia.

	All (*N* = 87)	Survivors (*N* = 69)	Non-survivors (*N* = 18)	*P*
Vital signs at admission				
Temperature (°C)	37.5 ± 0.7	37.6 ± 0.7	37.4 ± 0.9	0.345
Heart rate (per minute)	108 ± 19	107 ± 19	109 ± 21	0.728
MAP (mmHg)	84 ± 13	84 ± 14	86 ± 8	0.453
CVP (mmHg)	9 ± 3	9 ± 3	9 ± 2	0.813
Laboratory test at admission				
Platelet (*10^9/L)	160 ± 69	166 ± 69	91 ± 46	0.319
Creatinine (umol/L)	114 ± 56	117 ± 57	102 ± 53	0.323
TBil (umol/L)	23.9 ± 13.2	23.6 ± 13.0	25.4 ± 13.9	0.601
Albumin (g/L)	33 ± 4	33 ± 4	33 ± 4	0.649
cTnI (ug/L)	3.4 ± 5.7	3.3 ± 5.9	3.5 ± 4.7	0.963
Nt-ProBNP (pg/ml)	6658 ± 8615	6944 ± 9036	5372 ± 6625	0.606
PT (seconds)	16.7 ± 4.9	16.6 ± 5.0	16.9 ± 4.8	0.784
APTT-R	1.8 ± 3.8	1.9 ± 4.3	1.4 ± 0.4	0.555
Lactate (mmol/L)	2.0 ± 2.0	1.9 ± 2.1	2.6 ± 1.9	0.205
ScvO2 (%)	71 ± 8.1	71 ± 7.8	71 ± 9.6	0.956
NLR	12.3 (7.4–19.5)	11.8 (7.4–18.5)	17.4 (8.3–25.6)	0.224
Respiratory parameters at admission				
Tidal volume (ml)	410 (390–440)	410 (400–440)	400 (380–450)	0.4
$PaCO_2$ (mmHg)	39 (34–42)	39 (34.4–42)	38 (31.8–42.3)	0.602
P/F ratio	191 (160–228)	198 (165–229)	178 (155–207)	0.173
PEEP (cmH_2O)	8 (5–10)	8 (5–10)	8 (6–10)	0.324
Ppeak (cmH_2O)	22 (18–24)	21 (18–23)	24 (21.5–26.5)	0.016
Driving pressure (cmH_2O)	12 (10–15)	12 (10–14)	13 (11.5–17.5)	0.083
RR (per minute)	15 (15–18)	15 (15–18)	15 (15–17)	0.642
Treatment strategies				
Vasopressor	73(83.9%)	57 (82.6%)	16 (88.9%)	0.518
RRT	26 (29.9%)	16 (23.2%)	10 (55.6%)	0.008
ECMO	2 (2.3%)	2 (2.9%)	0	0.465
Neuroblockade agent	4 (4.6%)	2 (2.9%)	2 (11.1%)	0.138
RM	13 (14.9%)	10 (14.5%)	3 (16.7%)	0.818
Prone position	29 (33.3%)	24 (34.8%)	5 (27.8%)	0.574
GCs	14 (16.1%)	8 (11.6%)	6 (33.3%)	0.025
Immunosuppressor	1 (1.1%)	1 (1.4%)	0	0.607
Initial empiral antibiotics				
Antibiotics for GNB	84 (96.6%)	67 (97.1%)	17 (94.4%)	0.582
Effective for A.B.	51 (58.6%)	39 (56.5%)	12 (66.7%)	0.436
Antibiotics for GPB	61 (70.1%)	49 (71%)	12 (66.7%)	0.72
Anti-fungal drugs	30 (34.5%)	21 (30.4%)	9 (50%)	0.12
Antiviral drugs	6 (6.9%)	5 (7.2%)	1 (5.6%)	0.801
Virus co-exist	6 (6.9%)	4 (5.8%)	2 (11.1%)	0.428
Candida co-exist	4 (4.6%)	3 (4.3%)	1 (5.6%)	0.828
Target antibiotics				0.671
Tigercycline	56 (64.4%)	43 (62.3%)	13 (72.2%)	
Polymyxins	8 (9.2%)	6 (8.7%)	2 (11.1%)	
Other drugs*	19 (21.8%)	17 (24.6%)	2 (11.1%)	
Duration from admission to target antibiotics (hours)	15 (11–22)	16 (12–22)	12.5 (10.8–23.5)	0.463

ARDS, acute respiratory distress syndrome; A. baumannii (A. B.), Acinetobacter baumannii; MAP, mean arterial blood pressure; CVP, central venous pressure; TBil, total Bilirubin; cTnI, cardiac troponin I; Nt-ProBNP, N-terminal pro brain natriuretic peptide; PT, prothrombin time; APTT-R, activated partial thromboplastin time ratio; $ScvO_2$, Central venous oxygen saturation; NLR, neutrophil to lymphocyte ratio; $PaCO_2$, arterial partial pressure of carbon dioxide; P/F, ratio PaO_2/FiO_2; PEEP, positive end expiratory pressure; Ppeak, peak pressure; RR, respiratory rate; RRT, renal replacement therapy; ECMO, extracorporeal membrane oxygenation; RM, recruitment maneuver; GCs, glucocorticoids; GNB, gram negative bacteria; GPB, gram positive bacteria.

**Antibiotics that were effective for AB in vitro besides Tigercycline and Polymyxins, such as Ampicillin sulbactam, Cefoperazone sulbactam, Amikacin, Ceftazidime averbatan, Minocycline, Carbapenems et al.*

P-value for the comparison of survivors and non-survivors according to 28-day mortality.

TABLE 3 | Inflammatory and immune related markers of ARDS caused by *A. baumannii* pneumonia.

	All	Survivors ($n = 69$)	Non-survivors ($n = 18$)	*P*
Inflammatory markers				
PCT (ng/ml)	8.8 ± 13.7	7.8 ± 12.6	12.9 ± 17.1	0.165
BDG (pg/ml)	160 ± 326	155.3 ± 344	180.8 ± 246.8	0.729
GM test (pg/ml)	0.52 ± 0.87	0.55 ± 0.98	0.43 ± 0.21	0.606
hsCRP (mg/L)	106.9 ± 85.8	111.1 ± 86.4	92.8 ± 84.6	0.443
IL-6 (pg/ml)	100.9 ± 179.6	99.6 ± 193.2	105.5 ± 127.7	0.921
IL-8 (pg/ml)	225.4 ± 343.2	249.7 ± 379.7	138.2 ± 129.9	0.324
IL-10 (pg/ml)	17.2 ± 22.8	15.7 ± 23.4	22.3 ± 20.7	0.38
TNF-a (pg/ml)	28.6 ± 37.2	31.5 ± 40.8	16.7 ± 10.9	0.319
Immune parameters				
C3 (g/L)	0.80 ± 0.23	0.79 ± 0.23	0.85 ± 0.22	0.307
C4 (g/L)	0.18 ± 0.07	0.17 ± 0.07	0.20 ± 0.09	0.132
IgG (g/L)	10.8 ± 3.9	10.7 ± 3.6	11.1 ± 4.8	0.719
IgA (g/L)	2.6 ± 1.2	2.6 ± 1.3	2.8 ± 0.9	0.429
IgM (g/L)	0.95 ± 0.53	0.92 ± 0.5	1.1 ± 0.6	0.297
Lymphocyte subsets (cells/ul)				
White blood cell	13474 ± 8080	13584 ± 8743	13061 ± 5059	0.809
Neutrophil	11769 ± 7665	11659 ± 8170	12194 ± 5475	0.794
Monocyte	580 ± 372	559 ± 349	668 ± 459	0.299
Lymphocyte	963 ± 532	1016 ± 526	765 ± 525	0.084
B lymphocyte	206 ± 250	193 ± 221	252 ± 341	0.375
NK T cell	77 ± 72	84 ± 75	51 ± 49	0.087
T lymphocyte	671 ± 372	729 ± 364	452 ± 322	0.004
$CD4^+$ T cell	419 ± 252	443 ± 250	332 ± 245	0.095
$CD4^+CD28^+$ T cell	404 ± 245	427 ± 248	318 ± 221	0.097
$CD8^+$ T cell	221 ± 185	253 ± 191	104 ± 94	0.002
$CD8^+CD28^+$ T cell	117 ± 83	132 ± 83	59 ± 58	0.001
Memory $CD4^+$ T	292 ± 169	311 ± 162	221 ± 182	0.067
$45RA^+CD4^+$ T	126 ± 114	132 ± 119	103 ± 89	0.348
Naïve $CD4^+$ T	118 ± 106	124 ± 111	96 ± 88	0.324
$CD8^+DR^+$ T	131 ± 161	151 ± 174	58 ± 61.9	0.029
$CD8^+CD38^+$ T	128 ± 159	151 ± 172	44 ± 36	0.011
$CD4^+$ T/$CD8^+$ T	2.9 ± 1.4	2.5 ± 2.2	4.0 ± 2.8	0.018

ARDS, acute respiratory distress syndrome; A. baumannii, Acinetobacter baumannii; PCT, procalcitonin; BDG, (1,3)-β-D Glucan; GM, test Galactomannan test; hsCRP, hypersensitive C-reactive protein; IL, interleukin; TNF-a, tumor necrosis factor-a; C3, complement 3; Ig, immunoglobulin; NK T cell, natural killer T cell.
P-value for the comparison of survivors and non-survivors according to 28-day mortality.

TABLE 4 | Cox regression of lymphocyte subsets related parameters and survival.

	B	SE	Wald	OR	95%CI	*P*-value
$CD8^+$ T cell count (cells/ul)	1.3	0.438	8.789	3.667	1.553, 8.659	0.003
$CD8^+CD28^+$ T count (cells/ul)	2.043	0.723	7.992	7.714	1.871, 31.801	0.005
$CD8^+CD38^+$ T count (cells/ul)	0.995	0.436	5.222	2.705	1.152, 6.353	0.022

SE, standard error of the mean; OR, odds ratio; 95% CI, 95% confidence interval.

As for lymphocyte subsets: there was no significant difference in the total number of leukocytes and neutrophils between the two groups. The number of T cells (452 ± 322 vs. 729 ± 364/μl, $P = 0.004$), especially $CD8^+$ T cells (104 ± 94 vs. 253 ± 191/μl, $P = 0.002$) was significantly lower in non-survivors than in survivors. The total number of lymphocytes and $CD4^+$ T cells was also lower in non-survivors (765 ± 525 vs. 1,016 ± 526/μl, $P = 0.084$ and 332 ± 245 vs. 729 ± 364/μl, $P = 0.011$ respectively) (**Table 3**).

Parameters Associated With 28-Day Mortality

To clarify the factors independently associated with 28-day mortality, A cox proportional hazards model were performed. SOFA score, lactate level, P/F ratio and driving pressure that had been confirmed to be related to survival were included in the model as well as the parameters that were significantly different between the survivors and non-survivors in our study (Ppeak,

RRT and Glucocorticoids use). Lymphocyte related parameters were also included in the model separately. $CD8^+$ T cell count and its subtypes were independent factors associated with 28-day mortality of ARDS caused by *A. baumannii* pneumonia ($CD8^+$ T cell count: OR 3.667, 95% CI 1.553–8.659, $P = 0.003$; $CD8^+CD28^+$ T cell count: OR 2.043, 95% CI 1.871–31.801, $P = 0.005$; $CD8^+CD38^+$ T cell count: OR 2.705, 95% CI 1.152–6.353, $P = 0.022$) (**Table 4**).

To further analyze the influence of lymphocyte subsets related parameters that differed significantly between survivors and non-survivors in the univariate analysis on prognosis, ROC curve analysis was performed. The $CD8^+$ T cell count had the greatest discriminatory ability, with an area under the curve of 0.812. A cutoff value of 123 cells/μl at ICU admission was predictive of 28-day mortality for ARDS caused by *A. baumannii* with a sensitivity of 74.6% and specificity of 83.3% ($P < 0.0001$) (**Figure 2**).

Furthermore, we divided these ARDS patients into two groups according to the $CD8^+$ T cell count (<123 and ≥ 123 cells/μl). the accumulative survival rate from the Kaplan-Meier curve was significantly lower and ventilation free day was significantly shorter (14.5 vs. 21 days, $P = 0.001$) in patients with a lower $CD8^+$ T cell count, while 28-day mortality was significantly higher than that in patients with a higher $CD8^+$ T cell count (46.9 vs. 5.7%, $P < 0.0001$). The patients with lower $CD8^+$ T cell counts had lower P/F ratio, higher driving pressure at admission. The NLR, PCT level and CPIS at admission were also higher in patients with a lower $CD8^+$ T cell count (**Table 5**, **Figures 3A–E**). We divided the cohort into different severity of ARDS according to admission P/F ratio and found that patients with increasing severity of ARDS had progressively lower $CD8^+$ T cell counts (**Figure 4**).

DISCUSSION

To our knowledge, this is the first clinical study exploring the early alterations of lymphocyte subsets in ARDS caused by *A. baumannii* pneumonia. 28-day mortality of these patients was 20.7%. The T cell count, especially for $CD8^+$ T cells, at admission was independently associated with 28-day mortality. The $CD8^+$ T cell count was an early predictive marker for prognosis. So far, studies about *A. baumannii* and immunity have been limited to basic research, and there are limited data for clinical use. Our study first confirmed that T cell immunity might play an important role in ARDS caused by *A. baumannii* pneumonia, which could be important for clinical practice.

Immune disorder is the characteristic manifestation of sepsis, and increasing evidence shows that the immune system plays a bridging role between severe infection, organ damage and prognosis. However, the current view of how the two most complex syndromes, systemic inflammatory response syndrome and immune response syndrome, affect each other is still rudimentary (14, 15). The first step is to clarify the relationship between certain diseases and immune responses. There is a profound relationship between NLR and sepsis, NLR and ARDS, the $CD4^+$ T cell count and carbapenem-resistant Enterobacteriaceae (CRE) infection (16), and there has been growing interest in identifying biological sub-phenotypes of ARDS patients with similar host-response features for prognostic enrichment (3). Basic immunological research into *A. baumannii* infection is in full swing, along with research into the mechanism of host defense against the infection. For example, there has been in-depth study of outer membrane protein A (5, 17). However, there has been little clinical research on the relationship between immunity to *A. baumannii* infection and prognosis. In this study, we found that the $CD8^+$ and $CD8^+CD28^+$ T cell counts were independently associated with 28-day mortality in ARDS patients caused by *A. baumannii*. Clinically, this is the first-time providing evidence of Acinetobacter baumannii causing intracellular infection, which makes the understanding of this aspect go further.

A variety of immune cells are involved in resistance to ARDS caused by *A. baumannii* pneumonia (18). Large numbers of *A. baumannii* are taken up by alveolar macrophages as early as 4 h after infection. NK T cells are another cell type that act during the immune response against *A. baumannii*. Depletion of NK T cells in a murine pneumonia model caused impaired bacterial clearance and increased mortality. We found that the NK T cell count in non-survivors was lower than in survivors, which was consistent with previous research (19). DCs are the bridge between innate and adaptive immune responses, $CD4^+$ T cells differentiate toward a Th_1-polarizing phenotype through the activation of DCs (5). Subsequently, $CD4^+$ T-helper cells support the production of specific antibodies by B cells and promote the bactericidal activity of phagocytes that together clear the infection. Our previous study also illustrated that the $CD4^+CD28^+$ T cell count was a useful marker for early diagnosis of CRE infection and outcome prediction (16). It was not surprising to see that innate immune cells were involved in the defense against *A. baumannii*, but with the ability to cause intracellular infection, *A. baumannii* pneumonia should induce cellular immunity response. However, the relationship between the $CD8^+$ T cell count and *A. baumannii* has rarely been studied before (6). For the first time, our study illustrated the association between $CD8^+$ T cells and ARDS caused by *A. baumannii* pneumonia. The possible mechanisms were as follows: (1) *A. baumannii* directly invaded alveolar epithelial cells, and cytotoxic $CD8^+$ T cells directly recognized and killed infected epithelial cells (8); and (2) in addition to $CD8^+$ T cells, the $CD8^+CD38^+$ T cells also differed significantly between survivors and non-survivors with *A. baumannii* infection. Inflammatory reaction, antigen exposure and environmental factors have been shown to allow differentiation of the NK-like $CD8^+$ T cells. Therefore, $CD8^+$ cells may also act indirectly against *A. baumannii* infection, which could be important for improving protective immunity (20). Further laboratory and clinical studies are needed to explore the specific mechanism of $CD8^+$ T cells in *A. baumannii* infection.

Our study showed that the $CD8^+$ T cell count was an independent risk factor for 28-day mortality of ARDS caused by *A. baumannii* pneumonia, which could be explained by the difference in physical and biological sub-phenotypes

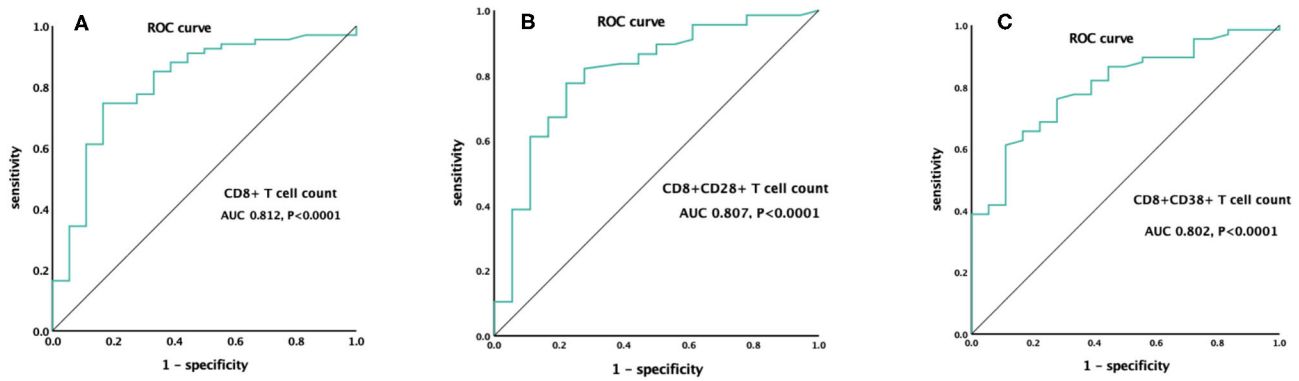

FIGURE 2 | ROC curve of $CD8^+$ T cell count **(A)**, $CD8^+CD28^+$ T cell count **(B)**, and $CD8^+CD38^+$ T cell count **(C)** for the prediction of 28-day mortality.

TABLE 5 | Comparison of ARDS patients with different $CD8^+$ T cell counts.

	$CD8^+$ T cell ≥123 ($n = 53$)	$CD8^+$ T cell<123 ($n = 32$)	*P*
Respiratory parameters of D1			
Tidal volume (ml)	410 (392–448)	400 (380–440)	0.428
PEEP (cmH_2O)	8 (5–9.5)	8 (6–10)	0.222
Ppeak (cmH_2O)	20.5 (18–23)	23 (20–25)	0.002
Driving pressure (cmH_2O)	11 (10–13)	14 (12–17)	<0.0001
RR (per minute)	21 (18–23)	23 (20–25)	0.018
P/F ratio	198 (171–235)	178 (157–212)	0.104
$PaCO_2$ (mmHg)	38 (34–42)	39 (33–42)	0.978
Inflammatory markers of D1			
NLR	10.1 (5.9–15.1)	19.2 (12.5–29.1)	<0.0001
PCT (ng/ml)	5.8 ± 11.3	12.8 ± 15.5	0.022
IL-6 (pg/ml)	120.4 ± 219.7	72.3 ± 96.1	0.35
IL-8 (pg/ml)	211.4 ± 317.2	234.3 ± 391	0.814
IL-10 (pg/ml)	18.3 ± 26.8	15.7 ± 15.6	0.692
TNF-a (pg/ml)	33.4 ± 44.6	19.3 ± 19.9	0.256
Other parameters			
CPIS	6 (4–7)	8 (7–9)	<0.0001
SOFA	11 (9–14)	12 (10–14)	0.271
Apache II score	18 (15–22)	20.5 (14–25.3)	0.774
Ventilation day (days)	5.5 (2.5–11)	6.6 (4–10.3)	0.586
28-day ventilation free day (days)	21 (16–25.5)	14.5 (0–20.9)	0.001
28-day Mortality	3 (5.7%)	15 (46.9%)	<0.0001

ARDS, acute respiratory distress syndrome; D1, the day at admission; D3, 3 days after admission; PEEP, positive end expiratory pressure; Ppeak, peak pressure; RR, respiratory rate; P/F ratio, PaO_2:FiO_2; PaCO2 arterial partial pressure of carbon dioxide; NLR, neutrophil to lymphocyte ratio; PCT, procalcitonin; IL, interleukin; TNF-a, tumor necrosis factor-a; CPIS, clinical pulmonary infection score; SOFA, sequential organ failure assessment; Apache II, Score acute physiology and chronic health evaluation II score.
P-value for the comparison of patients with higher (≥123cells/ul) and lower (<123cells/ul) $CD8^+$ T cell count.

of ARDS patients (3). From the perspective of biological phenotype, multiple large clinical ARDS trials used P/F ratio and driving pressure for prognostic enrichment. The $CD8^+$ T cell count was significantly associated with P/F ratio in ARDS caused by *A. baumannii* pneumonia and stratified according to P/F ratio. The proportion of patients with a lower $CD8^+$ T cell count was significantly higher in severe ARDS patients. The $CD8^+$ T cell count was also significantly associated with driving pressure, and patients with a lower T cell count needed higher driving pressure. Both severity of ARDS and driving pressure were strongly associated with survival rate (2, 21). From the perspective of biological phenotype, this might be related to the intensity of local inflammatory response. T cells, especially $CD8^+$ T cells, were significantly decreased in non-survivors, resulting in a significant increase in NLR. The adaptive immune response to *A. baumannii* was reduced, while the non-specific innate immunity mainly composed of neutrophils was enhanced, which

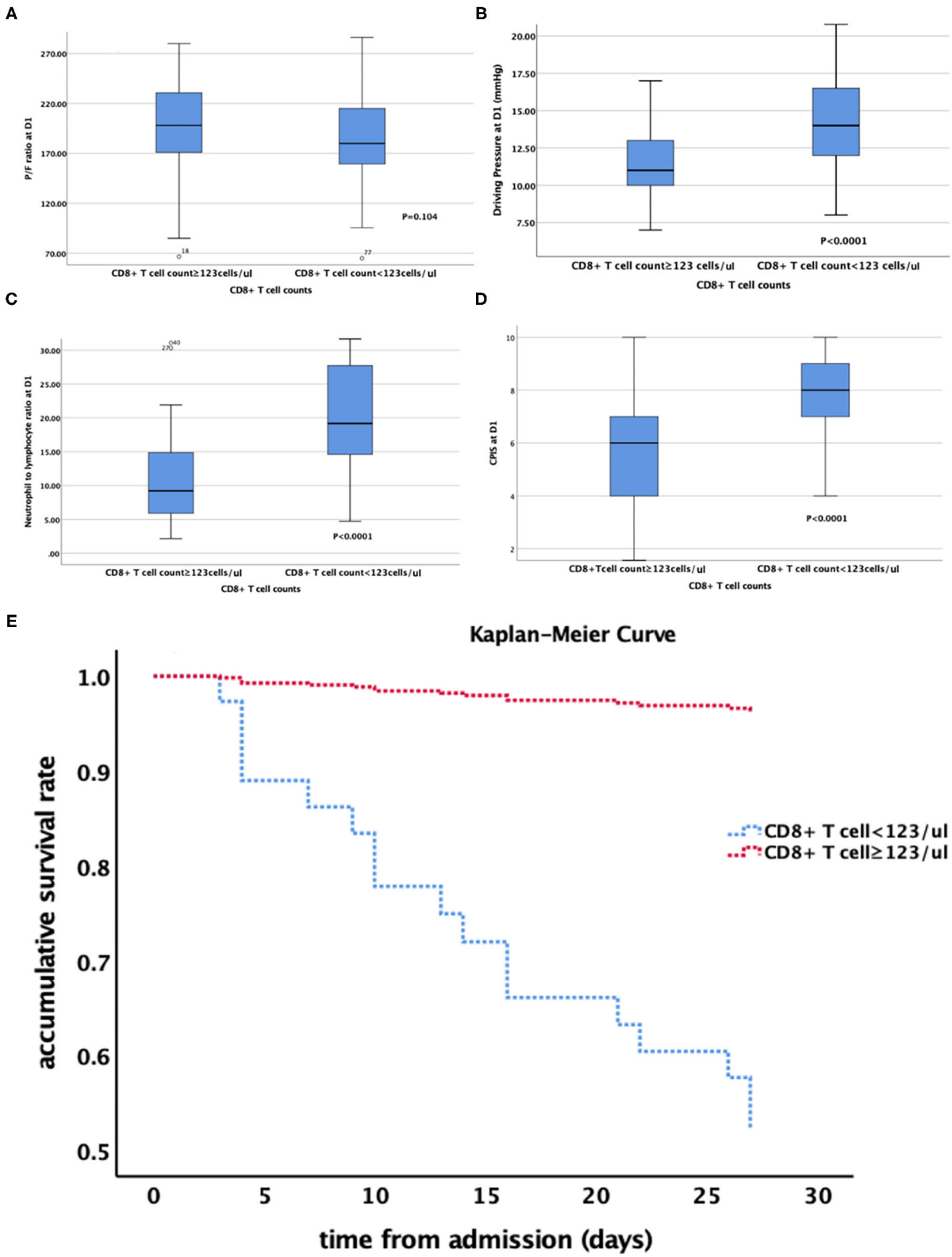

FIGURE 3 | (A–E) relationship between $CD8^+$ T cell count and **(A)** P/F ratio; **(B)** Driving Pressure; **(C)** Neutrophil to lymphocyte ratio; **(D)** CPIS. **(E)** the Kaplan-Meier curve of patients with different $CD8^+$ T cell counts. P/F ratio at D1 PaO_2:FiO_2 at admission; CPIS, clinical pulmonary infection score.

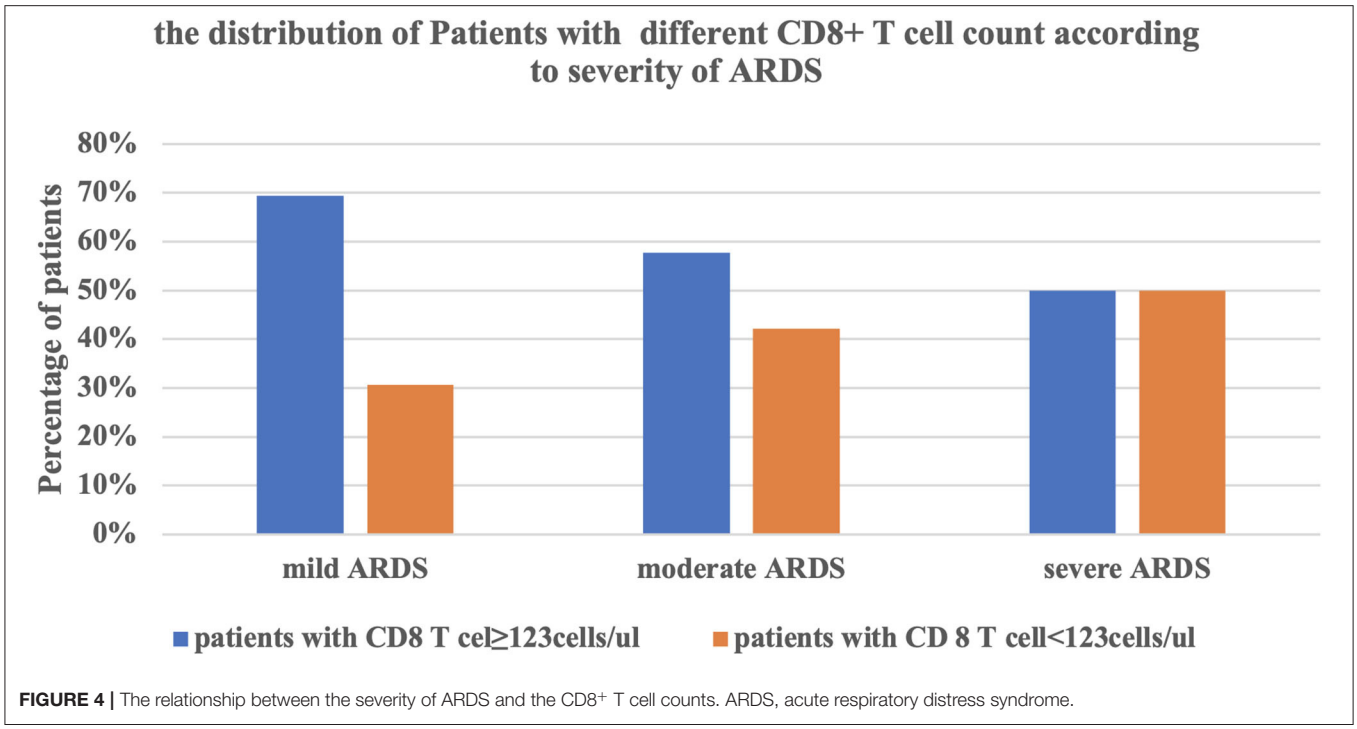

FIGURE 4 | The relationship between the severity of ARDS and the $CD8^+$ T cell counts. ARDS, acute respiratory distress syndrome.

led to enhancement of the local pro-inflammatory response, manifesting as higher CPIS.

There were several limitations to this study. First, the study lasted almost 3 years with extremely strict inclusion criteria. Only septic patients with ARDS whose only pathogen was *A. baumannii* were enrolled, and they needed to receive mechanical ventilation or vasopressor treatment for enrollment. Despite the relatively small sample size, it was large enough to illustrate the role of lymphocytes, especially $CD8^+$ T cells in patients with ARDS caused by *A. baumannii*. Second, the serum lymphocyte count might not be able to reflect the local infection situation. We need to further study the cell subgroup analysis of bronchoalveolar lavage fluid (BALF). However, there are challenges because, at present, the cell classification of BALF cannot be quantified as in routine blood tests, and there is no normal reference range for the cell classification; both of which need further research. Last, one key element that stands out from the existing studies is how much strain-to-strain variation of *A. baumannii* influences the interaction with host cells and observed phenotypes *in vivo*. A deeper understanding of the virulence factors of *A. baumannii* that are important for *in vivo* pathogenesis is needed (1).

CONCLUSIONS

Lower CD8+ T cell count was associated with higher severity and early mortality in ARDS patients caused by A. *baumannii* pneumonia, which could be valuable for outcome prediction.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of PUMCH (approval number: JS-1170). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WC and NC contributed to the conception of the study, data interpretation, and drafted the manuscript. HW, JZ, DL, GB, WH, and JC contributed to data collection and critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

FUNDING

This work was supported by National Natural Science Foundation of China (Nos. 82072226 and 81601657), Beijing Municipal Science and Technology Commission (No. Z201100005520049), Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (No. 2019XK320040), Tibet Natural Science Foundation [No. XZ2019ZR-ZY12(Z)], and Excellence Program of Key Clinical Specialty of Beijing in 2020 (No. ZK128001).

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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.

frontiers in Medicine

ORIGINAL RESEARCH
published: 12 November 2021
doi: 10.3389/fmed.2021.752508

Automatic Adjustment of the Inspiratory Trigger and Cycling-Off Criteria Improved Patient-Ventilator Asynchrony During Pressure Support Ventilation

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Background: Patient-ventilator asynchrony is common during pressure support ventilation (PSV) because of the constant cycling-off criteria and variation of respiratory system mechanical properties in individual patients. Automatic adjustment of inspiratory triggers and cycling-off criteria based on waveforms might be a useful tool to improve patient-ventilator asynchrony during PSV.

Method: Twenty-four patients were enrolled and were ventilated using PSV with different cycling-off criteria of 10% (PS_{10}), 30% (PS_{30}), 50% (PS_{50}), and automatic adjustment PSV (PS_{AUTO}). Patient-ventilator interactions were measured.

Results: The total asynchrony index (AI) and NeuroSync index were consistently lower in PS_{AUTO} when compared with PS_{10}, PS_{30}, and PS_{50}, ($P < 0.05$). The benefit of PS_{AUTO} in reducing the total AI was mainly because of the reduction of the micro-AI but not the macro-AI. PS_{AUTO} significantly improved the relative cycling-off error when compared with prefixed controlled PSV ($P < 0.05$). PS_{AUTO} significantly reduced the trigger error and inspiratory effort for the trigger when compared with a prefixed trigger. However, total inspiratory effort, breathing patterns, and respiratory drive were not different among modes.

Conclusions: When compared with fixed cycling-off criteria, an automatic adjustment system improved patient-ventilator asynchrony without changes in breathing patterns during PSV. The automatic adjustment system could be a useful tool to titrate more personalized mechanical ventilation.

Keywords: automatic adjustment system, pressure support ventilation, patient-ventilator asynchrony, cycling-off, trigger

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

Received: *03 August 2021*
Accepted: *11 October 2021*
Published: *12 November 2021*

Citation:
Liu L, Yu Y, Xu X, Sun Q, Qiu H, Chiumello D and Yang Y (2021) Automatic Adjustment of the Inspiratory Trigger and Cycling-Off Criteria Improved Patient-Ventilator Asynchrony During Pressure Support Ventilation. Front. Med. 8:752508. doi: 10.3389/fmed.2021.752508

INTRODUCTION

Pressure support ventilation (PSV) is the most widely used partial mode of assistance to minimize the effort of patients in breathing. During PSV, the assist is delivered by means of a pneumatic signal generated by patient effort and measured in the ventilatory circuit, i.e., flow or pressure (1). The ventilator usually cycles from inspiration to expiration when the inspiratory flow falls to a predetermined fraction of the peak inspiratory flow, which is the cycling-off criterion (2). Ideally, the ventilator trigger and cycling should coincide with the beginning and the end of the inspiratory effort of the patients (3). However, patient-ventilator asynchrony is common during PSV (4, 5), thereby contributing to the increased patient effort, increased duration of mechanical ventilation, and even increased mortality (6).

During PSV, prefixed pneumatic controllers can become progressively less effective, especially when patients have abnormal respiratory mechanics or ventilator over-assist (7). Delayed or missed triggers are sensed as an uncomfortable isometric load leading to increased effort intensity and pronounced dyspnea (8). Moreover, with prefixed cycling-off criteria, such as the default value of 30% peak flow in some ventilators, premature cycling is more frequent in patients with restrictive breathing patterns characterized by low respiratory system compliance and may result in double triggering. Delayed cycling occurs more frequently in patients with an obstructive pattern characterized by high resistance (6, 9). Different approaches for optimal ventilator triggering and cycling have been developed to minimize these problems, such as flow-triggering sensitivity and adjustable flow cycling during PSV.

It has been demonstrated that a noninvasive method based on flow and airway-pressure tracings was effective for detecting asynchrony (10–12). Therefore, an automatic adjustment system (IntelliCycleTM2.0) capable of automatically adjusting, breath by breath, the triggering and cycling-off criteria based on pressure-time and flow-time waveforms during PSV have been developed (see **Supplementary Material**).

The objective of our study was to show a reduction in patient-ventilator asynchrony with the use of an automatic adjustment system as compared with prefixed trigger and cycling-off criteria in patients with PSV.

METHODS

This unblinded crossover study was conducted in a 60-bed general intensive care unit of a teaching hospital affiliated with Southeast University in China. The protocol was approved by the Institutional Ethics Committee of Zhongda Hospital (number 2016ZDSYLL067-P01). Written informed consent was obtained from the legal primary decision-maker, which was the spouse of the patient or the parent or child if no spouse. The trial was registered at clinicaltrials.gov (NCT04091269).

Patients

Postoperative (abdominal surgery or orthopedic surgery) or acute respiratory failure patients were eligible when meeting all the following criteria: receiving invasive mechanical ventilation and being able to sustain PSV more than 1 h with inspiratory support $\leq$ 15 cm H_2O. Patients were excluded if (1) age $<$ 18 or $>$85 years; (2) tracheostomy at time of the study; (3) sedation level on the Richmond Agitation–Sedation Scale ≤ -2 or ≥ 2; (4) contraindication for nasogastric tube insertion, e.g., history of esophageal varices, gastroesophageal surgery in the previous 12 months, or gastroesophageal bleeding in the previous 7 days, international standard ratio $>$ 1.5, activated partial thromboplastin time $>$ 44 s, history of leukemia (13); and (5) hemodynamic instability (heart rate $>$ 140 beats/min, vasopressors required with $\geq$ 5 μg/kg/min dopamine/dobutamine, or $\geq$ 0.2 μg/kg/min norepinephrine).

Study Protocol

After obtaining consent, enrolled patients were switched to a Servo-i ventilator (Maquet, Solna, Stockholm, Sweden). A 16-F nasogastric feeding tube (NeuroVent Research Inc., Toronto, ON, Canada) with electrodes measuring the electrical activity of the diaphragm (EAdi) and balloons measuring esophageal (Pes) pressures was inserted through the nose and secured after confirming positioning according to the recommendations of the manufacturer. Static respiratory system compliance (C_{RS}), resistance (R_{RS}), and intrinsic positive end-expiratory pressure (PEEPi) were measured during volume control ventilation (without spontaneous drive) (see **Supplementary Material**).

Then sedation was decreased to maintain light sedation with the Richmond Agitation–Sedation Scale ranging from 0 to −2. As spontaneous breathing and EAdi recovered, patients were switched to an SV800 ventilator with IntelliCycleTM2.0 which can automatically adjust triggering and cycling-off criteria breath-by-breath, (Mindray, Shenzhen, China) and were ventilated by PSV with the pressure support level adjusted to a target tidal volume (V_T) of 6 ml/kg (of predict body weight, PBW). During the entire recording period, PEEPe and a fraction of inspired oxygen (FiO_2) were maintained as set by the clinician in charge of the patient.

During prefixed pneumatically controlled PSV, the inspiratory trigger was set at 1.5 L/min for flow triggering, and the rate of rise in pressure was set to 0.05 s in all patients. The cycling-off criteria were set to 10% (PS_{10}), 30% (PS_{30}), and 50% (PS_{50}). During automatic adjustment PSV, the inspiratory trigger was set as flow-trigger 1.5 L/min, the rate of rise in pressure was set to 0.05 s, and the cycling-off criterion was set to "AUTO" (PS_{AUTO}). Both the trigger and cycling-off criteria were adjusted by the automatic adjustment system according to an established algorithm based on the pressure-time and flow-time waveforms (**Supplementary Figures 1**, **2**). First, patients were ventilated with four independent modes (PS_{10}, PS_{30}, $PS_{50,}$ and PS_{AUTO}) applied in randomized order (**Supplementary Table 1**). Each independent condition was maintained for 20 min without washout periods (**Supplementary Figure 3**).

Data Acquisition and Analysis

Flow, airway pressure (P_{aw}), esophageal pressure (P_{es}), and EAdi were acquired during the 20-min time window in each condition at 100 Hz from the ventilator *via* an RS 232 interface connected to a computer. Data were stored for later offline

analysis (NeuroVent Research Inc., Toronto, ON, Canada). To quantify patient-ventilator interaction, all variables were calculated manually breath by breath from a stable 3-min period in each condition using customized software (NeuroVent Research Inc., Toronto, ON, Canada) by two independent researchers who were blinded to the patient number and assigned order of crossover treatments, and mean values were calculated. In the event of a mismatch, a third researcher was consulted.

Six types of asynchrony were analyzed as previously described by Thille et al. and Lamouret et al. (6, 14). Macro asynchronies include ineffective triggering, which is defined by the existence of a diaphragmatic signal without a respiratory cycle; auto-triggering is defined by the existence of a ventilator cycle without a diaphragmatic signal; and double triggering is defined by the presence of two successive inspiratory cycles without an intermediate expiration or with an interrupted expiration. Micro-asynchronies are defined by a time difference exceeding 200 ms between the onset of the EAdi and the early initial rise in Paw; between the 70% of peak EAdi and early decrease in airway pressure (the opening of the expiratory valve)-late cycling; and between the decrease in airway pressure and 70% of peak EAdi-premature cycling. For each subtype of asynchrony, a percentage of asynchronies was calculated as follows: the number of asynchrony events divided by the total neural respiratory rate (which corresponds to the total EAdi signals) × 100%. Macro-asynchrony index (AI), micro-AI, and total AI were calculated as the number of macro asynchrony events, micro-asynchrony, or total asynchrony events divided by the neural respiratory rate × 100%.

Triggering and cycling-off errors, which were classified as either too late (positive values) or too early (negative values) (13), breathing pattern, inspiratory effort, and inspiratory effort for triggering were measured (see **Supplementary Material**). To estimate the overall extent of asynchrony and dys-synchrony, the NeuroSync index was calculated by averaging the percentage errors in triggering and cycling-off for all breaths (13). The primary endpoint was the difference in the total AI between PS_{AUTO} and PSV with prefixed triggering and cycling-off criteria (PS_{10}, PS_{30}, and PS_{50}).

Statistical Analysis

All statistical analyses were carried out using SPSS 20 (Chicago, IL, USA). The values are stated as mean ± SD unless specified otherwise. Data from two *post-hoc* subgroups, a restrictive subgroup defined as having $C_{RS} < 40$ ml/cm H_2O with $R_{RS} < 12$ cm H_2O/LS, and an obstructive subgroup, defined as having $R_{RS} > 12$ cm H_2O/LS with $C_{RS} > 40$ ml/cm H_2O, were analyzed. The normal distribution of continuous variables was assessed by using the Shapiro–Wilk test. Log-transformation was used for skewed data. Variables were compared between modes using repeated-measures ANOVA followed by Bonferroni's *post-hoc* test. Categorical data were compared by the chi-square test followed by Bonferroni's *post-hoc* test. *P*-values <0.05 were considered significant.

TABLE 1 | Patient characteristics.

Parameter	All (*n* = 24)	Obstructive subgroup (*n* = 8)	Restrictive subgroup (*n* = 8)	Other patients (*n* = 8)
Sex, male/female	19/5	5/3	7/1	7/1
Age, year	68 ± 17	75 ± 9	65 ± 17	68 ± 23
APACHE II	17.1 ± 5.3	17.9 ± 4.0	18.7 ± 6.0	14.8 ± 6.5
Main diagnosis				
Pneumonia, *n* (%)	4 (16.7%)	–	4 (50%)	
Extrapulmonary sepsis, *n* (%)	2 (8.3%)	–	2 (25%)	
AECOPD, *n* (%)	8 (33.3%)	8 (100.0%)	–	
Abdominal surgery	4 (16.7%)	–	–	4 (50.0%)
Orthopedic surgery, *n* (%)	4 (16.7%)	–	–	4 (50.0%)
Severe trauma, *n* (%)	2 (8.3%)		2 (25%)	
RASS	0 (−1, 0)	0 (−1, 0)	−1 (−2, 0)	0 (−1, 0)
PBW, Kg	63 ± 8	63 ± 7	59 ± 9	65 ± 7
PaO_2, mm Hg	107 ± 36	96 ± 30	95 ± 16	135 ± 42
PaO_2/FiO_2	276 ± 90	362 ± 78	239 ± 76	227 ± 41
$PaCO_2$, mm Hg	39 ± 11	48 ± 14	36 ± 6	32 ± 4
pH	7.41 ± 0.06	7.39 ± 0.05	7.43 ± 0.03	7.41 ± 0.06
C_{RS}, ml/cm H_2O	45.8 ± 9.7	50.9 ± 5.8	34.1 ± 5.1	52.5 ± 3.5
R_{RS}, cm H_2O/L/S	12.1 ± 4.9	17.9 ± 4.1	9.2 ± 2.1	9.4 ± 1.7
PEEPi, cm H_2O	1.7 ± 2.0	3.6 ± 2.4	0.9 ± 0.2	0.7 ± 0.7

Data are provided as mean ± SD or median (interquartile range).

APACHE II, Acute Physiology and Chronic Health Evaluation II; RASS, Richmond Agitation-Sedation Scale; PBW, predictive body weight; C_{RS}, static compliance of the respiratory system; R_{RS}, resistance of respiratory system; PEEPi, static intrinsic positive end expiratory pressure.

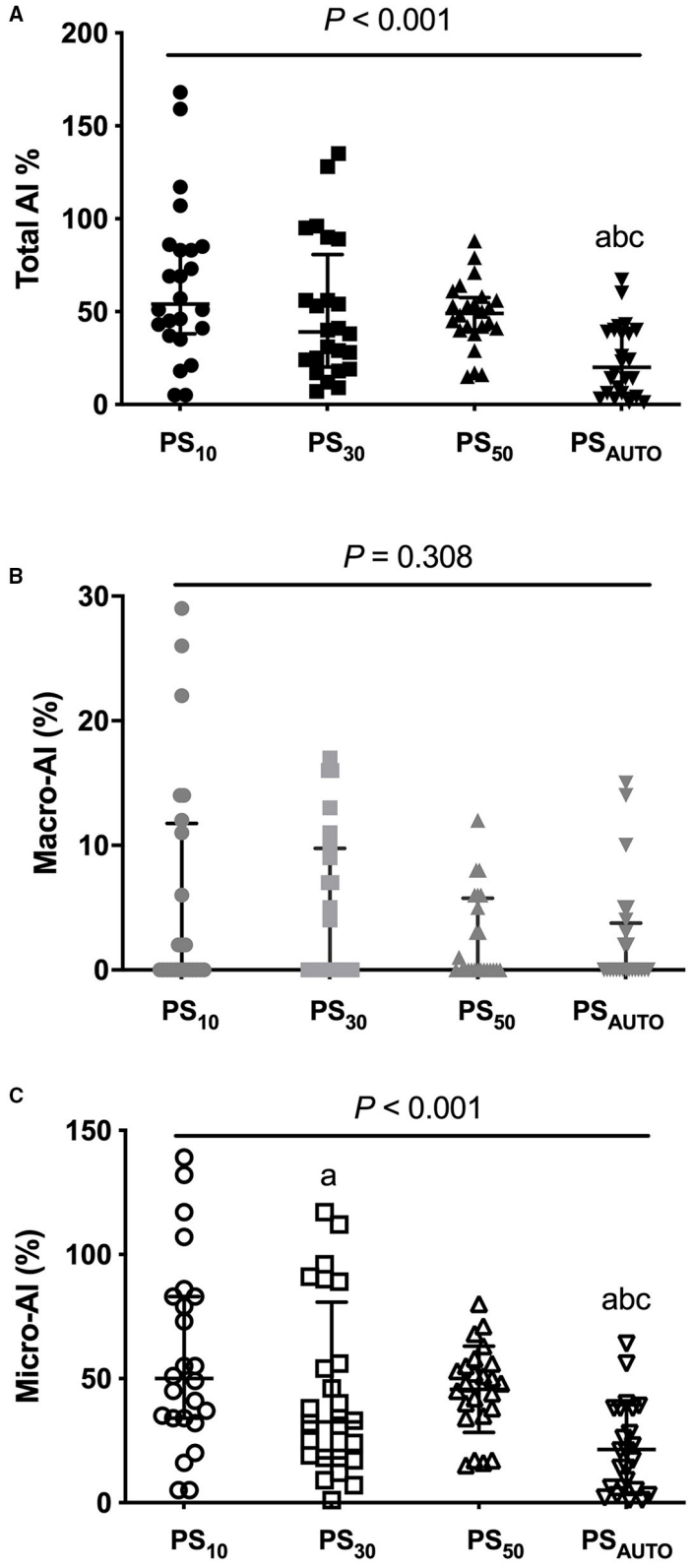

FIGURE 1 | Total AI **(A)**, macro-AI **(B)**, and micro-AI **(C)** in different modes. AI, asynchrony index; $PS_{10,}$ pressure support ventilation with cycling-off criteria set to 10%; $PS_{30,}$ pressure support ventilation with cycling-off criteria set to 30%; $PS_{50,}$ pressure support ventilation with cycling-off criteria set to 50%; $PS_{AUTO,}$ pressure support ventilation with automatic. Gray lines showed median (interquartile range). Compared with PS_{10}, $^{a}P < 0.05$; Compared with PS_{30}, $^{b}P < 0.05$; compared with PS_{50}, $^{c}P < 0.05$.

TABLE 2 | Asynchronies, NeuroSync index, inspiratory effort, and relative timing errors of cycling-off and trigger in different modes.

Parameters	PS_{10}	PS_{30}	PS_{50}	PS_{AUTO}	*P* value
Ineffective triggering, %	0.0 (0.0, 2.3)	0.0 (0.0, 0.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.4)	0.118
Auto-triggering, %	0.0 (0.0, 0.0)	0.0 (0.0, 3.3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.039
Double triggering, %	0.0 (0.0, 6.7)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.569
Premature cycling-off, %	0.0 (0.0, 2.6)	0.0 (0.0, 1.8)	5.4 (0.0, 22.5)[b]	0.0 (0.0, 1.8)[c]	<0.001
Late cycling-off, %	7.1 (0.0, 28.1)	1.8 (0.0, 20.8)	0.0 (0.0, 0.0)[a]	0.0 (0.0, 0.0)[a]	<0.001
Inspiratory trigger delay, %	38.3 (22.4, 48.9)	25.9 (11.4, 47.1)	30.3 (16.3, 45.6)	19.0 (5.0, 31.3)[abc]	<0.001
NeuroSync index, %	15.3 ± 8.2	13.3 ± 6.7[a]	13.1 ± 4.8	9.7 ± 4.4[abc]	<0.001
"Perfect" synchrony breath, %	18.5 (16.4, 20.7)	21.9 (19.5, 24.2)[a]	19.7 (17.5, 21.9)	42.2 (39.5, 44.9)[abc]	<0.001
"Acceptable" synchrony breath, % (95% CI)	81.1 (78.9, 83.2)	87.9 (86.0, 89.7)[a]	89.5 (87.8, 91.2)[a]	94.8 (93.5, 96.0)[abc]	<0.001
$PTP_{es-Trig}$, $cmH_2O.S.min^{-1}$	−3.1 (−6.0, −1.1)	−2.3 (−4.1, −1.1)	−2.0 (−3.6, −1.1)[a]	−1.9 (−3.7, −0.8)[ab]	<0.001
PTP_{es}, $cmH_2O.S.min^{-1}$	−17.1 (−88.2, −13.1)	−38.7 (−71.3, −10.6)	−40.8 (−58.0, −8.9)	−37.4 (−61.2, −9.1)	0.802

Data are provided as mean ± SD or median (interquartile range).
NeuroSync index is an overall indicator of patient-ventilator interaction, where 0% error, perfect; 100% error, zero patient-ventilator interaction; $PTP_{es-Trig}$, Pre-trigger Pes-time product; PTP_{es}, Pes-time product; PS_{10}, pressure support ventilation with cycling-off criteria set to 10%; PS_{30}, pressure support ventilation with cycling-off criteria set to 30%; PS_{50}, pressure support ventilation with cycling-off criteria set to 50%; PS_{AUTO}, pressure support ventilation with automatic adjustment system; CI, Confidence interval, "perfect" synchrony, relative timing errors of triggering and for cycling-off ≤10% of neural timings, "acceptable" synchrony, relative timing errors of triggering and for cycling-off ≤10% of neural timings.
Compared with PS_{10}, [a]$P < 0.05$; Compared with PS_{30}, [b]$P < 0.05$; Compared with PS_{50}, [c]$P < 0.05$.

RESULTS

The study included 24 patients, such as eight patients in the restrictive subgroup, eight patients in the obstructive subgroup, and eight other patients without obvious acute respiratory failure (C_{RS} > 40 ml/cm H_2O with R_{RS} < 12 cm H_2O/LS). Patient characteristics and lung mechanism are summarized in **Table 1**.

AI

Total AI was consistently lower in PS_{AUTO} when compared with PS_{10}, PS_{30}, and PS_{50}, ($P < 0.05$). The benefit of PS_{AUTO} in reducing total AI was mainly in the reduction of micro-AI but not macro-AI (**Figure 1**). The percentages of all kinds of asynchronies are reported in **Table 2**. Total AI and micro-AI were lower in PS_{AUTO} when compared with PS_{10} and PS_{30} in the obstructive subgroup and were lower in PS_{AUTO} when compared with PS_{50} in the restrictive subgroup (**Supplementary Table 2**).

NeuroSync Index

The NeuroSync index (average of the percentage errors of triggering and cycling-off) was consistently lower in PS_{AUTO} when compared with PS_{10}, PS_{30}, and PS_{50}, indicating improved patient-ventilator interaction (**Table 2**). **Figure 2** shows a plot of the percentage errors of triggering (*X*-axis) and cycling-off (*Y*-axis) for every breath. We have inserted a small centered box suggesting "perfect" asynchrony to be ≤10% of neural timing and a larger box suggesting "acceptable" asynchrony to be ≤33% of neural timing (15). There were more "Perfect" asynchrony breaths and "Acceptable" asynchrony breaths in PS_{AUTO} than in the fixed cycling-off criteria mode (PS_{10}, PS_{30}, and PS_{50}, all $P <$ 0.05; **Figure 2**).

Cycling-Off and Triggering Error

Automatic adjustment PSV significantly improved the relative cycling-off error when compared with PS_{10}, PS_{30}, and PS_{50} in the whole population (**Figure 3**). The relative cycling-off error in PS_{AUTO} was comparable with that in PS_{50} in the obstructive subgroup and was comparable with that in PS_{10} in the restrictive subgroup. PS_{AUTO} significantly shortened the absolute and relative triggering errors when compared with a prefixed trigger (PS_{10}, PS_{30}, or PS_{50}; **Figure 3**). The Absolute and relative triggering errors were significantly lower when compared with PS_{10}, PS_{30}, and PS_{50} in the obstructive subgroup but not in the restrictive subgroup (**Supplementary Figure 4**).

Respiratory Drive and Breathing Pattern

Inspiratory effort for triggering determined by $PTP_{es-trig}$ was significantly lower in PS_{AUTO} when compared in PS_{10} and PS_{30}; however, total inspiratory effort determined by PTP_{es} was not different among modes (**Table 3**). In the obstructive subgroup, $PTP_{es-trig}$ was significantly lower in PS_{AUTO} than in PS_{10}, PS_{30}, and PS_{50} ($P < 0.05$; **Supplementary Table 2**). Peak airway pressure was higher in PS_{10} than in other modes. There was no difference in the respiratory drive between modes (**Table 3**). Breathing patterns and respiratory drive in obstructive and restrictive subgroups are shown in **Supplementary Table 3**.

DISCUSSION

This study showed that when compared with PSV with prefixed pneumatic controllers, an automatic adjustment system decreased total AI and improved patient-ventilator interaction mainly through a decrease of micro-asynchronies. The automatic system was associated with the lower cycling-off error, triggering error, and triggering effort in PSV patients.

AI and NeuroSync Index

Both AI and the NeuroSync index are indicators that reflect the overall patient-ventilator interaction from different perspectives. PS_{AUTO} constantly reduced total AI and the NeuroSync

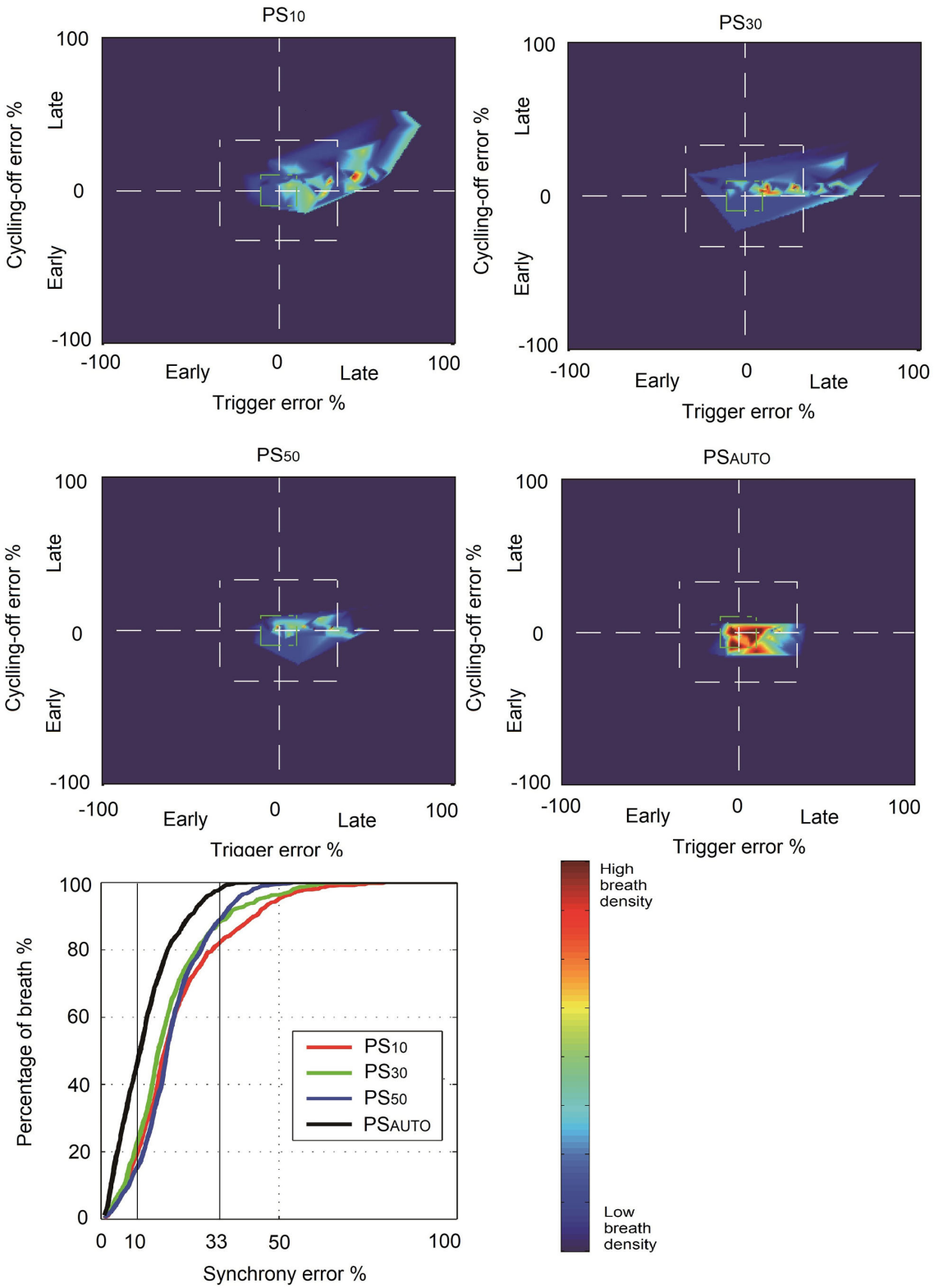

FIGURE 2 | Breath density graph for relative trigger (*X*-axis) and cycling-off (*Y*-axis) errors, for all breaths in all patients, during each ventilator mode. $PS_{10,}$ pressure support ventilation with cycling-off criteria set to 10%; $PS_{30,}$ pressure support ventilation with cycling-off criteria set to 30%; $PS_{50,}$ pressure support ventilation with cycling-off criteria set to 50%; $PS_{AUTO,}$ pressure support ventilation with automatic adjustment system; asynchrony error, breathes inside the box of percentage error of neural timings.

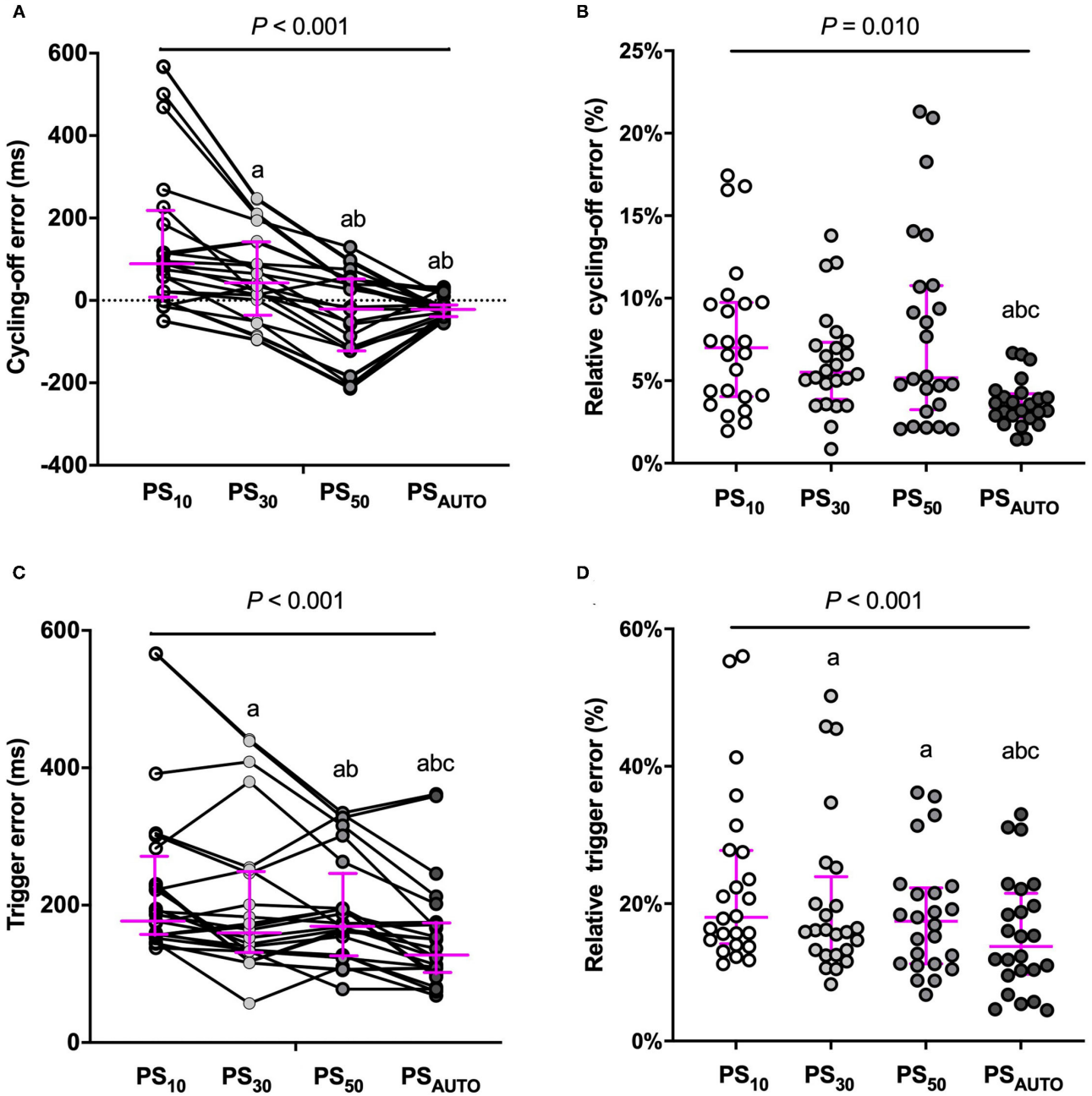

FIGURE 3 | Cycling-off error and trigger error in different modes. **(A)** cycling-off error, **(B)** relative cycling-off error, **(C)** trigger error, and **(D)** relative trigger error, *Y*-axis for cycling-off error: positive values indicate late cycling-off, and negative values indicate early cycling off. Magenta line showed median (interquartile range). ms, millisecond; PS_{10}, pressure support ventilation with cycling-off criteria set to 10%; PS_{30}, pressure support ventilation with cycling-off criteria set to 30%; PS_{50}, pressure support ventilation with cycling-off criteria set to 50%; PS_{AUTO}, pressure support ventilation with automatic. Compared with PS_{10}, $^{a}P < 0.05$; Compared with PS_{30}, $^{b}P < 0.05$; Compared with PS_{50}, $^{c}P < 0.05$.

index when compared with PSV with prefixed pneumatic controllers, indicating improved patient-ventilator interaction. Given that macro-asynchronies were rare, the benefit of PS_{AUTO} in reducing the total AI was mainly due to the reduction of micro-asynchronies. These findings agree with previous work comparing PSV and neurally adjusted ventilatory assist, which showed the difference in AI is found only in micro-asynchronies (14).

The present study showed a higher total AI (median of 23–57% during PS_{10}, PS_{30}, PS_{50}, and PS_{AUTO}) when compared with those in previous studies (range from 0 to 27%) (6, 16, 17). Despite the differences among study patients and ventilators

TABLE 3 | Breathing pattern and respiratory drive in different modes.

Parameter	PS_{10}	PS_{30}	PS_{50}	PS_{AUTO}	*P* value
Ppeak, cmH_2O	16.5 ± 4.2	15.4 ± 4.2[a]	15.4 ± 4.1[a]	14.6 ± 4.1[a]	<0.001
PEEP, cmH_2O	6.2 ± 1.7	6.1 ± 1.6	6.3 ± 1.5	6.6 ± 1.5	0.120
Vt, cmH_2O/kg	6.1 ± 0.2	6.1 ± 0.2	6.1 ± 0.3	6.0 ± 0.1	0.169
RR_N, breath/min	20.1 ± 5.6	19.3 ± 7.7	19.3 ± 5.9	20.5 ± 6.4	0.331
Ti_N, s	1.2 ± 0.0	1.1 ± 0.0	1.2 ± 0.0	1.1 ± 0.0	0.373
Te_N, s	2.2 ± 0.2	2.4 ± 0.2	2.7 ± 0.3	2.4 ± 0.2	0.129
TiN/TtN, %	37.0 ± 1.4	33.4 ± 1.6	35.7 ± 1.7	36.5 ± 1.5	0.042
Peak EAdi, μV	12.9 ± 1.7	12.0 ± 1.5	12.8 ± 1.9	12.4 ± 1.9	0.611
Peak EAdi, μV	8.1 ± 5.5	9.3 ± 6.1	8.0 ± 2.4	6.8 ± 2.0	0.864

Data are provided as mean ± SD.

PS_{10}, pressure support ventilation with cycling-off criteria set to 10%; PS_{30}, pressure support ventilation with cycling-off criteria set to 30%; PS_{50}, pressure support ventilation with cycling-off criteria set to 50%; PS_{AUTO}, pressure support ventilation with automatic adjustment system; Ppeak, peak airway pressure; PEEP, positive end expiratory pressure; Vt, tidal volume; RR, respiratory rate; Ti_N, neural inspiratory time; Te_N, neural expiratory time; Peak EAdi, peak diaphragm electrical activity.

Compared with PS_{10}, [a]$P < 0.05$; Compared with PS_{30}.

used, the major reason for the apparent differences between studies might relate to the calculation method for the AI. First, inspiratory trigger delay was included in the calculation of the AI in the present study, which provided about one-third to one-half of the total AI during PSV with prefixed pneumatic controllers. However, the previous study did not calculate inspiratory trigger delay in the AI (6). Second, we defined asynchrony as an error of 200 ms between the origin of the EAdi and ventilator insufflation, which was more sensitive than the threshold used in previous studies (6, 16–18). Therefore, the AI in the present study is more sensitive and comprehensive and therefore not comparable to those in other studies.

Cycling-Off Error

Cycling-off asynchrony is dependent on factors, such as the inspiratory effort, neural inspiratory time, assist levels, the time constant of the respiratory system, and cycling-off criteria of the patients (3). Consequently, the optimum flow cycling-off criteria vary among patients and can range from very low levels (5%) in patients with a restrictive condition (such as acute respiratory distress syndrome) (4, 19) to more than 50% in patients with an obstructive condition (such as chronic obstructive pulmonary disease) (5, 20, 21). A previous study showed in a mixed sample of patients that the use of a variable, real-time-adjusted termination criterion improved some indices of patient-ventilator asynchrony when compared with a fixed termination criterion (5% of peak inspiratory flow) (22). However, a termination criterion of 5% of peak inspiratory flow was not commonly used clinically during PSV. Our results showed a significant improvement in relative cycling-off error during PS_{AUTO} when compared with PSV with prefixed cycling-off criteria of 10%, 30%, and 50%. It was not unexpected that during PSV with prefixed pneumatic controllers, PS_{50} and PS_{10} were the "best" cycling-off settings with the lowest relative cycling-off errors in the obstructive and restrictive subgroups. In each subgroup, relative cycling-off error in PS_{AUTO} was comparable with the "best" cycling-off setting during PSV with a prefixed cycling-off.

Triggering Error

The present study showed the median delay for triggering during PS_{10}, PS_{30},PS_{50}, and PS_{AUTO} ranged from 187 to 130 ms. These values fall within the 80–540 ms range of values previously reported for PSV (1, 18, 23). Beloncle et al. reported absolute values for trigger delay < 200 ms in almost all patients, which was lower than that reported in the present study (18). The different ventilators and flow-trigger used in different studies might be one reason, and different types of the enrolled patients might be another reason for the difference in trigger delay. During PS_{AUTO}, the algorithm will trigger the ventilator to initiate the inspiratory phase when it detects a sudden increase of flow waveform, which reflects the inspiratory effort, leading to a reduced triggering delay. Furthermore, triggering delay was likely reduced as a consequence of reduced cycling-off delay during PS_{AUTO}, which led to a longer expiration time and lower PEEPi, especially in patients with obstructive conditions (5). Unfortunately, we did not measure PEEPi during each mode.

Of note, a single flow-trigger level in the present study made it hard to draw conclusions regarding the effect of the PS_{AUTO} mode on inspiratory triggering asynchronies when compared with lower flow-triggering (e.g., 1.0 L/min). From this perspective, a fixed flow-trigger of 1.5 L/min might be not sensitive enough. Considering the similar or shorter triggering delay and no obvious auto-triggering during PS_{AUTO}, automatic adjustment of triggering based on waveforms might be a useful tool for making the triggering setting easier.

Inspiratory Effort and Breathing Pattern

Because PS_{AUTO} significantly reduced triggering delay, it was not unexpected that it was associated with lower inspiratory effort for triggering. The present study showed a comparable breathing pattern and respiratory drive between PS_{AUTO} and PSV with prefixed pneumatic controllers. Of interest, neural expiratory time remained unchanged at the various cycling-off settings in the present study. These findings agree with previous work in which expiratory time did not change with the

increase in cycling-off criteria in chronic obstructive pulmonary disease patients (5, 20). However, the findings contradict those in previous studies which show an increased expiratory time in the presence of delayed cycling in acute lung injury (24, 25). Therefore, PS_{AUTO} improved the cycling-off criteria, which was demonstrated to affect the inspiratory time only at high-pressure support (20). Peak EAdi around 12 μV confirmed the absence of over-assistance during PSV in the present study.

Limitations

There are some limitations that should be noted. First, our study was conducted in a small group of patients. Second, respiratory mechanics were evaluated in patients under sedation who were not actively breathing, therefore, the results will be different from those measured during PSV. Third, patients were maintained at each mode setting for only 20 min, and steady-state conditions might not have been achieved. However, the duration was in line with that of several studies on the effects of cycling criteria modifications (4, 19).

CONCLUSIONS

An automatic adjustment system based on waveform was associated with less patient-ventilator asynchrony when compared with PSV with prefixed pneumatic controllers. Our results indicated that this system might be a useful tool to titrate more personalized mechanical ventilation, especially in patients with a high risk of patient-ventilator asynchrony.

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 Institutional Ethics Committee of Zhongda Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LL, YYa, DC, and HQ have given substantial contributions to the conception or the design of the manuscript. LL, YYu, XX, and QS to acquisition, analysis, and interpretation of the data. All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

FUNDING

This study was supported by the Clinical Science and Technology Specific Projects of Jiangsu Province [BE2020786 and BE2019749], the National Natural Science Foundation of China [Grant Numbers 81870066 and 81670074], the Natural Science Foundation of Jiangsu Province (BK20171271), Jiangsu Provincial Medical Youth Talent (QNRC 2016807), and Third Level Talents of the 333 High Level Talents Training Project in the fifth phase in Jiangsu (LGY2016051). This study received funding from Mindray (China). The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article, or the decision to submit it for publication.

ACKNOWLEDGMENTS

The authors thank Mr. Jinglei Liu, Xiaoyong Zhou, and Jun Chen (Shenzhen Mindray Bio-Medical Electronics Co., Ltd.) for helping to making the figures.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.752508/full#supplementary-material

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Conflict of Interest: LL and HQ received a grant from Mindray (China).

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

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frontiers in Medicine

SYSTEMATIC REVIEW
published: 15 November 2021
doi: 10.3389/fmed.2021.709642

Incidence and Mortality of Acute Respiratory Distress Syndrome in Patients With Burns: A Systematic Review and Meta-Analysis

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Objective: We conducted a systematic review and meta-analysis to comprehensively estimate the incidence and mortality of acute respiratory distress syndrome (ARDS) in overall and subgroups of patients with burns.

Data sources: Pubmed, Embase, the Cochrane Library, CINAHL databases, and China National Knowledge Infrastructure database were searched until September 1, 2021.

Study selection: Articles that report study data on incidence or mortality of ARDS in patients with burns were selected.

Data extraction: Two researchers independently screened the literature, extracted data, and assessed the quality. We performed a meta-analysis of the incidence and mortality of ARDS in patients with burns using a random effects model, which made subgroup analysis according to the study type, inclusion (mechanical ventilation, minimal burn surface), definitions of ARDS, geographic location, mean age, burn severity, and inhalation injury. Primary outcomes were the incidence and mortality of burns patients with ARDS, and secondary outcomes were incidence for different subgroups.

Data synthesis: Pooled weighted estimate of the incidence and mortality of ARDS in patients with burns was 0.24 [95% confidence interval (CI)0.2–0.28] and 0.31 [95% CI 0.18–0.44]. Incidences of ARDS were obviously higher in patients on mechanical ventilation (incidence = 0.37), diagnosed by Berlin definition (incidence = 0.35), and with over 50% inhalation injury proportion (incidence = 0.41) than in overall patients with burns. Patients with burns who came from western countries and with inhalation injury have a significantly higher incidence of ARDS compared with those who came from Asian/African countries (0.28 vs. 0.25) and without inhalation injury (0.41 vs. 0.24).

Conclusion: This systematic review and meta-analysis revealed that the incidence of ARDS in patients with burns is 24% and that mortality is as high as 31%. The incidence rates are related to mechanical ventilation, location, and inhalation injury. The patients with burns from western countries and with inhalation injury have a significantly higher incidence than patients from Asian/African countries and without inhalation injury.

Systematic Review Registration: identifier: CRD42021144888.

Keywords: ARDS, incidence, mortality, burn patients, meta

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

Received: *14 May 2021*
Accepted: *17 September 2021*
Published: *15 November 2021*

Citation:
Wang B, Chenru W, Jiang Y, Hu L, Fang H, Zhu F, Yu Q, Zhu B, Wu G, Sun Y and Xia Z (2021) Incidence and Mortality of Acute Respiratory Distress Syndrome in Patients With Burns: A Systematic Review and Meta-Analysis. Front. Med. 8:709642. doi: 10.3389/fmed.2021.709642

INTRODUCTION

Acute respiratory distress syndrome is very common in critically ill patients. After years of basic and clinical research, its diagnosis and treatment are improving daily, but the associated mortality rate is still as high as 30% (30-day mortality) (1). The causes of ARDS are diverse and, excluding cardiac-induced conditions, can include severe infection, shock, trauma, and burns. These injuries can induce diffuse pulmonary interstitial and alveolar edema, resulting in acute hypoxic respiratory insufficiency or failure (2). Among the causes of ARDS, severe burns can also cause a series of pathophysiological changes in various organs of the body. Among them, the lung is one of the earliest organs to be damaged, and damage to the lung is one of the main causes of death in severely burned patients (3). Although many studies have reported the incidence, treatment, and outcome of ARDS, there is no meta-analysis of ARDS in patients with burns. Our objective is to comprehensively collect published literature on ARDS in patients with burns and assess the incidence/mortality in overall and subgroups of the patient with burns.

METHODS

Literature Search

We retrieved studies from Pubmed, Embase, the Cochrane Library, CINAHL databases, and the China National Knowledge Infrastructure database. The retrieval time for each database is from the formation of the database to September 1, 2021. We searched the databases by combining subject words and free words. Search terms included "Respiratory Distress Syndrome, Adult," AND "incidence OR Mortality," AND "burn." Detailed search strategies are provided in **Appendix 1**. We evaluated the qualifications of the identified publications and independently extracted data from the studies selected. Differences were resolved through a consensus.

Study Selection

Inclusion criteria were as follows: (1) study type was an observational study, case-control study, cohort study, or randomized controlled trial; (2) subjects were patients with burns; (3) incidence or mortality of ARDS was reported; (4) articles were written in English or Chinese. Exclusion criteria were as follows: (1) studies with obvious abnormal and incomplete data sets; (2) repeated publishing of the same batch of data by multiple articles; (3) sample size of the study was <20; (4) research subjects were special populations, such as children or pregnant women; (5) research subjects were only patients with inhalation injury; (6) any limitation in the length of stay and death; (7) comments, reviews, or lectures.

Data Extraction

We extracted the characteristics of the study (author, publication year, study type, study area and centers, sample size, and study quality), basic characteristics of the research subject (average age, total body surface area (TBSA), full-thickness burn injury, inhalation injury), ARDS cases, and ARDS-related deaths. Two researchers separately collected the data and cross-checked the sampling of the other.

Abbreviations: ARDS, acute respiratory distress syndrome; TBSA, total body surface area; AECC, American-European Consensus Conference.

Quality Assessment

Methodological quality assessment studies were also conducted by two separate researchers. We took the same type of meta-analysis "Incidence and Mortality of Acute Respiratory Distress Syndrome in Children: A Systematic Review and Meta-Analysis" as a reference, and used the evaluation tools of the research for evaluation. Our study refers to the quality evaluation in the relevant literature, and the quality of each method (bias risk) was based on a list of 13 items (4). The list of 13 items is provided in **Appendix 2**.

Quantitative Data Synthesis

Statistical Pooling and Evaluation of Heterogeneity

We conducted a meta-analysis with the Meta package (metaprop, version R3.5.3). The data were converted with four estimation methods, and a normality test was performed on the data before the meta-analysis. In accordance with the test results, the method closest to a normal distribution was selected. Then, we combined the data (ARDS incidence and mortality) and performed a heterogeneity analysis. The confidence interval (CI) was 95%, and the statistical heterogeneity was judged by calculating I^2. We choose a fixed effects model or a random effects model based on p-value and I^2. A sensitivity analysis was performed to investigate the stability of the meta-analysis. The funnel plot method was used to judge publication bias.

Subgroup Analyses

We performed a subgroup meta-analysis to obtain the rate of special groups of patients with burns and explore potential sources of heterogeneity. We assessed factors, including the study type, inclusion (mechanical ventilation, minimal burn surface), definitions of ARDS, geographic location, mean age, burn severity, and inhalation injury. Divided by these factors, the combined weighted estimates were used to derive the incidence and mortality of ARDS in different subgroups. The statistical tests were all two-sided with a level of $\alpha = 0.1$.

RESULTS

Study Characteristics

The search identified 712 reports potentially pertaining to the morbidity and mortality of ARDS in patients with burns. After screening, 35 publications on incidence (5–39) and 9 on mortality (5, 7, 9, 11, 24, 32–34, 38) were considered to be eligible (**Figure 1**). The basic characteristics of the included studies, with respect to incidence and mortality, are shown in **Supplementary Tables 1**, **2**. Most of the studies were conducted in a single center. The research population of "Incidence" was 10,899 and that of "Mortality" was 2,771. These data were from multiple countries on multiple continents; however, most of the studies were carried out in the United States, Canada, China, and Spain. The research time window of all the included studies was from 1978 to 2021. The study subjects were patients with burn,

with ARDS-related records. In most of the publications, the age limit of the patients was over 18 years. In 1994, the American-European Consensus Conference (AECC) definition of ARDS was published, which had problems with lack of a criterion for acute onset, the need for a pulmonary artery catheter, and difficult hypoxemia criteria. Therefore, a new definition of ARDS, called the Berlin definition, was published, in 2012 (40). Since the definition of ARDS was constantly being adjusted with the development of clinical guidelines and practice, some studies continued to clarify the criteria used in the definition of ARDS. Most studies provide burn-related data, such as mean TBSA (%), mean full-thickness burn injury (%), and proportion with inhalation injury (%).

Quality Assessment

The methodological quality of the study was good (average score of "Incidence" 77.1 [50–88]; the average score of "Mortality" 80.6 [69–86]). The detailed quality assessment is shown in **Supplementary Tables 3**, **4**.

Quantitative Data Synthesis

Overall Incidence and Mortality of ARDS in Patients With Burns

The incidence of pooled weighted ARDS in patients with burns was 0.24 [95% CI 0.2–0.28] (**Figure 2**). Patients with burns had a pooled weighted ARDS mortality of 0.31 [95% CI 0.18–0.44] (**Figure 3**). Studies assessing burn patient incidence (I^2 = 98%) and burn patient mortality (I^2 = 99%) showed significant heterogeneity. The heterogeneity of "incidence" and "mortality" is so high that they challenge the relevance of the studies, and they could come from the differences in the inclusion criteria of patients (such as mechanical ventilation and minimal burn surface), definitions of ARDS, geographic location, mean age, burn severity, and inhalation injury, so we made the subgroup analysis to get the accurate incidence of special burn patients. Due to the number of studies included in mortality analysis being only 9, we did not divide these studies into subgroups.

Incidence of ARDS in Patients With Burns by Different Study Type

Considering the type of study that may influence the incidence of ARDS in patients with burns, we divided the studies into two types (retrospective and prospective). There are 15 retrospective studies and 3 prospective studies; the "retrospective" subgroup has 6,685 patients in total, and the "prospective" subgroup has 245 patients. For patients with burns in the retrospective studies, the incidence of ARDS was 0.24 [95% CI 0.18–0.3], while that for burns patients in the retrospective studies, the incidence of 0.15 [95% CI 0.06–0.39]. I^2 was 99 and 86%, respectively. No statistical difference was noted between them (p = 0.33) (**Supplementary Figure 1**; **Table 1**).

Incidence of ARDS in Patients With Burns and on Mechanical Ventilation

We found a total of eight studies containing mechanical ventilation in the inclusion criteria. The number of patients with burns and mechanical ventilation was 2,630, and for these patients, the incidence of ARDS was 0.37 [95% CI 0.29–0.44], and the heterogeneity was decreased to 93% (**Supplementary Figure 2**; **Table 1**).

Incidence of ARDS in Patients With Burns and TBSA ≥20%

Some "incidence" studies used TBSA (%) as an inclusion criterion, which included TBSA ≥1, 20, 30%, and so on. There were nine studies that set TBSA to ≥20% as an inclusion criterion, two studies set TBSA to ≥30%, and one study set TBSA to ≥50%. The minima burn surfaces of all these patients (n = 1127) were over 20%. The incidence of ARDS in these patients was 0.32 [95% CI 0.21–0.42], and heterogeneity was 92% (**Supplementary Figure 3**; **Table 1**).

Incidence of ARDS Defined by AECC and Berlin Definition

We found nine studies that defined ARDS by the Berlin definition and six studies by the AECC definition, and the number of patients was 2,738 and 1,989, respectively. The incidence of ARDS defined by the Berlin definition was 0.35, and the incidence of ARDS defined by the AECC definition (41) was 0.3 (**Supplementary Figure 4**). There was no significant difference between these subgroups (p = 0.61; **Table 1**).

Incidence of ARDS in Patients With Burns by Location

We divided the studies into Western research projects and Asian-African groups based on geography. The incidence of ARDS in burn patients in Western countries was 0.28 ([95% CI 0.27–0.33], I^2 = 99%, N = 22), and the incidence in Asian and African countries was 0.25 ([95% CI 0.22–0.29], I^2 = 95%, N = 13) (**Supplementary Figure 5**). There was no difference between the subgroups (P = 0.38; **Table 1**).

Incidence of ARDS in Patients With Burns by Mean Age

For studies where the average age of patients was 20–39 years, we combined the incidence of ARDS, and the outcome was 0.25 [95% CI 0.14–0.36]. For the subgroups with ages of 40–59 years, the incidence was 0.27 [95% CI 0.21–0.33] (**Supplementary Figure 6**). No statistical difference was found in this comparison (P = 0.73; **Table 1**).

Incidence of ARDS in Patients With Burns by Mean TBSA (%)

The incidence of ARDS in the TBSA ≥ 30% burn group is a little bit higher than the TBSA < 30% (**Table 1**). The results were mean TBSA ≥ 30%,0.26 [95% CI 0.21–0.31], N = 21, I^2 = 95% vs. mean TBSA < 30%0.22 [95% CI 0.15–0.29], N = 9, I^2 = 99% (**Supplementary Figure 7**).

Incidence of ARDS in Patients With Burns by Average Full-Thickness (%)

The incidence of ARDS in patients with burns and an average full-thickness of over 10% was 0.24 ([95% CI 0.17–0.35], N = 14, I^2 = 98%). Those with an average full-thickness ≤10% had an incidence of 0.19 ([95% CI 0.05–0.7], N = 2, I^2 = 94%;

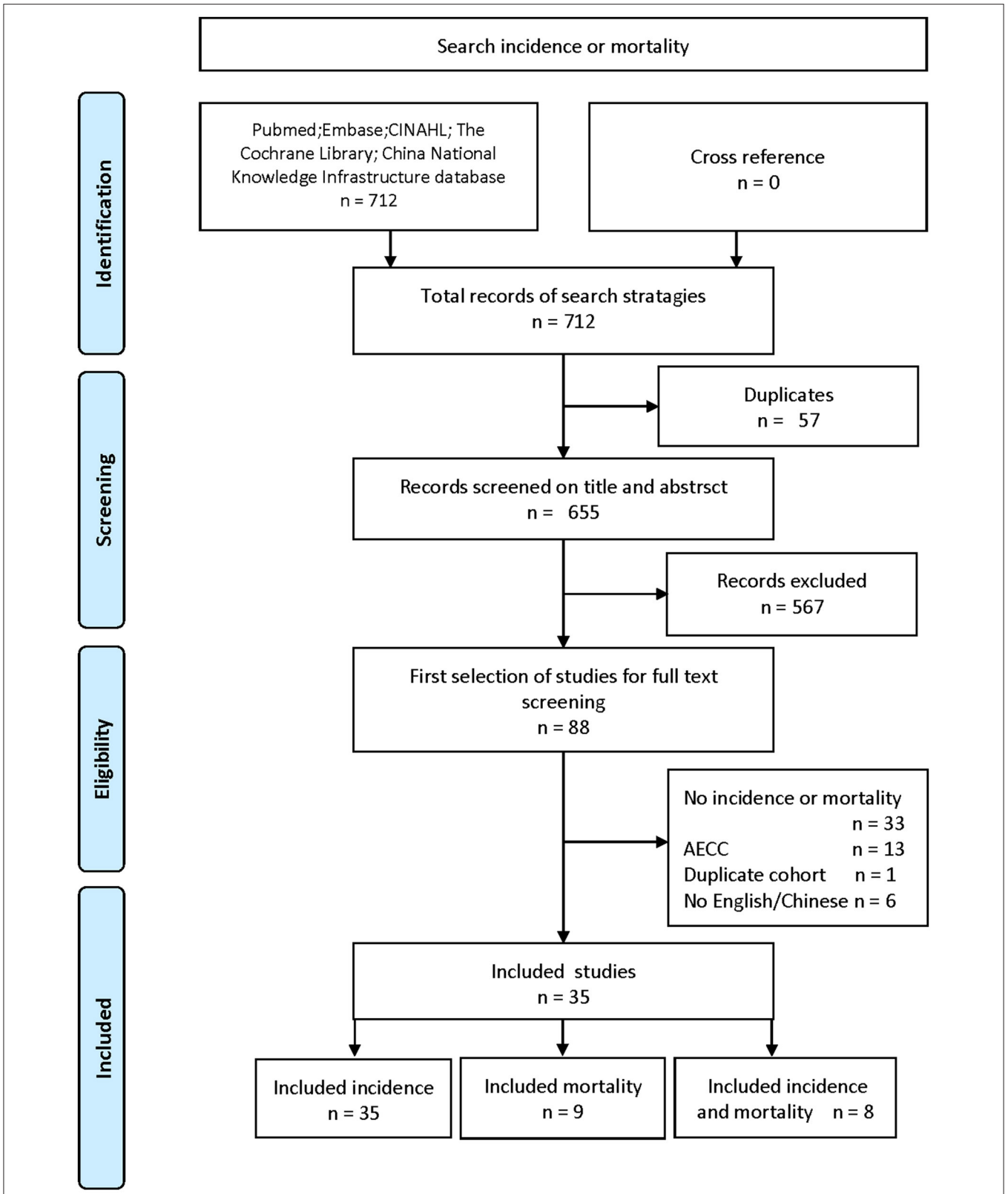

FIGURE 1 | Flowchart of literature searching and inclusion.

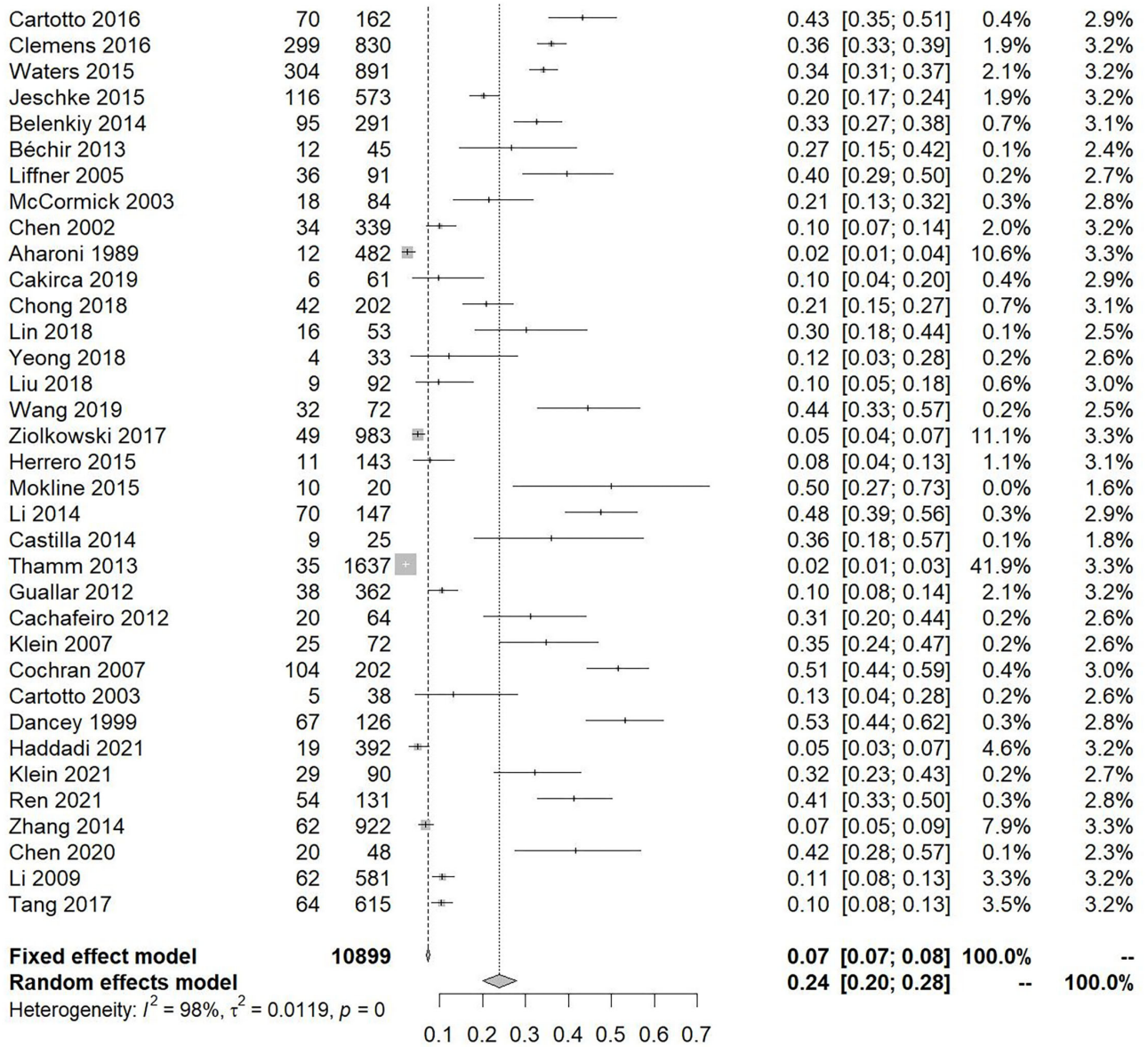

FIGURE 2 | Forest plot showing the overall incidence of acute respiratory distress syndrome in patients with burns.

Supplementary Figure 8). The incidence was not significantly different between these groups ($P = 0.74$; **Table 1**).

Incidence of ARDS in Patients With Burns by Inhalation Injury Proportion (%)

The incidence rate in the subgroup with over 50%inhalation injury proportion in patients with burns were 0.41 ([95% CI 0.34–0.48], $N = 4$, $I^2 = 49\%$), which is significantly higher than that of the subgroup with <50% inhalation injury proportion (0.24 [95% CI 0.17–0.3], $N = 18$, $I^2 = 99\%$ (**Supplementary Figure 9**). There was a significant difference between these subgroups ($p < 0.01$; **Table 1**).

Publication Bias and Sensitivity Analysis

We used a funnel plot to test for publication bias in 35 incidence and 9 mortality studies. The inverted funnel plot suggested there was a little bit of bias in studies reporting incidence and no obvious publication bias in mortality (**Supplementary Figures 10**, **11**). To assess whether

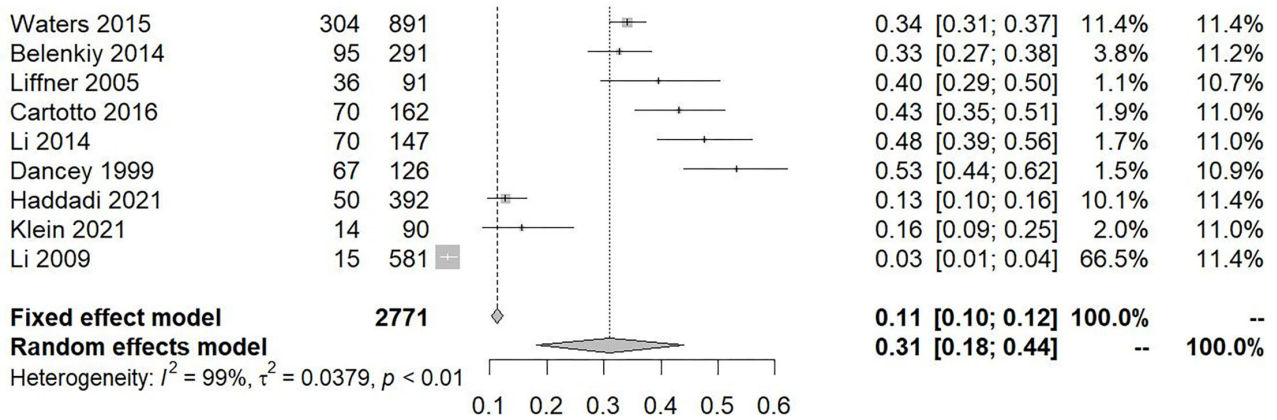

FIGURE 3 | Forest plot showing the overall mortality of acute respiratory distress syndrome in patients with burns.

the pooled incidence or mortality of ARDS in this meta-analysis was stable, a sensitivity analysis was performed. The effect estimation of sensitivity analysis showed that regardless of pooled incidence or pooled mortality, the results were stable (**Supplementary Figures 12**, **13**).

DISCUSSION

This systematic review and meta-analysis included the first large-scale analysis of the incidence and mortality rates of ARDS in patients with burns. We calculated the pooled incidence and mortality of ARDS in patients with burns, as well as those in subgroups with alternative definitions, average age, TBSA, full-thickness burn injury, and inhalation injury proportion. These findings can help guide clinicians in assessing and diagnosing ARDS in patients with burns in the future and play an important role in the allocation of medical resources for disease and its prevention.

We selected several influencing factors related to ARDS which are common in most studies on the condition. These were used in the subgroup analysis and included study type, mechanical ventilation, minima burn surface within inclusion criteria, ARDS definition, geographic location, age, TBSA, full-thickness burn injury, and inhalation injury. We compared the rates and found that the "prospective-study type" might prevent ARDS from happening (incidence = 0.15), which may be caused by different types of treatment and healthcare. The incidences of ARDS were obviously higher in patients who is with mechanical ventilation (incidence = 0.37), whose minima burn surface were over 20% (incidence = 0.32), and which subgroup is with over 50% inhalation injury proportion (incidence = 0.41) than the common burn patients (incidence = 0.24). What is more, I^2 decreases while the rate increases, which makes the incidence more credible. In our result, mechanical ventilation, location, and inhalation injury were, again, identified as risk factors of ARDS.

We found that the more severe the inhalation injury, the higher the incidence, which is in line with the majority of previous research conclusions. The patients with burns and inhalation injury have a significantly higher incidence of ARDS compared with those without inhalation injury. As such, it can be concluded that inhalation injury was an independent risk factor for ARDS. However, using the new Berlin definition of ARDS (incidence = 0.35), it was clear the rates were higher than when using the older AECC definition (incidence = 0.30). From the perspective of diagnostic criteria, The PaO_2/FiO_2 requirements of Berlin are higher (40). The reason why the incidence of Berlin is higher than that of AECC is that the level of medical treatment has improved significantly with the development of time. The development of sophisticated testing equipment has enabled physicians to discover more patients with potential ARDS. The result shows that ARDS was more common in the subgroup of burns patients aged 40–59 years (incidence = 0.27) than the subgroup of burns patients aged 20–39 years (incidence = 0.25). However, the number of 40–59 years group studies (N = 18, n = 7,542) is higher than 20–39 years group (N = 10, n = 3,970), which means burns are common in 20–39 years group, but ARDS was common in 40–59 years group. Although the results are surprising, they should not be a problem. We can design a large targeted prospective study to prove this result further.

As this article is a meta-analysis of a single-group rate, we encountered the common problem of high heterogeneity. The I^2 of incidence was > 80%, regardless of whether heterogeneity was calculated for the "incidence" rates or the "mortality" rates. As a result, we chose to use a random effects model in the analysis. We explored the possible sources of heterogeneity in the studies of incidence by subgroup meta-analysis. Although we tried a lot of factors that may cause high levels of heterogeneity, including study type, inclusion, definition, location, mean age, TBSA, etc., we could not find a single model to account for these factors together. In the series of "incidence" studies, except

TABLE 1 | Pooled estimation of incidence of acute respiratory distress syndrome in burn patients and its subgroup.

Factors	Subgroups	Studies, *n*	No. of patients	Proportion [95% CI][a]	I^2[b]	*P*-value for heterogeneity	*P*-value for subgroup differences
Study type	Retrospective	15	6,685	0.24 [0.18–0.30]	99%	<0.01	0.33
	Prospective	3	245	0.15 [0.06–0.39]	86%	<0.01	
Inclusion	With mechanical ventilation	8	2,630	0.37 [0.29–0.44]	93%	<0.01	–[g]
	minima burn surface ≥20%	9	1,127	0.32 [0.21–0.42]	92%	<0.01	–
Definition[c]	Berlin	9	2,738	0.35 [0.31–0.40]	81%	<0.01	0.61
	AECC	6	1,989	0.30 [0.08–0.51]	98%	<0.01	
Location	Western	22	9,100	0.28 [0.27–0.33]	99%	<0.01	**0.01**
	Asian/African	13	12,659	0.25 [0.22–0.29]	95%	<0.01	
Mean age	20y−39y	10	3,097	0.25 [0.14–0.36]	98%	<0.01	0.73
	40y−59y	18	7,542	0.27 [0.21–0.33]	97%	<0.01	
TBSA[d]	<30%	9	4,763	0.22 [0.15–0.29]	99%	<0.01	0.22
	≥30%	21	3,877	0.28 [0.22–0.34]	95%	<0.01	
FT[e]	≤10%	3	970	0.29 [0.09–0.49]	97%	<0.01	0.91
	>10%	15	5,691	0.30 [0.23–0.37]	99%	<0.01	
II[f]	<50%	18	6,909	0.24 [0.17–0.30]	99%	<0.01	**<0.01**
	≥50%	4	387	0.41 [0.34–0.48]	49%	0.12	

[a] *95% CI: 95% confidence interval.*
[b] *I^2: heterogeneity of the studies.*
[c] *Definition: which definition of acute respiratory distress syndrome used in the studies, the American-European Consensus Conference (AECC) definition or the Berlin definition.*
[d] *TBSA, total body surface area.*
[e] *FT, full-thickness (FT) burn injury.*
[f] *II: the proportion of patients combined inhalation injury of the total sample.*
[g] *"–" means the date is not available.*
Bold values mean statistically significant.

for the "study style- prospective," "definition- Berlin" subgroups, and "inhalation injury-≥50%" whose heterogeneity was slightly reduced ($I^2 < 90$), the remaining studies were more than 90% heterogeneous, with the vast majority being over 95%. When we compared the I^2 with other "a single-group rate" meta-analysis (28, 42), we found that high heterogeneity was common. Therefore, it might be acceptable that I^2 was 99% for the "mortality" study. For the subgroup of patients with burns and over 50% inhalation injury proportion, the incidence of ARDS (0.41) was precise because $I^2 = 49\%$. In addition to the heterogeneous sources suggested by the statistical results, we speculate that the inclusion criteria for each study could also be a main source of heterogeneity. We included diversiform literature, which were recording data related to ARDS and "burns." Patients with burns in some of the studies had different therapeutic schedules. Besides, some studies only analyzed mechanically ventilated patients with burns. The funnel plots showed that the distribution of "incidence" was asymmetric. The bias was very strong ($p = 0.01$). These variations in methodology and patient sampling may be the reason for the high heterogeneity. The distribution for "mortality" was visually symmetrical based on the results of the funnel plot. Furthermore, after sensitivity testing, the aggregated weighted ARDS morbidity and mortality were stable.

This meta-analysis has several advantages. First, this is the first comprehensive systematic analysis of ARDS in patients with burns. Most of the previous studies on the subject were based on specific groups (large area burns, burns with inhalation injuries, etc.). Comparing the findings here with previous studies, we note that this study is more thorough in including overall types of patients with burns. This leads to a more comprehensive and accurate assessment of the incidence and mortality rates of ARDS. Second, we use a rigorous screening method to exclude studies from different subject areas conducted by the same authors, while conducting detailed quality assessments of the articles included. Third, we made the most of the more than 8,000 samples; refining the study population classification according to different indicators, obtaining the incidence rates of different subgroups, and determining the relevant risk factors for ARDS. However, there are also some limitations in our research. First, our target population includes overall patients with burns. While the sensitivity analysis shows that the incidence and mortality rates are stable, we do recognize that there are many influencing factors, such as mechanical ventilation, definition, geographic location, inclusion criteria, age, burn severity, and inhalation injury in ARDS. The influence of all these various factors causes a substantial amount of heterogeneity in the data. Second, we were unable to retrieve data on individual patients and only conducted a meta-analysis on the results of each study. We used these data to determine the risk factors of ARDS based on the rate of events and characteristics of the study population. In subsequent studies, it would be advantageous to arrange a large and multicenter cohort of burn victims to address these issues.

CONCLUSION

This systematic review and meta-analysis revealed that the incidence of ARDS in patients with burns is 24% and that mortality is as high as 31%. The incidence rates are related to mechanical ventilation, location, and inhalation injury. Patients with burns from western countries and with inhalation injury have a significantly higher incidence than patients from Asian/African countries and without inhalation injury.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

BW, ZX, YS, and GW: substantial contributions to the conception and design of the study. BW, WC, YJ, LH, and GW: acquisition, analysis, and interpretation of data for the study. BW, WC, YJ, HF, FZ, QY, and BZ: drafting of the article. BW, GW, YS, and ZX: revising the article critically for important intellectual content. GW, YS, and ZX: final approval of the version submitted for publication. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by CAMS Innovation Fund for Medical Sciences (2019-I2M-5-076), the National Natural Science Foundation of China (81772125), and Shanghai Sailing Program (18YF1422900).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.709642/full#supplementary-material

Supplementary Figure 1 | Forest plot: incidence for the retrospective and prospective subgroups.

Supplementary Figure 2 | Forest plot showing the incidence of acute respiratory distress syndrome in patients with burns and on mechanical ventilation.

Supplementary Figure 3 | Forest plot showing the incidence of acute respiratory distress syndrome in patients with burn and TBSA ≥ 20%.

Supplementary Figure 4 | Forest plot: incidence for the subgroups of American-European Consensus Conference definition and Berlin definition.

Supplementary Figure 5 | Forest plot: incidence for the subgroups of Western countries and Asian and African countries.

Supplementary Figure 6 | Forest plot: incidence for the subgroups of 20–39- and 40−59-year-olds.

Supplementary Figure 7 | Forest plot: incidence for the subgroups of mean total body surface area <30 and ≥30%.

Supplementary Figure 8 | Forest plot: incidence for the subgroups of inclusion of full-thickness burn injury ≤10 and >10%.

Supplementary Figure 9 | Forest plot: incidence for the subgroups of patients with combined inhalation injury <50 and ≥50%.

Supplementary Figure 10 | Funnel plot of incidence studies.

Supplementary Figure 11 | Funnel plot of mortality studies.

Supplementary Figure 12 | Sensitive analysis for incidence of acute respiratory distress syndrome in patients with burns.

Supplementary Figure 13 | Sensitive analysis for the mortality of acute respiratory distress syndrome in patients with burns.

Supplementary Table 1 | Characteristic of studies included in meta-analysis of incidence in burn patients.

Supplementary Table 2 | Characteristic of studies included in meta-analysis of mortality in burn patients.

Supplementary Table 3 | Quality assessment of the included studies on incidence of acute respiratory distress syndrome in burn patient with full-text.

Supplementary Table 4 | Quality assessment of the included studies on mortality of acute respiratory distress syndrome in burn patient with full-text.

Appendix 1 | Search strategies of PubMed, Embase, CINAHL databases, and China National Knowledge Infrastructure database.

Appendix 2 | Quality assessment of the included studies.

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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.

frontiers in Medicine

ORIGINAL RESEARCH
published: 22 November 2021
doi: 10.3389/fmed.2021.753620

Implementation of Nurse-Led, Goal-Directed Lung Physiotherapy for Older Patients With Sepsis and Pneumonia in the ICU

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

Received: *05 August 2021*
Accepted: *31 October 2021*
Published: *22 November 2021*

Citation:
Sun J, Cui N, Han W, Li Q, Wang H, Li Z, Cheng W, Luo H and Zhao M (2021) Implementation of Nurse-Led, Goal-Directed Lung Physiotherapy for Older Patients With Sepsis and Pneumonia in the ICU. Front. Med. 8:753620. doi: 10.3389/fmed.2021.753620

Objectives: This study aimed to investigate the effect of nurse-led, goal-directed lung physiotherapy (GDLPT) on the prognosis of older patients with sepsis caused by pneumonia in the intensive care unit.

Methods: We conducted a prospective, two-phase (before-and-after) study over 3 years called the GDLPT study. All patients received standard lung therapy for sepsis caused by pneumonia and patients in phase 2 also received GDLPT. In this study, 253 older patients (age $\geq$ 65 years) with sepsis and pneumonia were retrospectively analyzed. The main outcome was 28 day mortality.

Results: Among 742 patients with sepsis, 253 older patients with pneumonia were divided into the control group and the treatment group. Patients in the treatment group had a significantly shorter duration of mechanical ventilation [5 (4, 6) vs. 5 (4, 8) days; $P = 0.045$], and a lower risk of intensive care unit (ICU) mortality [14.5% (24/166) vs. 28.7% (25/87); $P = 0.008$] and 28 day mortality [15.1% (25/166) vs. 31% (27/87); $P = 0.005$] compared with those in the control group. GDLPT was an independent risk factor for 28 day mortality [odds ratio (OR), 0.379; 95% confidence interval (CI), 0.187–0.766; $P = 0.007$].

Conclusions: Nurse-led GDLPT shortens the duration of mechanical ventilation, decreases ICU and 28-day mortality, and improves the prognosis of older patients with sepsis and pneumonia in the ICU.

Keywords: goal-directed lung physiotherapy, older patients, sepsis, pneumonia, intensive care unit

INTRODUCTION

Aging of the population is a critical worldwide trend. The proportion of individuals older than 60 years has tripled over the last 50 years and will triple again before 2050. This aging has major consequences on the health system, including the intensive care unit (ICU). In the USA, almost half (48.7%) of the patients admitted to an ICU are aged 65 years or older, and patients aged 85 years or older account for 7 to 25% of the admission rate (1, 2). The rate of pneumonia increases rapidly with age. Approximately 19% of adults hospitalized with pneumonia have an ICU admission,

including 60.7% of patients aged 65 years or older (3). Pneumonia in older patients can lead to cardiopulmonary failure, sepsis, and even systemic multiple organ failure, and they have a high mortality rate (4). Older people with pneumonia are at risk for a longer hospital stay, extended antibiotic therapy, and higher healthcare costs (5, 6). Therefore, an appropriate treatment protocol for pneumonia in older patients needs to be determined.

Because of age-related changes in the body, comorbidity, and malnutrition, the onset of pneumonia is insidious, rapid, and critical, and clinical treatment is difficult in older patients (2, 7, 8). Lung physiotherapy plays an important role in treatment of older patients with pneumonia (2, 7, 8). Lung physiotherapy can help patients in reducing the accumulation of airway secretion, clearing the respiratory tract, preventing a collapsed lung, improving lung compliance, and reducing comorbidities (9, 10). Nurses are responsible for most respiratory treatment in China. However, there is little evidence for the effect of nurse-led GDLPT on the prognosis of pneumonia in older patients with sepsis. In a previous study, we found that nurse-led GDLPT improved the outcomes in patients with sepsis and pneumonia (11). In this study, we carried out a retrospective analysis of older patients (age $\geq$ 65 years) with sepsis and pneumonia to evaluate whether GDLPT affects the clinical outcome.

MATERIALS AND METHODS

Study Design and Patients

The GDLPT study was a prospective, two-phase (before-and-after) study conducted in Peking Union Medical College Hospital of China from January 2017 to January 2020. Details of this study, including the inclusion and exclusion criteria, have been published previously (11). The study period was divided into two stages of phase 1 and phase 2. During phase 1 (January to December 2017), patients received standard physiotherapy for pneumonia, and patients in phase 2 (February 2018 to January 2020) also received GDLPT. The two study periods were separated by a 1 month washout period that was dedicated to teaching the GDLPT protocol to all nursing and medical staff. The study protocol was approved by the ethics committee of Peking Union Medical College Hospital (approval number: JS-1170). All family members agreed to participating in the study and signed an informed consent form, and the study was registered at chictr.org.cn (identifier: ChiCTR-ROC-17010750).

Figure 1 shows a flow diagram of patient screening and selection for this study. In the nurse-led GDLPT study, 609 of 742 patients were diagnosed with sepsis caused by pneumonia, of whom 253 (41.5%) were older than 65 years. Demographics, comorbidities, clinical parameters, and laboratory data were analyzed.

Intervention and Comparisons

The protocols for pneumonia in the pre- and post-protocol groups are shown in **Figure 2**. Details of this study, including study details such as the intervention objective, methods, and intervention frequency, were the same as those in our previous study (11). The **Supplementary File** provides additional evidence relevant to the intervention and comparisons.

Data Collection

Baseline data of the patients, including sex, age, underlying diseases, the Sequential Organ Failure Assessment (SOFA) score, the Acute Physiology and Chronic Health Evaluation

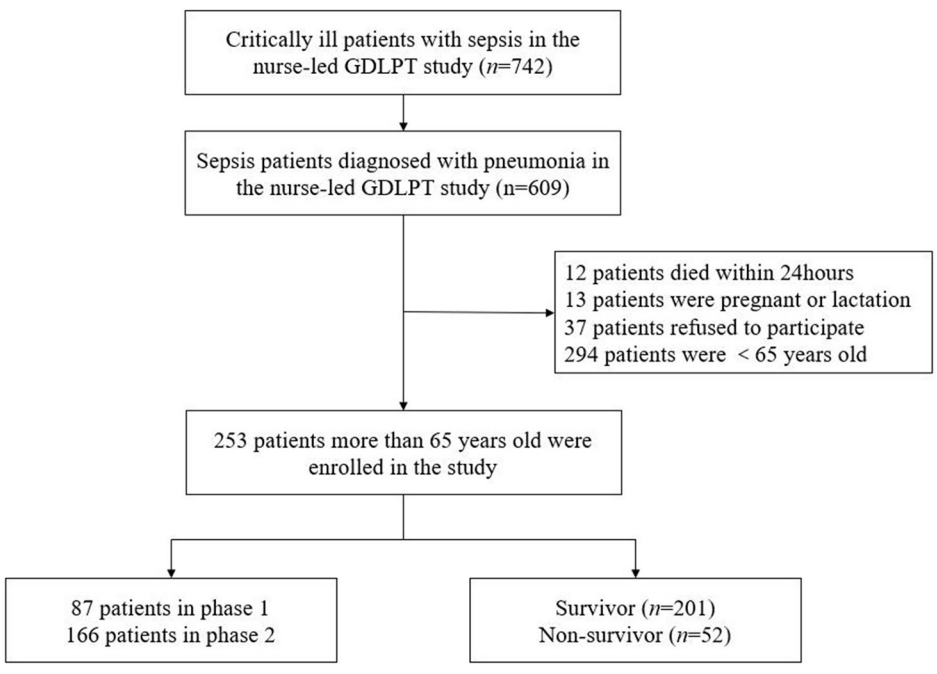

FIGURE 1 | The flowchart of patients screening and selection in this study.

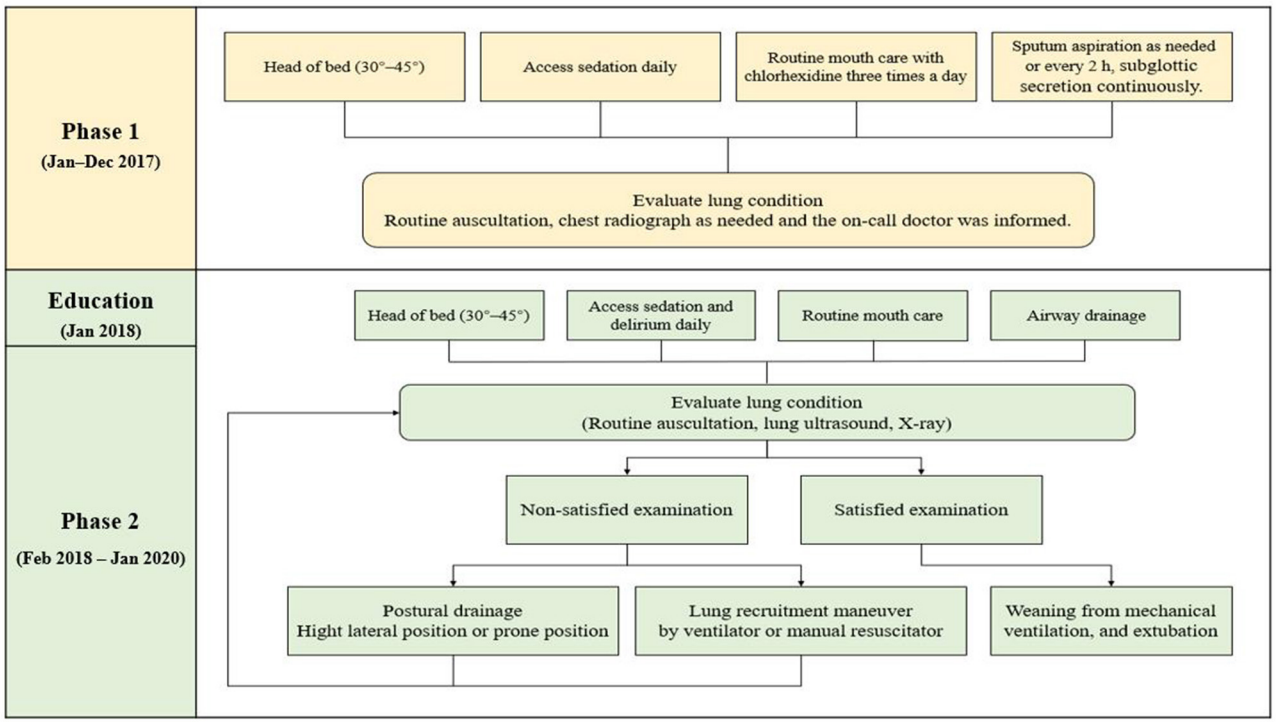

FIGURE 2 | The protocols for pneumonia in the pre- and post-protocol groups.

(APACHE) II score, and the Clinical Pulmonary Infection Score (CPIS), were analyzed. Vital signs, laboratory parameters, arterial blood gases, ventilatory parameters, life-sustaining treatments, and infection-related data during admission were also included. The data used in this study were the worst values in the first 24 h after ICU admission. The primary outcomes of this study were 28 day mortality. The secondary outcomes were the duration of ventilation, the length of the ICU stay, and the ICU mortality rate.

Statistical Analysis

Data were analyzed by IBM SPSS version 21.0 (IBM Corp., Armonk, NY, USA). The frequency and percentage and mean and standard deviation were calculated for descriptive statistics. Bivariate analysis was performed using the chi-square test for categorical variables and the *t* test or one-way analysis of variance for continuous variables. Logistic regression analysis was performed with 28 day mortality as the dependent factor, which was significant ($p < 0.2$) in univariate analysis.

RESULTS

Baseline Characteristics

Among 742 patients with sepsis, 253 patients who were older than 65 years were included in this study. **Table 1** shows the clinical characteristics of the patients who were enrolled in this study. The median age of the patients was 72 years (interquartile range: 68–78 years) and 62.1% (157/253) were men. At admission to the ICU, the mean SOFA score was 11.49 ± 3.95, the median APACHE II score was 18 (12–18), and the median CPIS score was 6 (5–8). Ninety-two (36.4%) patients had heart failure, 19 (7.5%) had chronic obstructive pulmonary disease, 74 (29.2%) had diabetes mellitus, 3 (1.2%) had liver cirrhosis, 44(17.4%) with tumors, and 18 (7.1%) had chronic renal failure. There were no significant differences in age, sex, underlying diseases, source of admission, disease severity scores (APACHE II, SOFA, and CPIS scores), vital signs (heart rate, respiratory rate, and mean arterial pressure), ventilatory parameters, arterial blood gases, clinical laboratory evaluation, life-sustaining treatments, coexisting pathogens, or drug therapy between the two groups after ICU admission.

There was no significant difference in the ICU duration between the groups. Patients in the treatment group had a significantly shorter duration of mechanical ventilation [5 (4, 6) vs. 5 (4, 8) days, $P = 0.045$], and a lower ICU mortality [14.5% (24/166) vs. 28.7% (25/87); $P = 0.008$] and 28 day mortality [15.1% (25/166) vs. 31% (27/87); $P = 0.005$] compared with those in the control group.

Clinical Differences Between Survivors and Non-survivors

The clinical characteristics of all patients and for survivors and non-survivors (28 day) are shown in **Table 2**. Non-survivors had a higher APACHE II score, higher CPIS score, faster respiratory rate, higher carbon dioxide partial pressure on ICU admission, and longer mechanical ventilation compared with survivors (all $P < 0.05$). The rates of heart failure and chronic renal failure

TABLE 1 | Characteristics of patients in the control and treatment groups at ICU admission.

Variables	Sepsis (*n* = 253)	Control (*n* = 87)	Treatment (*n* = 166)	*P*-value
Age (years)	72 (68,78)	72 (68,79)	72 (68,77)	0.512
Sex (male)	157 (62.1)	55 (63.2)	102 (61.4)	0.892
Underlying diseases, *n* (%)				
Chronic obstructive pulmonary disease	19 (7.5)	7 (8)	12 (7.2)	0.806
Heart failure	92 (36.4)	39 (44.8)	53 (31.9)	0.054
Diabetic mellitus	74 (29.2)	25 (28.7)	49 (29.5)	1
Liver Cirrhosis	3 (1.2)	1 (1.1)	2 (1.2)	1
Tumor	44 (17.4)	10 (11.5)	34 (20.5)	0.082
Chronic renal failure	18 (7.1)	8 (9.2)	10 (6)	0.44
Source of admission, *n* (%)				
Internal medicine	40 (15.8)	16 (18.4)	24 (14.5)	0.469
Surgery	75 (29.6)	23 (26.4)	52 (31.3)	0.47
Emergency	62 (24.5)	18 (20.7)	44 (26.5)	0.357
Outside hospital	76 (30.0)	24 (27.6)	52 (31.3)	0.567
Disease severity scores				
APACHE II score	18 (16,22)	18 (15,21)	19 (16,22.25)	0.373
Sequential organ failure score	11.49 ± 3.95	11.23 ± 3.88	11.62 ± 4	0.457
Clinical pulmonary infection score	6 (5,8)	8 (6,9)	8 (6,9.3)	0.789
Vital signs				
Heart rate (beats/min)	99 (86.5,115.5)	101 (90,115)	98 (85,116)	0.38
Respiratory rate (breaths/min)	22 (17,27)	22 (17,26)	22 (18,27)	0.748
Mean artery pressure (mm Hg)	88.02 ± 12.64	88.32 ± 12.82	87.86 ± 12.58	0.781
Ventilator parameters				
Tide volume (ml)	420 (390,480)	430 (400,480)	410 (390,482.5)	0.192
Inhalation oxygen concentration (%)	0.35 (0.3,0.4)	0.35 (0.28,0.40)	0.35 (0.31,0.4)	0.064
Artery blood gas				
Lactic acid (mmol/L)	2 (1,2)	2 (1,2)	2 (1,2)	0.673
Arterial oxygen pressure (mm Hg)	95.7 (78.45,116.84)	94.76 (80.7,116.8)	96 (77.87,116.97)	0.706
Carbon dioxide partial pressure (mm Hg)	39 (35.7,43.45)	39 (35.6,42.1)	38.95 (35.85,44.03)	0.742
Oxygen index	284 (207.5,360.5)	287 (227,380)	277.5 (202.75,348.5)	0.203
Clinical laboratory evaluation				
Creatinine (umol/L)	86 (67.5,146)	107 (73,169)	81 (61.5,144.25)	0.086
Albumin level (g/L)	32 (29,35)	32 (28,35)	31.5 (29,34)	0.597
Total bilirubin (umol/L)	16.7 (14.1,24.35)	16.5 (13.4,24.2)	16.7 (14.38,24.73)	0.247
Life-sustaining treatments, *n* (%)				
Need for mechanism ventilation	238 (94.1)	83 (95.4)	155 (93.4)	0.589
Need for vasopressor	163 (64.4)	53 (60.9)	110 (66.3)	0.41
Need for RRT	53 (20.9)	14 (16.1)	39 (23.5)	0.195
Coexisting pathogens, *n* (%)				
Bacteria	216 (85.4)	78 (89.7)	138 (83.1)	0.192
Fungal	26 (10.3)	7 (8)	19 (11.4)	0.515
Else	5 (2)	0 (0)	5 (3)	0.168
Drug therapy, *n* (%)				
Antibiotics for GNB	189 (74.7)	64(73.6)	125 (75.3)	0.763
Antibiotics for GPB	237 (93.7)	83(95.4)	154 (92.8)	0.588
Antifungal drugs	85 (33.6)	31(35.6)	54 (32.5)	0.675
Outcomes				
Ventilation day (days)	5 (4,7)	5 (4,8)	5 (4,6)	0.045
ICU duration (days)	10 (5,19)	9 (6,20)	10 (4,18.25)	0.699
ICU mortality, *n* (%)	49 (19.4)	25 (28.7)	24 (14.5)	0.008
28 day mortality, *n* (%)	52 (20.6)	27 (31)	25 (15.1)	0.005

Continuous variables are expressed as mean ± standard deviation or median (interquartile range). P-values reflect comparisons between the control and treatment groups. ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation II; oxygen index, (partial pressure of oxygen) / (fraction of inspirated oxygen); RRT, continuous renal replacement therapy; GPB, Gram-positive bacteria; GNB, Gram-negative bacteria.

TABLE 2 | Characteristics of the study population in survivors and non-survivors according to 28 day mortality.

Variables	Sepsis (*n* = 253)	Non-Survival (*n* = 52)	Survival group (*n* = 201)	*P*-value
Age (years)	72 (68,78)	73 (69,78)	71 (68,78)	0.214
Sex (male)	157 (62.1)	34 (65.4)	123 (61.2)	0.633
Underlying diseases, *n* (%)				
Chronic obstructive pulmonary disease	19 (7.5)	7 (13.5)	12 (6.0)	0.079
Heart failure	92 (36.4)	28 (53.8)	64 (31.8)	0.006
Diabetic mellitus	74 (29.2)	20 (38.5)	54 (26.9)	0.124
Liver Cirrhosis	3 (1.2)	1 (1.9)	2 (1.0)	0.5
Tumor	44 (17.4)	13 (25.0)	31 (15.4)	0.149
Chronic renal failure	18 (7.1)	10 (19.2)	8 (4.0)	0.001
Source of admission, *n* (%)				
Internal medicine	40 (15.8)	6 (11.5)	34 (16.9)	0.348
Surgery	75 (29.6)	16 (30.8)	59 (29.4)	0.866
Emergency	62 (24.5)	12 (23.1)	50 (24.9)	0.858
Outside hospital	76 (30.0)	16 (30.8)	60 (29.9)	1
Disease severity scores				
APACHE II score	18 (16, 22)	21.5 (17, 26)	18 (15, 21)	0.001
Sequential organ failure score	11.49 ± 3.95	12.33 ± 3.82	11.27 ± 3.97	0.085
Clinical pulmonary infection score	6 (5, 8)	8 (6, 9)	6 (5, 8)	0.0001
Vital signs				
Heart rate (beats/min)	99 (86.5,115.5)	105 (90,119.75)	98 (85,114)	0.064
Respiratory rate (breaths/min)	22 (17,27)	24 (20,28)	21 (17,27)	0.039
Mean artery pressure (mm Hg)	88.02 ± 12.64	86.58 ± 13.63	88.39 ± 12.38	0.358
Ventilator parameters				
Tide volume (ml)	420 (390,480)	410 (392.5,480)	420 (390,490)	0.425
Inhalation oxygen concentration (%)	0.35 (0.3,0.4)	0.37 (0.32,0.42)	0.35 (0.3,0.4)	0.188
Artery blood gas				
Lactic acid (mmol/L)	2 (1, 2)	2 (1, 2)	2 (1, 2)	0.727
Arterial oxygen pressure (mm Hg)	95.7 (78.45,116.84)	103.35 (78.28,118.69)	93.31 (78.83,115.44)	0.125
Carbon dioxide partial pressure (mm Hg)	39 (35.7,43.45)	41 (36.25,46.23)	38.8 (35.5,42.85)	0.035
Oxygen index	284 (207.5,360.5)	282.5 (218.25,365.75)	284 (206.5,360.5)	0.952
Clinical laboratory evaluation				
Creatinine (umol/L)	86 (67.5,146)	114 (74.25,146.25)	83 (62,146)	0.103
Albumin level (g/L)	32 (29,35)	31 (29,33)	32 (28.5,35)	0.375
Total bilirubin (umol/L)	16.7 (14.1,24.35)	17.2 (12.73,40.63)	16.5 (14.2,23.5)	0.957
Life-sustaining treatments, *n* (%)				
Need for mechanism ventilation	238 (94.1)	51 (98.1)	187 (93)	0.319
Need for vasopressor	163 (64.4)	35 (67.3)	128 (63.7)	0.745
Need for RRT	53 (20.9)	17 (32.7)	36 (17.9)	0.034
Coexisting pathogens, *n* (%)				
Bacteria	216 (85.4)	47 (90.4)	169 (84.1)	0.377
Fungal	26 (10.3)	7 (13.5)	19 (9.5)	0.442
Else	5 (2)	0 (0)	5 (2.5)	0.587
Drug therapy, *n* (%)				
Antibiotics for GNB	189 (74.7)	37 (71.2)	152 (75.6)	0.591
Antibiotics for GPB	237 (93.7)	51 (98.1)	186 (92.5)	0.205
Antifungal drugs	85 (33.6)	21 (40.4)	64 (31.8)	0.253
Received nurse-led GDLPT	166 (65.6)	25 (48.1)	141 (70.1)	0.005
Outcomes				
Mechanical ventilation days (days)	5 (4, 7)	5.5 (5, 12)	5 (4, 6)	0.0001
ICU duration (days)	10 (5, 19)	11 (7, 20)	9 (5, 19)	0.22

Continuous variables are expressed as mean ± standard deviation or median (interquartile range). P-values reflect comparisons between the survivor and non-survivor groups. ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation II; oxygen index, (partial pressure of oxygen) / (fraction of inspirated oxygen); RRT, continuous renal replacement therapy; GPB, Gram-positive bacteria; GNB, Gram-negative bacteria; GDLPT, goal-directed lung physiotherapy.

TABLE 3 | Multivariate logistic regression analysis for predicting 28 day mortality in older patients with sepsis and pneumonia.

Parameters	OR	95% CI	*p*-value
Heart failure	2.779	1.360–5.679	0.005
Tumor	2.825	1.181–6.757	0.020
Inhalation oxygen concentration	2.438	0.094–63.291	0.592
Creatinine	0.999	0.995–1.003	0.564
Need for continuous renal replacement therapy	2.450	1.122–5.351	0.025
Received nurse-led GDLPT	0.379	0.187–0.766	0.007
Mechanical ventilation days	1.147	1.055–1.247	0.001

GDLPT, goal-directed lung physical therapy; OR, odds ratio; CI, confidence interval.

were significantly higher in non-survivors than in survivors (both $P < 0.05$). The requirement for renal replacement therapy was significantly more frequent in the in non-survivors compared with survivors (32.7 vs. 17.9%, $P = 0.034$). Importantly, more patients received nurse-led GDLPT in survivors than in non-survivors (70.1 vs. 48.1%, $P = 0.005$).

Risk Factors for 28 Day Mortality in Older Patients With Sepsis Caused by Pneumonia

Multivariate logistic regression analysis identified five factors that independently predicted 28-day mortality in patients with sepsis who were diagnosed with pneumonia. These factors were nurse-led GDLPT [odds ratio (OR), 0.379; 95% confidence interval (CI), 0.187–0.766; $P = 0.007$], heart failure (OR, 2.779; 95% CI, 1.360–5.679; $P = 0.005$), tumor (OR, 2.825; 95% CI, 1.181–6.757; $P = 0.02$), need for renal replacement therapy (OR, 2.450; 95% CI, 1.122–5.351; $P = 0.025$), and mechanical ventilation days (OR, 1.147; 95% CI, 1.055–1.247; $P = 0.001$). GDLPT was a protective factor for 28 day mortality (**Table 3**).

DISCUSSION

Pneumonia is frequently encountered in older patients admitted to the ICU, with an incidence rate of >60% in those with sepsis (6). In numerous clinical studies, lung physiotherapy was analyzed in patients with various critical diseases (12, 13, 19). However, little is known about nurses providing lung physiotherapy to older patients with sepsis and pneumonia. Furthermore, the effect of lung physiotherapy on the prognosis of these patients is unclear. In this study, we found that nurse-led GLDPT was associated with shorter ventilation days, and reduced ICU mortality and 28 day mortality rates.

With aging, there are significant changes in the anatomical and physiological function of the lungs. Older people are more likely to develop pulmonary complications and underlying diseases, including COPD, aspiration, pneumonia, tumor, heart failure, chronic renal failure, and have a poor prognosis (14). The GDLPT protocol has several advantages over conventional physiotherapy. One advantage is that the frequency of oral care is determined by the Beck Oral Assessment Scale score and mucosal-plaque score. Another advantage is that enhancement of airway drainage is conducted every 4 h for 20 to 30 min each time, with a vibration frequency of 20 to 30 Hz. Additionally, the cough strength is evaluated every 6 h. Older people with a weak cough are more likely to have nosocomial pneumonia and aspiration pneumonia (15). In the USA, the incidence of aspiration pneumonia in older patients is 30.9 cases per 10,000 people, which is twice that in patients aged < 65 years (16). A further advantage is that airway humidification is evaluated regularly to maintain humidification at degree II (17). For patients with specific pulmonary consolidation, goal-directed patient positioning is actively used. The frequency of turning over is adjusted, and a lung recruitment maneuver is also performed through mechanical ventilation or a manual resuscitator. Therefore, as a non-invasive intervention strategy, nurse-led GDLPT is useful for older patients with pneumonia.

In this nurse-led GDLPT study, pain assessment, delirium assessment, and active early activities were carried out every 6 h by nurses. Delirium varies from 11 to 42% in older patients and has adverse outcomes and high health care costs (18). Up to 60% of delirious patients were unrecognized unless actively screened, and sedative medications and deeper sedation are associated with the development of delirium (20). According to the patient's delirium status, early activities were carried out, such as sitting at the wheel and early walking. Frailty in older patients is also a risk of a longer ICU stay, prolonged ventilation duration, and increased mortality. Early exercise is the most effective intervention for debilitating syndrome and significantly improves muscle strength. In this nurse-led GDLPT study, old patients without delirium were able to get out of bed into a wheelchair early or walk early after therapy. Additionally, patients with intermittent delirium were able to perform bedside wheelchair activity, and patients with continuous delirium were able to receive passive movement in bed or sitting upon the bed. The nurse-led GDLPT protocol was formulated in the critical clinical setting and designed using more than 20 years of clinical experience, with specific items and strong operability. This therapy enabled good management of older patients.

In this study, nurse-led GDLPT significantly shortened the duration of ventilation. Prolonged mechanical ventilation might result in an increased incidence of ventilator-associated pneumonia, which is clinically meaningful, especially for older patients with pneumonia. A high frequency of antibiotic use and antibiotic resistance in patients is caused by ventilator-associated pneumonia. The prevalence of multidrug resistance is increasing, and ventilator-associated pneumonia caused by multidrug resistance is often fatal in the ICU (21). Several factors such as the CPIS score, and the APACHE II score contribute to a high percentage of multidrug resistance in the ICU and are important reasons for the poor prognosis of older patients with sepsis and pneumonia (22).

At present, older patients with a critical illness are frequently admitted in the ICU. However, data on older patients with pneumonia are relatively rare, and there have been few evidence-based medical reports (23). This study was a retrospective analysis based on data from a previous nurse-led GDLPT study. All collected data, including vital signs, ventilatory parameters, and laboratory indicators, were obtained from electronic information systems. Data were double checked to

minimize the risk of data entry errors and there were missing data. Therefore, prospective, randomized, controlled trials are required to further investigate the role of nurse-led GDLPT on older patients with pneumonia. The nurse-led GDLPT study was a prospective, before-and-after study in a single center. Therefore, a multicenter study needs to be performed to further examine the details of GDLPT and validate its wide applicability in older patients with pneumonia.

CONCLUSIONS

Managing pneumonia in critically ill older patients is a complex issue. Aging, comorbidities, frailty, and other factors in older patients significantly increase the management requirements and risks for those with critical illness. Nurse-led GDLPT significantly shortens the duration of ventilation and improves the 28 day mortality rate in older patients with sepsis and pneumonia. Nurse-led GDLPT is a new clinical intervention for the refined management of older patients with pneumonia, and it promotes the recovery of older patients with severe pneumonia.

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

The studies involving human participants were reviewed and approved by the Institutional Review Board of Peking Union Medical College Hospital (No. JS-1170). The study was registered at chictr.org.cn (identifier: ChiCTR1900025850). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NC, QL, HW, and JS contributed to the conception of the study, data interpretation, and drafted the manuscript. WH, HL, and MZ contributed to the data collection and data analysis. WC and ZL contributed to data collection and interpretation and critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

FUNDING

The work was supported by National Natural Science Foundation of China (No. 82072226), Beijing Municipal Science and Technology Commission (No. Z201100005520049), Fundamental Research Funds for the Central Universities (No. 3332021018), Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (No. 2019XK320040), Tibet Natural Science Foundation (No. XZ2019ZR-ZY12(Z)), and Excellence Program of Key Clinical Specialty of Beijing in 2020 (No. ZK128001).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.753620/full#supplementary-material

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frontiers in Medicine

SYSTEMATIC REVIEW
published: 22 November 2021
doi: 10.3389/fmed.2021.731196

Comparative Efficacy and Safety of Four Different Spontaneous Breathing Trials for Weaning From Mechanical Ventilation: A Systematic Review and Network Meta-Analysis

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OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

Received: 26 June 2021
Accepted: 19 October 2021
Published: 22 November 2021

Citation:
Yi L-J, Tian X, Chen M, Lei J-M, Xiao N and Jiménez-Herrera MF (2021) Comparative Efficacy and Safety of Four Different Spontaneous Breathing Trials for Weaning From Mechanical Ventilation: A Systematic Review and Network Meta-Analysis. Front. Med. 8:731196. doi: 10.3389/fmed.2021.731196

Background: Spontaneous breathing trial (SBT) has been used to predict the optimal time of weaning from ventilator. However, it remains controversial which trial should be preferentially selected. We aimed to compare and rank four common SBT modes including automatic tube compensation (ATC), pressure support ventilation (PSV), continuous positive airway pressure (CPAP), and T-piece among critically ill patients receiving mechanical ventilation (MV).

Methods: We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify studies that investigated the comparative efficacy and safety of at least two SBT strategies among critically ill patients up to May 17, 2020. We estimated the surface under the cumulative ranking curve (SUCRA) to rank SBT techniques, and determined the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation method. Primary outcome was weaning success. Secondary outcomes were reintubation, SBT success, duration of acute care, and intensive care unit (ICU) mortality. Statistical analysis was conducted by using RevMan 5.4, Stata, and R software.

Results: We enrolled 24 trials finally. Extubation success rate was significantly higher in ATC than that in T-piece (OR, 0.28; 95% CI, 0.13–0.64) or PSV (OR, 0.53; 95% CI, 0.32–0.88). For SBT success, ATC was better than other SBT techniques, with a pooled OR ranging from 0.17 to 0.42. For reintubation rate, CPAP was worse than T-piece (OR, 2.76; 95% CI, 1.08 to 7.06). No significant difference was detected between SBT modes for the length of stay in ICU or long-term weaning unit (LWU). Similar result was also found for ICU mortality between PSV and T-piece. Majority direct results were confirmed by network meta-analysis. Besides, ATC ranks at the first, first, and fourth place with a SUCRA of 91.7, 99.7, and 39.9%, respectively in increasing weaning success and SBT success and in prolonging ICU or LWU length of stay among four SBT strategies. The confidences in evidences were rated as low for most comparisons.

Conclusion: ATC seems to be the optimal choice of predicting successful weaning from ventilator among critically ill patients. However, randomized controlled trials (RCTs) with high quality are needed to further establish these findings.

Keywords: spontaneous breathing trials, weaning, mechanical ventilation, meta-analysis, systematic review

INTRODUCTION

Successful weaning from mechanical ventilation (MV) refers to the gradual transition from total artificial ventilation support to spontaneous breathing. Delayed disconnection from ventilator can be associated with numerous complications, such as ventilator-associated pneumonia, airway trauma, and multiple-organ failure (MOF) (1–3). The risk of complications and mortality may accrue with increasing duration of MV (4). Therefore, it is essential to timely and safely liberate patients from mechanical ventilator when they have restored the ability of spontaneous breathing (5–8).

Spontaneous breathing trial (SBT) is one of the most common approaches to facilitate the disconnection from MV (9). Evidence-based guidelines have also recommended to conduct SBT immediately before extubation for the purpose of assessing whether a patient is able to restore the ability of spontaneous breath, and thus determine the optimal time for disconnecting from ventilator (10–14). At present, T-piece, continuous positive airway pressure (CPAP), pressure support ventilation (PSV), and automatic tube compensation (ATC) are the most common ventilation techniques (11, 12, 15–20). SBT strategies focused in this study can be categorized into three categories as follows: (a) providing constant or dynamic ventilatory support to counteract the resistance of the endotracheal tube such as PSV and ATC (21–23), (b) providing continuous positive pressure in both inspiration and expiration to enhance breathing mechanics and reduce the effort needed by mechanically ventilated patients with airflow obstruction such as CPAP (24–27), and (c) accelerating spontaneous breath of patients without positive pressure support such as T-piece, which is related to more frequent respiratory activity and consumption of more oxygen (28, 29).

Disconnection from mechanical ventilator should be conducted when patients do not experience any intolerable events after accomplishing SBT (5). However, it is still conflicting as to which SBT should be preferentially selected in route daily practice. Although many studies comparing the efficacy and safety of more than two SBT strategies have been published (21, 22, 30–40, 94), only one (32) investigated the comparative efficacy and safety of all available SBT modes simultaneously at one analysis and suggested that ATC might be superior to T-tube or CPAP for extubation success and tolerance. It must be noted that the reliability of these findings should be interpreted cautiously because these findings were generated from a single-center trial with a limited sample size. Moreover, standard ventilators were utilized in this study, which deeply compromised the accurate compensation of ATC, provided an for the workload imposed by the tube (32). Furthermore, a direct meta-analysis (41) evaluated the efficacy of common types of SBTs, and revealed that patients receiving PSV (vs. T-tube) were more likely to obtain successful extubation. However, this meta-analysis ignored the variations in populations (children and adult) and study design (randomized and quasi-randomized trials) and only provided fragmentary pairwise results, all of which limited the value of pooled results.

As an expansion of direct meta-analysis, network meta-analysis (NMA) can simultaneously combine multiple treatments (more than two) in an individual analysis at one time. Consequently, it can make comprehensive assessments of the differences between all available treatments and clearly display the hierarchies of available treatments (42, 43). We therefore conducted the present NMA of randomized controlled trials (RCTs) to comprehensively compare and rank four common SBT strategies among critically ill patients who required invasive MV for at least 24 h through evaluating weaning success, reintubation, SBT success, duration of acute care, and ICU mortality.

METHODS

We conducted the present study and reported all pooled results according to the preferred reporting items for systematic review and meta-analysis for NMA (PRISMA-NMA) (44). The completed PRISMA-NMA checklist is available in **Supplementary Table 1**. No informed consent and institutional ethical approval if the patients were required because all analyses were completed based on published data.

Information Sources

We conducted a systematic literature search in PubMed, EMBASE, and CENTRAL from their inception until to May 17, 2020, and the latest search was updated on May 28, 2021. No restriction on language was imposed. The following terms were used to construct search strategy based on principle of combination of medical subject heading (MeSH) and text words: "ventilator weaning," "spontaneous breathing trial," "artificial respiration," "random," and various SBT techniques. Details of electronic search strategies and results identified are summarized in **Supplementary Table 2**. Any disagreements about study retrieval were solved based on consensus between two authors.

Study Selection

All identified potentially eligible records were firstly imported into EndNote to develop a literature database, and then duplicate records were automatically eliminated by software.

In the next step, two authors (LJY and XT) independently evaluated eligibility of unique records through screening titles and abstracts. Finally, they retrieved full-texts of all potentially relevant studies for further checking eligibility. To avoid literature omissions, clinical trial registry (such as www.clinicaltrials.gov) was also searched for unpublished and undergoing trials. Moreover, reference lists of included studies and relevant reviews were also manually screened to identify additional studies. Any controversies were solved based on consensus or adjudication with a third author (MC).

Selection Criteria

For inclusion, a study should meet the following criteria: (a) enrolled adult patients suffering from respiratory failure who received invasive MV for at least 24 h regardless of gender; (b) compared at least two SBT techniques (T-piece, CPAP, ATC, or PSV); (c) reported at least one of the following outcomes including weaning success, reintubation, SBT success, duration of acute care, and ICU mortality; (d) used a RCT design with full-text. Moreover, abstract with sufficient information was also considered. A study was excluded if it covered at least one of the following criteria: (a) evaluated SBT methods in tracheostomized patients or in patients receiving noninvasive ventilation; (b) SBTs was only used as a part of the comprehensive weaning strategy; (c) with insufficient information and additional data cannot be added from authors; (d) used ineligible study design such as crossover design, quasi-randomized trials, observational studies, and commentary; and (e) duplicate study with poor methodology and insufficient data.

Definition of Outcome

Our primary outcome was weaning success, which was defined as the absence of reintubation and/or resumption of ventilatory support for 48 h after extubation (45, 94). Secondary outcomes included reintubation rate (which was defined as the rate of reintubation within 48 h following extubation) (45, 94), successful SBT (if the patient showed no signs of intolerance when the SBT was performed, the SBT was considered successful) (45, 94), duration of ICU or long-term weaning unit (defined as the time from randomization to ICU or LWU) (46), and ICU mortality (defined as rate of the number of deaths during staying in ICU was divided by the number of all patients) (46).

Data Extraction

Two authors independently extracted the following relevant information from eligible studies with a predesigned standard information extraction sheet:(a) details of the studies including the first author's name, publication year, country, publication type, study design, types of intervention and control;(b) population characteristics including ventilation time before SBT, age, and severity of the disease; (c) reported outcomes including primary and secondary outcomes. What's more, we also extracted the information about quality of included studies. Discrepancies were resolved through consulting a third author. Leading author was contacted *via* email if the information of interest is absent.

Risk of Bias Assessment

Two independent authors assessed the methodological quality by using the Cochrane risk of bias assessment tool from the following seven items (47, 48): random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other bias. Each item was labeled as low, unclear, or high risk of bias according to the evaluation criteria (47). Among these target outcomes, all except for two (ICU mortality and ICU duration) depended on subjective judgement, which means the existence of different detection bias; therefore we performed risk of bias assessment respectively. We usually assume that blinding of outcome assessment was generally low risk of bias for objective outcomes.

Geometry of the Network

Network plots were produced to visualize the body of available evidence. In network geometry, each node represents a treatment and each line between the nodes represents a direct comparison. The size of the nodes and the thickness of the lines are proportional to total sample size and precision, respectively.

Statistical Analysis

All analyses were done using RevMan 5.3 (used for pairwise meta-analysis) and R version 3.6.1 (used for conducting NMA with gemtc package, assessing global heterogeneity, and calculating the surface under the cumulative ranking curve [SUCRA]) and STATA version 15.0 (used for estimation of inconsistency and local heterogeneity, funnel plot, and contribution plot).

Methods for Direct Treatment Comparisons

We conducted a pairwise meta-analysis for all comparisons by using the DerSimonian–Laird (DL) random-effects model. Odds ratio (OR) with 95% confidence interval (CI) was calculated for dichotomous outcome, whereas standardized mean difference with 95% CI was calculated for continuous outcome. We used Chi square and I^2 statistic simultaneously to evaluate the heterogeneity across studies. I^2 statistic measures the proportion of the overall variation that is attributable to between-study heterogeneity and $I^2 \geq 50\%$ was deemed as substantial heterogeneity (49, 50). For studies with multiple arms, outcome data were extracted from each group that meets the inclusion criteria, and then were created independent pairwise comparisons (43).

Methods for Indirect and Mixed Comparisons

For each endpoint, a Bayesian random-effects NMA (51, 52) was conducted to combine direct and indirect results. We calculated the relative ranking probabilities of being the best, second best for each weaning method, and so on. What's more, we also employed the SUCRA to estimate the ranking probabilities for available weaning methods on various outcomes (53). When one weaning technique is regarded as the best one without uncertainty, SUCRA value equals 1. If not, we draw an opposite conclusion (53, 54).

Assessment of Consistency and Heterogeneity

To explore the inconsistency of the entire network, the design-by treatment interaction model was used (55, 56). By using the "ifplot" command, inconsistency factor (IF) was calculated in each closed loop (a loop is made up of three technologies) to estimate the local inconsistencies, with values near 1 denoting statistical consistency (57, 58). Besides, a node-splitting method was undertaken to assess the potential inconsistency between the direct and indirect evidence for each comparison, which is a node in a direct acyclic graph (59). A P of more than 0.05 was deemed as consistent, which implied that the information from both sources of evidence contains enough similarities to be combined (60). A global heterogeneity was quantified using the I^2-statistic. The prediction intervals for the pooled ORs provided a limited range in which the relative effect of a future similar study is expected to be involved (61, 62). The predictive interval plot, considering the extent of heterogeneity, was used to assess the magnitude of uncertainty in the estimated effect size for the NMA (63). If uncertainty is affected by heterogeneity, discordances exist between the confidence intervals of relative treatment effects and their predictive intervals.

Contribution Plot and Publication Bias

A contribution plot revealed the influence of each direct comparison to the estimation of the network summary effects, which helped to make an objective appraisal of the overall quality of evidence from NMA (58, 64). A comparison-adjusted funnel plot was constructed to inspect the small-study effects when sufficient number of eligible studies were analyzed in a single pair of comparison (<10) (65).

GRADE Evaluation on Quality of Evidence

We evaluated the certainty of evidence contributing to all network estimates of the primary outcomes by using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework (66). Disagreements„ if any, were resolved by consulting a third researcher.

RESULTS

Study Selection and Characteristics

After assessment of 105 full-text articles, 24 publications involving 4,241 subjects were included to investigate the efficacy of T-piece, PSV, CPAP, and ATC in critically ill patients weaning from MV (21, 22, 30–40, 45, 67–75, 94). We designed **Figure 1** to outline the details of capturing and selecting studies.

The baseline characteristics of included articles are summarized in **Supplementary Table 3**. The majority of the studies were designed double-arm trials (21/24, 87.5%) (21, 30, 31, 33–37, 39, 40, 45, 67–75, 94). Publication year was between 1991 and 2020, and the number of participants of individual study ranged from 14 to 578. To illustrate the head-to-head comparisons involved in the NMA, network plots for four outcomes were delineated in **Figure 2**. T-piece (20 studies) (21, 22, 31–33, 35, 37–40, 45, 67–73, 75, 94) and PSV (20 studies) (22, 31–33, 35–39, 45, 67, 69–75, 94) were the most frequently investigated SBT methods, whereas CPAP (six studies) (21, 22, 30, 32, 34, 38, 40, 68) and ATC(six studies) (32, 34, 36, 74) acquired fewer samples, thus suggesting a higher potential deviation in traditional meta-analysis.

Methodological Quality of Studies

Out of 24 RCTs, seven (29.1%) (32, 33, 35, 36, 45, 74, 75) did not describe the method of generating random sequence. Eight RCTs (33.3%) (33, 35, 36, 38, 39, 71, 74, 75) did not report the details of allocation concealment, which could cause potential selection bias. Besides, one study (34) stated that personnel supervising of the SBTs failed to conceal allocation, and was therefore considered to present a high risk of bias. For subjective outcomes (weaning success, reintubation, and SBT success), eight studies (21, 22, 30, 31, 34, 38, 68, 94) provided details on blinding of outcome assessors, and three articles (37, 67, 71) did not evaluate outcomes in a blinded manner. Since all studies stated a clear patient flow or used intention-to-treat analysis, there was no hint of attrition bias. What's more, no study selectively reported results. Risk of bias summary was documented in **Supplementary Table 4**.

Weaning Success

The effects of four extubation strategies on weaning success from pairwise metaanalyses can be found in **Figure 2A**. Among six direct comparisons in direct random-effects meta-analysis, ATC was associated with increased weaning success rate compared with T-piece (OR, 0.28; 95% CI, 0.13 to 0.64) and PSV (OR, 0.53; 95% CI, 0.32 to 0.88), respectively. Remaining comparisons were not statistically significant (see **Supplementary Figure 1**).

In NMA, ATC was superior to the T-piece (OR, 0.34; 95% CI, 0.17 to 0.65) and PSV (OR, 0.5; 95% CI, 0.27 to 0.92) in terms of weaning success, respectively. Besides, an improvement effect of weaning success was detected for the comparison between PSV and T-piece (OR, 0.68; 95% CI, 0.45 to 0.98). **Figure 3A** reported all pooled results of the NMA.

Reintubation

Of all 24 eligible RCTs, 17 (21, 22, 30–32, 37–40, 45, 67–69, 71–73, 94) reported the reintubation within 48 h following extubation, which included six direct comparisons (**Figure 2B**). CPAP could slightly decrease reintubation compared with T-piece (OR, 2.76; 95% CI, 1.08 to 7.06). All pooled results from traditional meta-analysis can be found in **Supplementary Figure 2**.

In NMA, all comparisons did not show significant effects on reintubation. All pooled results can be found in **Figure 3B**.

SBT Success

Of all eligible RCTs, 13 (21, 22, 32, 34, 39, 45, 67, 68, 70–73, 94) reported SBT success, which included six direct comparisons (**Figure 2C**). In all direct comparisons, the comparative efficacy of T-piece vs. PSV (OR, 0.61; 95% CI, 0.46 to 0.80), T-piece vs. ATC (OR, 0.17; 95% CI, 0.06 to 0.50), PSV vs. ATC (OR, 0.42; 95% CI, 0.20 to 0.90), and CPAP vs. ATC (OR, 0.21; 95% CI, 0.08 to 0.58) reached statistical significance. All pooled results from direct comparisons can be obtained in **Supplementary Figure 3**.

The results of comparisons of SBT success in our NMA are presented in **Figure 3C**. ATC exerted a trend of high SBT success

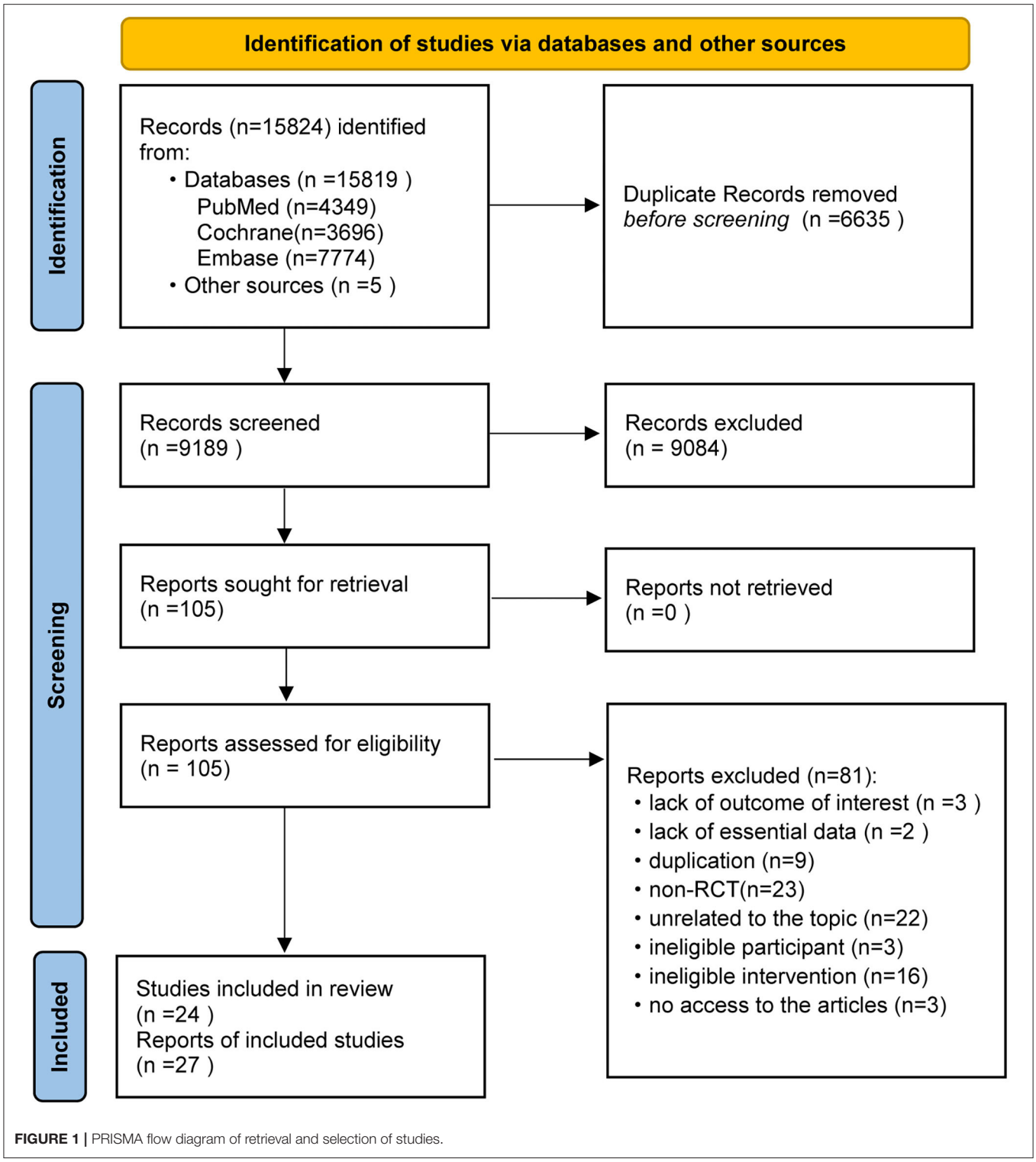

FIGURE 1 | PRISMA flow diagram of retrieval and selection of studies.

when compared with T-piece (OR, 0.21; 95% CI, 0.1–0.45), PSV (OR, 0.35; 95% CI, 0.16–0.73), and CPAP (OR, 0.22; 95% CI, 0.08–0.52), respectively. PSV had significant superiority over T-piece in SBT success (OR, 0.59; 95% CI, 0.43–0.84).

ICU or LWU Length of Stay

Of all included RCTs, seven (31, 32, 36, 39, 69–71) reported ICU or LWU length of stay, which included six direct-comparisons (**Figure 2D**). In all six direct-comparisons, no

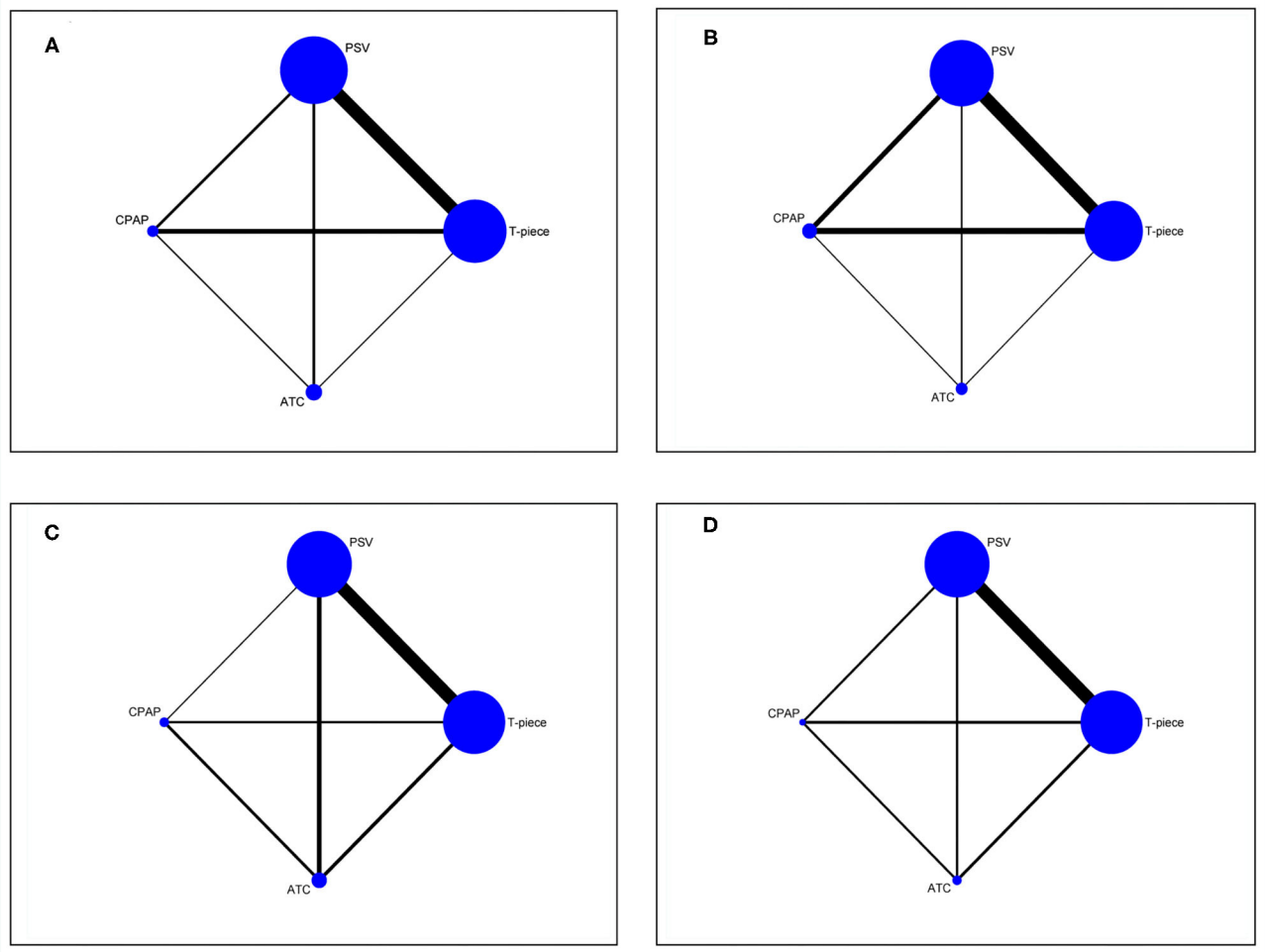

FIGURE 2 | Evidence structure of eligible comparisons for network meta-analysis. **(A)** weaning success. **(B)**. reintubation. **(C)** SBT success. **(D)** ICU or LWU length of stay. All SBT techniques are represented as blue solid circles, and existing head-to-head (direct) comparisons are drawn as black solid lines. The size of every node is proportion to the number of randomly assigned participants (sample size) and the width of the lines is proportion to the number of RCTs for each pairwise comparison. PSV, pressure support ventilation; CPAP, continuous positive airway pressure; ATC, automatic tube compensation.

major differences between the four extubation technologies were observed (**Supplementary Figure 4**). In NMA, no significant difference was observed in any comparisons (**Figure 3D**).

ICU Mortality

Of all 24 eligible studies, 10 RCTs (31, 35, 39, 45, 67, 69–71, 73, 94) which focused exclusively on T-piece and PSV investigated the ICU mortality. Direct evidence supports that there was no significant difference in the effect of PSV and T-piece (OR, 1.19; 95% CI, 0.89 to 1.59) without heterogeneity ($I^2 = 0\%$) (**Supplementary Figure 5**).

Assessment of Consistency and Heterogeneity

The test of global inconsistency detected no significant difference between the consistency and inconsistency models for four outcomes ($P = 0.690$ for weaning success, $P = 0.523$ for reintubation, $P = 0.951$ for STB success, and $P = 0.308$ for ICU or LWU length of stay, respectively). For four outcomes, test for local inconsistency showed that all loops were consistent (**Supplementary Figure 6**). Predictive interval plot indicated 33.3%, 0.00%, 33.3%, and 0.00% of the comparisons for weaning success, reintubation, SBT success, and ICU or LWU length of stay respectively, and therefore no outcomes was substantially affected by the estimated heterogeneity in the network (**Supplementary Figure 7**). The common heterogeneity through the Bayesian meta-analysis was 0.224 for weaning success, 0.020 for reintubation, 0.036 for SBT success, and 0.000 for ICU or LWU length of stay.

SUCRA and Ranking of all Treatments

We showed the mean values of SUCRA for providing the hierarchy ranking of different weaning technologies on weaning success, reintubation, SBT success, and ICU or LWU length of stay. According to SUCRA, T-piece ranked fourth, second, third, and second on increase of weaning success, reintubation, SBT

A

T-piece	1.46 (1.02, 2.24)	1.53 (0.72, 3.42)	2.93 (1.53, 5.98)
0.68 (0.45, 0.98)	PSV	1.05 (0.46, 2.35)	2 (1.08, 3.76)
0.65 (0.29, 1.38)	0.95 (0.42, 2.17)	CPAP	1.92 (0.79, 4.74)
0.34 (0.17, 0.65)	0.5 (0.27, 0.92)	0.52 (0.21, 1.27)	ATC

B

T-piece	1.05 (0.81, 1.36)	**2.76 (1.08, 7.06)**	1.00 (0.23, 4.43)
1.17 (0.83, 1.85)	PSV	0.81 (0.23, 2.77)	0.67 (0.32, 1.38)
2.04 (0.82, 5.78)	1.73 (0.69, 4.79)	CPAP	0.72 (0.15, 3.54)
0.85 (0.36, 2.37)	0.72 (0.31, 1.79)	0.42 (0.12, 1.42)	ATC

C

T-piece	**0.61 (0.46, 0.80)**	0.85 (0.38, 1.88)	**0.17 (0.06, 0.50)**
0.59 (0.43, 0.84)	PSV	2.51 (0.83, 7.64)	**0.42 (0.20, 0.90)**
0.99 (0.45, 2.16)	1.66 (0.74, 3.71)	CPAP	**0.21 (0.08, 0.58)**
0.21 (0.1, 0.45)	**0.35 (0.16, 0.73)**	**0.22 (0.08, 0.52)**	ATC

D

T-piece	0.10 (0.01, 0.19)	-0.24 (-0.75, 0.27)	0.00 (-0.51, 0.51)
1.52 (0.74, 6.87)	PSV	0.08 (-0.43, 0.58)	-0.02 (-0.58, 0.54)
0.81 (0.08, 12.3)	0.51 (0.04, 5.39)	CPAP	0.13 (-0.37, 0.64)
1.39 (0.12, 21.42)	0.87 (0.07, 9.89)	1.7 (0.08, 38.98)	ATC

FIGURE 3 | Summary for four outcomes of different SBT techniques. **(A)** weaning success. **(B)** reintubation. **(C)** SBT success. **(D)**. ICU or LWU length of stay. If available, the upper right half presented results from pairwise meta-analysis and the left lower half showed the results from network meta-analysis. For direct comparison, odds ratios (ORs) below 1 favor the row-defining treatment. For indirect comparison, ORs below 1 favor the column-defining treatment. For numerical data, the number in each cell represented the effect size of the treatment in upper left area minus the treatment in bottom right area. Significant results are in bold print. PSV: pressure support ventilation, CPAP: continuous positive airway pressure, ATC: automatic tube compensation.

success and ICU or LWU length of stay, among all strategies, with a probability of 85.2%, 51.7%, 49.8%, and 44.3%, respectively. Whereas ATC had a probability of 91.7%, 62.1%, 99.7% and 39.9% to rank first, first, first, and fourth for each corresponding outcome above (**Supplementary Table 5**). However, considering that the sample sizes of different interventions varied greatly, the results might be highly biased and should be interpreted with caution. The ranking of all SBT technologies is depicted in **Supplementary Figure 8**.

Contribution Plot and Publication Bias

According to the contribution plots of the network (see **Supplementary Figure 9**), the comparison of T-piece (mode A) vs. PSV (mode B) or PSV (mode B) vs. ATC (mode D) in the four entire networks showed 26.4% and 24.3% for weaning success, 32.7% and 23.9% for reintubation, 31.0% and 18.5% for SBT success, 29.5% and 19.2% for ICU or LWU length of stay, respectively.

We performed comparison-adjusted funnel-plot analysis for four outcomes (**Supplementary Figure 10**). The funnel plots were relatively asymmetric, highlighting that there is a significant risk of publication bias in our study.

GRADE Evaluation on Quality of Evidence

According to GRADE, the quality of evidence ranged from very low to high, but was rated as low and as very low for most comparisons. In terms of T-piece vs. PSV, the quality was low for ICU or LWU length of stay and weaning success, and was very low for SBT success and reintubation, whereas moderate for ICU mortality. Quality of evidence was low for the overall ranking of

treatment for weaning success, reintubation, ICU or LWU length of stay, and SBT success (**Supplementary Table 6**).

DISCUSSION

Summary of Main Findings

This is the first NMA on this topic. After completing all analyses, we obtained several important findings: (a) Evidence from direct and NMA showed that ATC obtained superior weaning success compared to T-piece and PSV. Besides, the direct evidence demonstrated patients receiving PSV (vs. T-piece) appeared to be more likely to be extubated successfully; (b) Direct evidence suggested that T-piece had higher reintubation rate vs. CPAP, but these findings were not be supported by network evidence; (c) Direct evidence indicated that ATC was superior to others in SBT success, PSV was also better than T-piece in terms of this given outcome, and all statistically significant findings were detected in network meta-analyses; (d) In terms of prolonging ICU or LWU length of stay, no weaning technologies have been shown superior to another which were determined both directly and thorough NMA; (e) Compared with T-piece, PSV did not show different effects on the ICU mortality, whereas this conclusion was supported by direct evidence only; (f) The ranking of all weaning modes was ATC, CPAP, PSV, and T-piece in enhancing weaning success; (g) For increasing SBT success, the ranking of all weaning modes was ATC, PSV, T-piece, and CPAP; (h) The ranking of all weaning modes was ATC, T-piece, PSV, and CPAP in terms of reintubation rate; and (i) For prolonging ICU or LWU length of stay, the ranking of all weaning modes was CPAP, T-piece, PSV, and ATC.

Automatic tube compensation is a new mode of ventilatory assistance. It potentially simulates spontaneous breathing without the endotracheal tube, and so it has been called as "electronic extubation" (76, 77). There are several possible explanations for this clinical observation that ATC might be more efficacious than other investigated SBT techniques performed before extubation in critical patients. First and foremost, according to the actual flow that assists the spontaneously breathing intubated patient (78), ATC gives dynamic pressure support during the breathing cycle, which can automatically compensate for the non-linear resistance added by the artificial airway (21, 76, 79). This characteristic of ATC causes a reduction in the work of breathing (17, 80), and thus increases the probability of successful extubation (81). Secondly, ATC is able to maintain the natural and variable breathing pattern to the greatest extent (82, 83), which can more closely represent the postextubation scenario. This potential advantage of ATC can improve synchronization between patient and ventilator, and then promote respiratory comfort (82, 84, 85). Meanwhile, it can result in more significant predictive values for successful weaning and extubation (23). Last but not least, as a result of auto-positive end expiratory pressure (PEEP), ineffective ventilator-triggering is more likely to be less common with ATC than with PSV (77). Hence, ATC is ideally suitable for the weaning process (24).

Though direct evidence suggested that T-piece had higher reintubation rate when compared with CPAP, this finding was not supported by network evidence. Since network evidence combined the direct and indirect evidence in the same analytical model and more eligible RCTs were included, these results were more reliable and accurate.

Pressure support ventilation is widely used to overcome the additional work of breathing and pressure–time product exerted by the endotracheal tubes (18, 22, 86). Consequently, it can significantly decrease the endocrine stress response and relieve the clinical picture of intolerance (37, 38, 87). Furthermore, PSV allows patients to control the respiratory rate and the inspiratory flow during the spontaneous inspiration, thereby diminishing the oxygen consumption of respiratory muscles and preventing fatigue (88–90). These may be the primary reasons why PSV SBTs result in both higher SBT and extubation success rates compared with a T-piece SBT. This finding is broadly in line with previous work. A moderate-quality evidence (91) demonstrated that some intubated subjects who previously failed a weaning trial through the T-tube but continued a weaning trial with PSV were extubated successfully. A latest large-scale multicenter trial also compared PSV and T-piece ventilation in adults and noted that PSV SBT produced significantly higher rates of successful extubation, not adversely influencing reintubation rates (70).

Agreements and Disagreements in the Current Literature

It was worth mentioning that several studies have exclusively investigated the efficacy and safety of at least two modalities of ventilator weaning, but primary studies comparing all the approaches have but one and cannot identify subtle clinical differences due to small sample size. To date, three traditional pairwise metaanalyses with full-text have been performed to evaluate the comparative efficacy of PSV vs. T-piece (46, 92)and PSV vs. other alternative SBT techniques (41) in patients ready to be liberated from MV. However, no head-to-head meta-analysis comparing all SBTs with each other has been reported. Consequently, that in which SBT technique is superior remains to be elucidated.

The results of Ladeira et al. (46) indicated an improvement in PSV group for successful SBTs among patients with simple weaning, but no difference between these two strategies for weaning success, ICU mortality, reintubation, ICU and LWU length of stay was found. Li et al. (92) found no difference between PSV SBT mode and T-piece SBT mode in all outcomes reported in the above-mentioned trial. Burns et al. (41)verified that extubation only tended to be more successful during PSV as compared with T-piece, but there was no difference between PSV vs. CPAP and PSV vs. ATC. After excluding an outlier trial, authors observed that patients undergoing PSV are more likely to pass an SBT. In contrast to previous metaanalyses, we comprehensively evaluated four common SBT technologies and obtained more informative findings. Firstly, we found that PSVs were associated with higher weaning success and SBT success, which is in agreement with previous

results, but only these findings were confirmed by network metaanalyses. In addition, our analysis supported that ATC is an important weaning alternative for critically ill patients. Without increasing the reintubation rate and ICU or LWU length of stay, ATC provides clinical benefits in improving weaning success and SBT success. We also firstly make hierarchies of four different SBT technologies including T-piece, PSV, CPAP, and TAC, all of which were not reported in previous studies.

Strengths and Limitations

Our NMA has certain important strengths including (a) We designed comprehensive search algorithms to obtain and identified eligible studies in critically ill patients, thereby minimizing information bias and enhancing generalizability; (b) NMA method allowed us to assess the results from both direct comparison and mixed-treatment comparisons, and thus optimally addressing the relative effectiveness of those SBT techniques; (c) We just included RCTs, which were the highest level of evidence; so we deemed that our pooled results can reflect closely the true effectiveness of the four most commonly performed SBT modes; and (d) We rated the certainty of evidence by the GRADE approach when explaining each unique comparison and across the network.

Nevertheless, some limitations in this study merited further discussion, including (a) Due to paucity of available data, we introduced criteria for pooling ventilation techniques. Many of the trials included varied in the level of pressure or did not specify whether PEEP was added; however, when implementing similar weaning strategies, we considered them to be in a clinically similar condition and combined them into a single group. This action may induce potential heterogeneity. (b) Since few publications existed, it is impossible to assess the impact of the mode of ventilation on other important indicators, such as hospital length of stay, hospital mortality, total duration of MV, and adverse events. Currently, most of the researchers monitored patients only during ICU stay, and very little data was available when they moved into the general ward. Further studies with a larger number of patients are warranted to consider these problems to gain full insight into the real effect of various extubation strategies. (c) No trials were designed to evaluate the impact of ATC and CPAP on ICU mortality in present. Also, we only captured 10 RCTs by directly comparing PSV and T-piece focusing on this parameter; thus larger studies with excellent designs are warranted to make up the gap. (d) It is important that neither patients nor personnel could be blinded after randomization as different SBT technologies had different requirements at the different preparation stages. We believe that this factor has potential influence on the results. However, the majority of weaning and extubation studies were not free from this limitation. (e) We did not specifically stratify all interventions in the current study, which may introduce a potential bias. However, the major aim of this NMA is to generally determine the comparative efficacy and safety of available macroscopic SBT techniques. Certainly, we suggest conducting future studies to further specifically differentiate the efficacy and safety of different regimes (e.g., low, middle, or high PSV) of each SBT technique.

Implications for Further Research

Spontaneous breathing trials are an integrated component of the weaning assessment, so the "weaning condition" of a patient entering to SBT will influence the accuracy of different SBT methods. On the basis of the difficulty and duration of the weaning process, patients are divided into three categories: simple weaning, difficult weaning, and prolonged weaning (12, 93). In this review, the target patients in most of the studies included belonged to simple weaning, and our analysis supported the selection of ATC as an important alternative for this group. Hence, if one method to perform SBT has any superiority over the other, improvement in weaning outcome is more likely to be expected in selected populations at higher risk for prolonged weaning and difficult weaning. Further studies should be conducted to establish this classification and to confirm how related clinical outcomes are affected in each category of weaning, finalizing the optimal weaning strategy in specific weaning situations. Meanwhile, researchers should pay more attention to ATC weaning mode to clarify its role in weaning patients off mechanical ventilation.

It must be noted that, as an objective marker of identifying the severity, the MV duration before conducting SBT can reflect the demands for ventilation, the risk of suffering from infection, and refractory bronchospasm, all of which were positively associated with worse prognosis. A previous study (69) has revealed that the MV duration before conducting SBT may greatly increase the risk of weaning failure within 48 h. However, the role of this factor under the different SBT modes (PSV, T-piece, CPAP, and ATC) and among specific populations is unclear, which should be further clarified in future studies.

CONCLUSIONS

In summary, the present NMA demonstrated that ATC is an alternative mode of ventilation for critically ill patients. Our finding should be interpreted with caution as it generates from RCT with small sample sizes. Further large scale and well-designed studies are needed to confirm this point.

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

L-JY, XT, MC, and MJ-H: conception and design. XT and MJ-H: administrative support. L-JY, XT, and MC: provision of study materials or patients. L-JY, XT: collection and assembly of data. L-JY and XT: data analysis and interpretation. L-JY, XT, MC,

J-ML, NX, and MJ-H: manuscript writing and final approval of manuscript. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

I would like to acknowledge my teammates for their wonderful collaboration. In addition, we would particularly like to express our appreciation to all authors listed in all the primary studies that were included in the current review.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.731196/full#supplementary-material

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

frontiers in Medicine

BRIEF RESEARCH REPORT
published: 16 December 2021
doi: 10.3389/fmed.2021.785409

Impact of Plasma 5 Hydroxyindoleacetic Acid, a Serotonin Metabolite, on Clinical Severity in Acute Respiratory Distress Syndrome

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Acute respiratory distress syndrome (ARDS) is characterized by dysregulated vascular permeability. The clinical outcomes remain poor, and the disease burden is widespread. We demonstrated that plasma 5-hydroxyindoleacetic acid (5-HIAA), a serotonin metabolite, is a pivotal severity indicator of ARDS. Serotonin is an effector of cellular contraction and a modulator of vascular permeability. Plasma 5-HIAA levels were significantly elevated in severe ARDS cases with shock status ($p = 0.047$) and positively correlated with SOFA ($p < 0.0001$) and APACHE-II score ($p < 0.0001$). In the longitudinal analysis, plasma 5-HIAA levels were also a strong independent predictor of mortality rate ($p = 0.005$). This study indicates that plasma 5-HIAA is a biomarker of ARDS severity and highlights the importance of evaluating vascular leakage levels for ARDS treatment.

Keywords: ARDS, serotonin, 5-HIAA (5-hydroxyindoleacetic acid), vascular permeability, shock

OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

Received: *29 September 2021*
Accepted: *25 November 2021*
Published: *16 December 2021*

Citation:
Tanaka T, Mori M, Tashiro M and Izumikawa K (2021) Impact of Plasma 5 Hydroxyindoleacetic Acid, a Serotonin Metabolite, on Clinical Severity in Acute Respiratory Distress Syndrome. Front. Med. 8:785409. doi: 10.3389/fmed.2021.785409

INTRODUCTION

The concept of acute respiratory distress syndrome (ARDS) was first introduced over 50 years ago (1); however, its mechanism of pathogenesis remains poorly understood, while its disease burden is substantial. In addition, a large number of cases are complicated by septic shock, which further increases morbidity and mortality. ARDS and septic shock are characterized by dysregulated vascular permeability (2). One of the major mechanisms that regulate vascular permeability is cellular contraction (3), which can be induced via the serotonin and RhoA/Rho-associated protein kinase (ROCK) signaling pathway in certain cell types (4). Serotonin (5-hydroxytryptamine [5-HT]) is a classical neurotransmitter in the central nervous system; however, 95% of 5-HT production in the body is generated in peripheral tissues, where a variety of pleiotropic effects are elicited, including vasoconstriction, proliferation, and inflammation (5).

We recently reported the effect of plasma 5-hydroxyindoleacetic acid (5-HIAA), a serotonin metabolite, on the clinical outcomes of sepsis (6), with an increase in plasma 5-HIAA levels in patients with severe septic shock. In addition, we demonstrated the potential role of serotonin in vascular permeability through *in vitro* ROCK activation experiments (6). Burdens of vascular leak remain a large issue in several diseases, such as ARDS (any etiology including COVID-19), viral hemorrhagic fever, and dengue fever. Our conceptual hypothesis of the serotonin-ROCK pathway approach to regulating vascular permeability could be a common approach for all types of these

diseases. In this study, plasma 5-HIAA measurements were performed using high-performance liquid chromatography on plasma samples from 157 ARDS patients. In addition, we statistically analyzed its association with disease severity and mortality.

METHODS

Plasma samples were collected on day 0 from 157 randomly selected ARDS patients, and the SAILS Research Materials dataset was obtained from the National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center, USA. Data sets that were analyzed in this report were from patients who were diagnosed with ARDS on day 0, had a ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) of 300 or less, and had bilateral infiltrates on chest radiography that were consistent with pulmonary edema without evidence of left atrial hypertension (7). Plasma 5-HIAA levels were measured by high-performance liquid chromatography at the SRL laboratory (Tokyo, Japan). Baseline information and disease severity indices of the Sequential Organ Failure Assessment (SOFA) score from 137 subjects, and Acute Physiology and Chronic Health Evaluation (APACHE) II score from 157 subjects were obtained from the NHLBI dataset. Statistical analysis was performed using GraphPad Prism, version 6.07 (San Diego, CA, USA). Between alive and death groups during 90 days of follow-up, Fisher's exact tests were used for sex and shock distribution difference analyses, and Mann–Whitney *U*-tests were used for age, SOFA score, APACHE II score, and plasma 5-HIAA level difference analyses. Analysis of plasma 5-HIAA level differences between ARDS patients with and without shock was performed using the Mann–Whitney *U*-test. Spearman's correlation test was used to analyze the correlations between disease severity indices (SOFA score and APACHE II score) and plasma 5-HIAA levels. Further, for the survival rate analyses, we constructed a binary logistic regression model for cross-sectional analysis and a Cox hazard model for longitudinal analysis.

RESULTS

Baseline clinical characteristics are shown in **Table 1**. Between alive and death groups, significant differences were identified in age (median 55 years old in alive group vs. median 63 years old in death group, $p = 0.004$), shock status (61 vs. 87%, $p < 0.001$), APACHE-II score (24 vs. 26, $p = 0.004$), and plasma 5-HIAA level (8.6 ng/ml vs. 14.6 ng/ml, $p < 0.001$). The plasma 5-HIAA levels were higher in the ARDS/shock+ group compared to the ARDS/shock- group (11.5 ng/mL vs. 7.1 ng/mL, $p = 0.047$) (**Figure 1**). Plasma 5-HIAA levels were positively correlated with SOFA scores ($r = 0.40$, $p < 0.0001$) (**Figure 2A**) and APACHE II scores ($r = 0.40$, $p < 0.0001$; **Figure 2B**). In the cross-sectional survival rate analysis, age (odds ratio [OR] 1.03, $p = 0.005$), shock status (OR 4.1, $p = 0.002$), APACHE-II score (OR 1.1, $p = 0.005$), and plasma 5-HIAA level (OR 1.03, $p < 0.001$) were significantly associated with mortality (**Table 2**), while shock (OR 3.7, $p = 0.008$) and plasma 5-HIAA levels (OR 1.02, $p = 0.005$) remained significant in the multivariate analysis (**Table 2**). In the longitudinal analysis, age (hazard ratio [HR] 1.03, $p = 0.004$), shock status (HR 3.3, $p = 0.003$), APACHE-II score (HR 1.06, $p = 0.004$), and plasma 5-HIAA level (HR 1.01, $p < 0.001$) were significantly associated with mortality in the univariate analyses (**Table 3**). In multivariate analysis, plasma 5-HIAA level (adjusted hazard ratio [aHR] 1.01, $p = 0.005$) as well as shock status (aHR 2.7, $p = 0.02$) remained significantly associated with mortality (**Table 3**). These results strongly suggest that plasma 5-HIAA levels could be an indicator of disease severity in patients with ARDS.

TABLE 1 | Characteristics of 157 ARDS patients.

Characteristics	All ($n = 157$)	Alive ($n = 105$)	Death ($n = 52$)	p
Sex (female)	82 (52%)	56 (53%)	26 (50%)	0.7
Age	[a]59 (46–68)	[a]55 (43–65)	[a]63 (55–71)	0.004
Shock	109 (69%)	64 (61%)	45 (87%)	<0.001
SOFA score ($n = 137$)	[a]11 (8–13)	[a]11 (8–13) ($n = 89$)	[a]11 (9–13) ($n = 48$)	0.2
APACHE II score	[a]25 (20–30)	[a]24 (18–29)	[a]26 (24–32)	0.004
Plasma 5-HIAA (ng/ml)	[a]9.4 (5.5–24.3)	[a]8.6 (5–16.5)	[a]14.6 (6.9–49.7)	<0.001

Characteristics of all (n = 157), alive (n = 105), and death (n = 52) during 90 days of follow-up are shown. Between alive and death groups, Fisher's exact tests were used for sex and shock distribution difference analyses, and Mann–Whitney U-tests were used for age, SOFA score, APACHE II score, and plasma 5-HIAA level difference analyses.
[a]Median (interquartile range) are shown.

DISCUSSION

The pathogenesis of ARDS consists of endothelial-epithelial injury, a dysregulated inflammatory response, and fibrosis. To address its inherent heterogeneity, several studies have focused on categorizing the disease by phenotyping based on clinical characteristics and associated blood biomarkers (2, 8). Although the etiologies of ARDS are diverse and complex, supportive treatments are provided, and the clinical effects of these interventions are often limited. In this study, we revealed that plasma 5-HIAA levels were significantly higher in ARDS cases with shock compared to ARDS cases without shock and its was positively correlated with SOFA score and APACHE-II. Such a strong association between plasma 5-HIAA levels and ARDS disease severity was also identified in the longitudinal mortality rate analysis.

An ideal disease biomarker should have a clear correlation with the disease's pathophysiological factors, and must provide specific contexts such as early diagnosis and guide the successful

Abbreviations: ARDS, acute respiratory distress syndrome; 5-HIAA, 5-hydroxyindoleacetic acid; ROCK, RhoA/Rho-associated protein kinase; 5-HT, 5-hydroxytryptamine; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; SSRIs, selective serotonin reuptake inhibitors; POC, point-of-care; Ang-2, angiopoietin 2; eNAMPT, extracellular nicotinamide phosphoribosyltransferase; sRAGE, soluble receptor for advanced glycation endproducts; miRNAs, microRNAs.

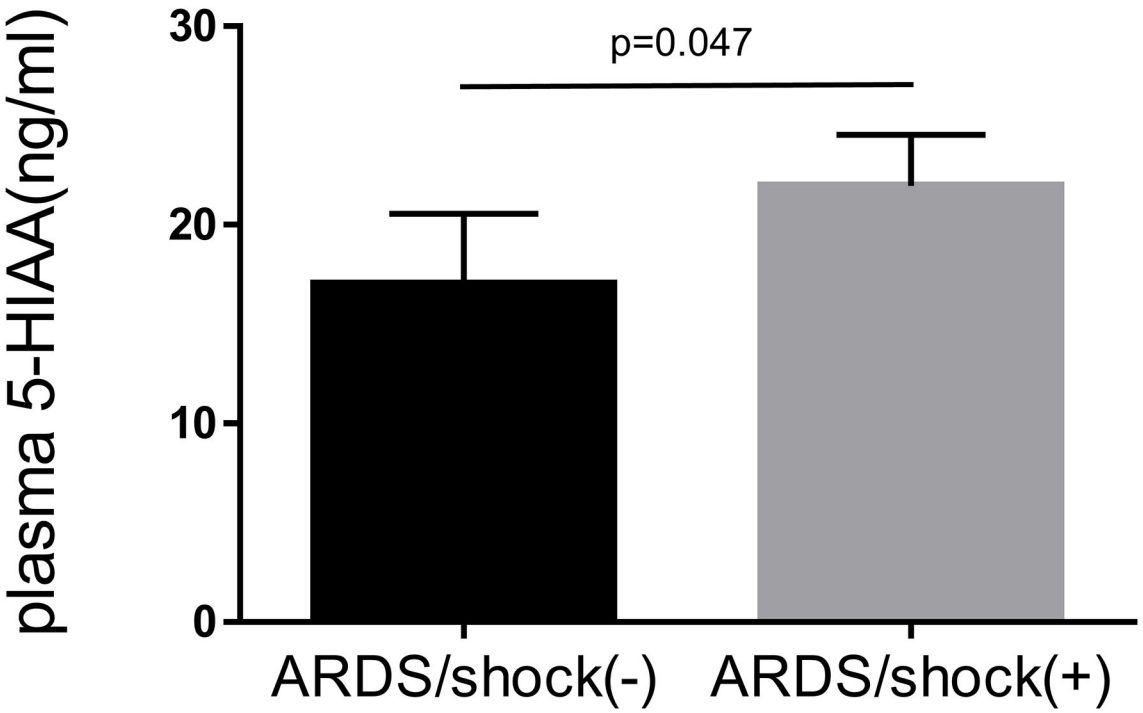

FIGURE 1 | Plasma 5-HIAA levels in patients with ARDS. Comparison of plasma 5-HIAA levels between ARDS/shock+ and ARDS/shock- patients was performed using the Mann–Whitney *U*-test the 5-HIAA levels were higher in the ARDS/shock+ group compared to the ARDS/shock- group (median 7.1 ng/mL vs. 11.5 ng/mL, $p = 0.047$).

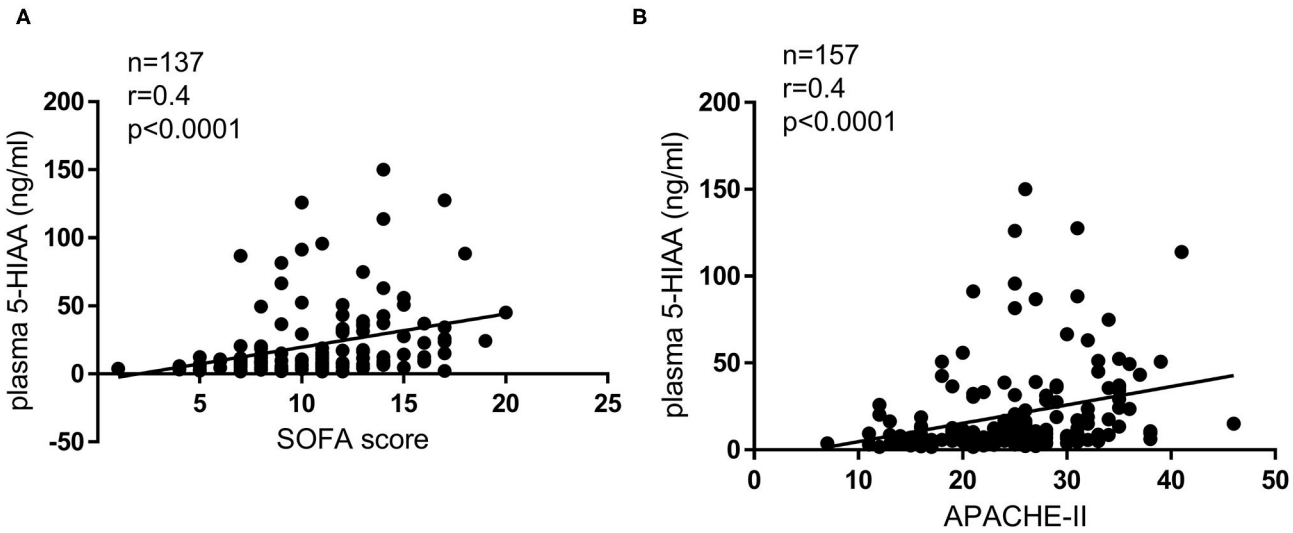

FIGURE 2 | Correlation between disease severity indices and plasma 5-HIAA levels. Correlation between SOFA score and plasma 5-HIAA level **(A)**, APACHE II score, and plasma 5-HIAA level **(B)**; Spearman's correlation test. A positive correlation between plasma 5-HIAA levels and clinical disease severity indices was observed ($r = 0.40$, $p < 0.0001$, $r = 0.40$, $p < 0.0001$).

development of novel therapeutic strategies. However, although numerous studies have been conducted, there are no targeted therapies to treat ARDS. There exists a critical gap between biomarker discovery and translation to clinical use. The clinical and biological heterogeneity of ARDS is a pivotal barrier in identifying effective treatments. However, the development of rapid point-of-care (POC) tests remains a priority. Introducing novel POC tests for biomarkers in blood or other body

TABLE 2 | Differences in mortality rate based on clinical variables evaluated by cross-sectional analysis.

	Univariate analysis		Multivariate analysis	
Variables ($n = 157$)	**[a]OR (95% [b]CI)**	***p***	**[a]OR (95% [b]CI)**	***p***
Sex (female)	0.9 (0.4–1.7)	0.7	–	–
Age	1.03 (1.01–1.06)	0.005	1.02 (0.9–1.04)	0.1
Shock	4.1 (1.7–10)	0.002	3.7 (1.4–9.5)	0.008
APACHE-II score	1.1 (1.02–1.1)	0.005	1.03 (0.9–1.1)	0.3
Plasma 5-HIAA (ng/ml)	1.03 (1.01–1.04)	<0.001	1.02 (1.007–1.04)	0.005

Binary logistic regression model analyses of the mortality rate during 90 days of follow-up are shown. Variables with significance ($p < 0.05$) in the univariate analysis were used for multivariate analysis.
[a]OR, odds ratio; [b]CI, confidential interval range.

TABLE 3 | Mortality rate difference in clinical variables, by longitudinal analysis.

	Univariate		Multivariate	
Variables ($n = 157$)	**[a]HR (95% [b]CI)**	**p**	**[c]aHR (95% CI)**	***p***
Sex (female)	0.9 (0.5–1.6)	0.8	–	–
Age	1.03 (1.01–1.05)	0.004	1.01 (0.9–1.03)	0.2
Shock	3.3 (1.5–7.3)	0.003	2.7 (1.2–6.0)	0.02
APACHE-II score	1.06 (1.02–1.09)	0.004	1.02 (0.9–1.1)	0.3
Plasma 5-HIAA (ng/ml)	1.01 (1.007–1.02)	<0.001	1.01 (1.003–1.02)	0.005

Cox hazard model analyses of the mortality rate during 90 days of follow-up are shown. Variables with significance ($p < 0.05$) in the univariate analysis were used for multivariate analysis.
[a]HR, hazard ratio; [b]CI, confidential interval range; [c]aHR, adjusted hazard ratio.

fluids could lead to potentially significant clinical trials for biomarker-guided, cell-specific therapies (e.g., epithelial targeted therapies or endothelial barrier permeability modifiers) (9).

Recently, ARDS biomarkers have been categorized based on their possible pathogenesis and pathways, and have mostly been assessed as diagnostic and prognostic biomarkers. Candidate diagnostic biomarkers that have been well studied include the following: angiopoietin 2 (Ang-2), high mobility group box nuclear protein 1, interleukin 1 beta, interleukin 1 receptor antagonist, interleukin 6, interleukin 8, macrophage inflammatory protein-1a, extracellular nicotinamide phosphoribosyltransferase (eNAMPT), soluble receptor for advanced glycation end products (sRAGE), vascular endothelial growth factor, selectins, and surfactants (8, 10). Furthermore, researchers have thoroughly investigated candidate prognostic biomarkers, including Ang-2, eNAMPT, sRAGE, protein C, and soluble intercellular adhesion molecule-1 (8, 10). To pursue breakthrough therapeutic strategies, the role of microRNAs (miRNAs) as biomarkers or pharmacologic targets has been increasingly investigated (11). In addition, contrary to conventional chemical detection methods for biomarker candidates, recently, a new method, metabolomics, has been applied, allowing for the simultaneous detection of a large set of metabolites from a single sample (12). However, these markers are still far from successfully transitioning to clinical therapeutic development.

In this study, we adopted the coupled hypothesis from our previous study (6), focusing on the serotonin-ROCK pathway approach for the regulation of vascular permeability in ARDS. Several studies have revealed that ROCK inhibition leads to the attenuation of endothelial vascular hyperpermeability in lung injury (13, 14). Several studies have focused on the analysis of the involvement of serotonin in the pathology of ARDS and targeted serotonin as a therapeutic intervention and have shown that serotonin antagonism improves the clinical efficacy of respiratory failure in animal models and human cases. Serum serotonin levels may be associated with pulmonary hypertension in patients with septic ARDS (15). Serotonin receptor blockage contributes to favorable outcomes in a porcine ARDS model (16). One study indicated that platelet entrapment in the lungs and 5-HT release are in part responsible for early respiratory failure. 5-HT inhibition contributes to a favorable outcome of acute respiratory failure (17). These studies indicate the feasibility of the involvement of serotonin in the pathology of ARDS and targeted serotonin as a therapeutic intervention. In addition, from various perspectives, ARDS research has been drawn into focus by the SARS-CoV-2/COVID-19 pandemic and has come to be conducted based on the recent analysis of severe cases of COVID-19; thus, several papers focusing on the action of selective serotonin reuptake inhibitors (SSRIs) have been published. Fluvoxamine [SSRI and a sigma-1 receptor (S1R) agonist] prevented clinical deterioration of symptomatic COVID-19 in a small placebo-controlled randomized trial in the United States. The authors mentioned that the rationale for administering fluvoxamine is its agonistic effect in attenuating the damaging effects of the inflammatory response (18). A larger randomized placebo-controlled study conducted in Brazil found that patients administered fluvoxamine had a lower risk of hospitalization in a COVID-19 emergency setting or transfer to a tertiary hospital due to COVID-19 deterioration (19). Further, a large observational study conducted in France showed that the use of antidepressants (SSRIs) was significantly and substantially associated with a reduced risk of intubation or death (20). The mechanism underlying the role of SSRIs in these results remains uncertain. However, several hypotheses were discussed in these reports, such as its anti-inflammatory action, antiplatelet activity, and antiviral effects on SARS-CoV-2. Serum serotonin levels were increased in COVID-19 cases, including COVID-19-related ARDS. They focused on platelet hyperreactivity in the pathogenesis of COVID-19. However, COVID-19 non-related ARDS is inconclusive because of the small number and heterogeneity of patients for assessment (21). In addition, one review mentioned a potential benefit of SSRIs in the treatment and prevention of inflammatory lung diseases (e.g., COVID-19, ARDS, COPD, and pneumonia) (22), since SSRIs have anti-inflammatory properties. Serotonin transporter inhibitors and ROCK inhibitors have already been approved and applied for treatment, including certain diseases, depression worldwide, and vasospasm of subarachnoid hemorrhage complications in Japan and China, respectively. As mentioned above, ROCK inhibitors have been applied to animal models of lung injury. However, from the viewpoint of clinical application to humans, approved drugs are limited to Japan and China. As for serotonin

antagonism, SSRIs are strongly recognized as drugs in the central nervous system, and the function of peripheral serotonin has been attracting attention, but there are few demonstrative cases in animal experiments targeting lung disorders. For these reasons, the application has not yet progressed to clinical applications. However, as mentioned above, there is a growing body of evidence in COVID-19 clinical studies to promote the application of SSRIs to human patients.

Serotonin storage is abundant in platelets, and activation of platelets is induced by inflammation, and the release of serotonin from platelets increases (23). In addition, since it is stored mostly in the enterochromaffin cells of the intestinal tract (24), the release of serotonin is a possible event due to intestinal barrier dysfunction during septic shock (25, 26). If these two factors are proposed as clinical evaluation indicators in the future, they may become more sensitive to the indicators of the combination of plasma 5-HIAA, platelet activation, and intestinal barrier dysfunction. Clinical indicators that may reflect vascular permeability may be the doses of vasopressors and fluid balance, so attempts to quantify these two indicators and combine the evaluation with plasma 5-HIAA might be more accurate in the evaluation in the future.

In this study, plasma 5-HIAA levels were measured using HP liquid chromatography. However, it is technically possible to perform mass analysis (TOF-MAS) as well. Recently, since more hospital laboratories are introducing TOF-MAS for bacterial identification, measurement of plasma 5-HIAA levels by TOF-MAS, with more rapid time would be available.

Our study has several limitations: First, the involvement of 5-HT-ROCK signaling is highly assumed in the clinical observations of these results in our study; however, the complete mechanism of 5-HT or ROCK-associated vascular permeability regulation could not be evaluated using a molecular basis approach. In our previous study, we demonstrated that plasma 5-HIAA levels can be a predominant biomarker of septic shock severity and a novel role of 5-HT in vascular permeability via the ROCK activation pathway. Given that we showed partial elucidation of the involvement of serotonin/ROCK in the regulation of *in vitro* experiments in our previous study (6), additional work should consider the feasibility of clinical trials using these inhibitors to examine the effect on the regulation of vascular permeability in the lung of ARDS. Second, since this data set provided only ARDS patients, comparative analyses including healthy controls or non-ARDS ICU patients were not available. Third, serotonin levels were not directly measured in the present study. Another study in which plasma serotonin and 5HIAA were measured simultaneously in septic shock subjects revealed that more severe cases showed low-serotonin and high-5-HIAA results over time (27). This trend may be because activated serotonin is immediately metabolized to 5-HIAA, which matches with our hypotheses and results. Fourth, the changes in plasma 5-HIAA levels over time were not monitored because of limited data sources. The trend in the time course of plasma 5-HIAA levels would have revealed a more precise understanding of the association between serotonin and vascular leakage in the treatment clinical course.

As a general perception of the pathophysiology of ARDS, there is considerable crosstalk in its pathogenesis (2, 8), and a variety of causes of ARDS also make it difficult to discuss its pathogenesis in a simple manner. We think that the results of our study do not necessarily reflect the whole and accurate phenomenon of ARDS, possibly reflecting one aspect among many. We believe that the same composition of difficulties in showing a positive result study of ARDS in several clinical trials. We would like to emphasize that the biomarkers (plasma 5-HIAA) demonstrated in this study could be used as prognostic factors, in addition to the existing therapeutic drug candidates (SSRIs or ROCK inhibitors) that can directly regulate vascular hyperpermeability.

In this study, we demonstrated the possibility of using plasma 5-HIAA as a prognostic biomarker of ARDS severity. Plasma 5-HIAA (a serotonin metabolite) could be an ideal and unique target to allow the successful transition of a novel clinical treatment targeting the serotonin-ROCK pathway through biomarker development. Furthermore, comprehensive *in vitro* experiments and clinical data assessment are required to reveal the detailed involvement of the serotonin and ROCK pathways in ARDS pathogenesis.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Nagasaki University Hospital (approval number 16072514). The NHLBI Research Materials Distribution Agreement (RMDA) was concluded between Nagasaki University Hospital and NHLBI. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

TT designed the study and wrote and edited the original draft of the manuscript. MM performed statistical analyses. TT and MM acquired the data set. MT reviewed the study design and edited the manuscript. KI supervised the study and edited the manuscript. All authors approved the study design and manuscript.

FUNDING

This study was supported by grants from JSPS KAKENHI, grant 2016–2019 [16K09544].

ACKNOWLEDGMENTS

This manuscript was prepared using SAILS Research Materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the SAILS or the NHLBI. We would like to thank Editage (www.editage.com) for English language editing.

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

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frontiers in Medicine

BRIEF RESEARCH REPORT
published: 22 December 2021
doi: 10.3389/fmed.2021.720920

Positive End-Expiratory Pressure Setting in COVID-19-Related Acute Respiratory Distress Syndrome: Comparison Between Electrical Impedance Tomography, PEEP/FiO_2 Tables, and Transpulmonary Pressure

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

Received: *05 June 2021*
Accepted: *25 November 2021*
Published: *22 December 2021*

Citation:
Gibot S, Conrad M, Courte G and Cravoisy A (2021) Positive End-Expiratory Pressure Setting in COVID-19-Related Acute Respiratory Distress Syndrome: Comparison Between Electrical Impedance Tomography, PEEP/FiO_2 Tables, and Transpulmonary Pressure. Front. Med. 8:720920. doi: 10.3389/fmed.2021.720920

Introduction: The best way to titrate the positive end-expiratory pressure (PEEP) in patients suffering from acute respiratory distress syndrome is still matter of debate. Electrical impedance tomography (EIT) is a non-invasive technique that could guide PEEP setting based on an optimized ventilation homogeneity.

Methods: For this study, we enrolled the patients with 2019 coronavirus disease (COVID-19)-related acute respiratory distress syndrome (ARDS), who required mechanical ventilation and were admitted to the ICU in March 2021. Patients were monitored by an esophageal catheter and a 32-electrode EIT device. Within 48 h after the start of mechanical ventilation, different levels of PEEP were applied based upon PEEP/FiO_2 tables, positive end-expiratory transpulmonary (P_L)/ FiO2 table, and EIT. Respiratory mechanics variables were recorded.

Results: Seventeen patients were enrolled. PEEP values derived from EIT ($PEEP_{EIT}$) were different from those based upon other techniques and has poor in-between agreement. The $PEEP_{EIT}$ was associated with lower plateau pressure, mechanical power, transpulmonary pressures, and with a higher static compliance (Crs) and homogeneity of ventilation.

Conclusion: Personalized PEEP setting derived from EIT may help to achieve a more homogenous distribution of ventilation. Whether this approach may translate in outcome improvement remains to be investigated.

Keywords: ARDS, COVID-19, PEEP, electrical tomography impedance, mechanical ventilation

INTRODUCTION

Despite progresses in acute respiratory distress syndrome (ARDS) management, the best way to titrate a positive end-expiratory pressure (PEEP) is not straightforward (1). The "right" PEEP should allow for optimized lung recruitment while minimizing over-distention. To this aim, clinicians can use PEEP-FiO_2 tables (2), transpulmonary pressure (P_L) (3), or electrical impedance tomography (EIT).

The transpulmonary pressure is measured using an esophageal balloon catheter that approximates the pleural pressure. Using this technique, PEEP has to be set to maintain the end-expiratory P_L above zero to avoid collapse of dependent dorsal lung regions, and the end-inspiratory P_L below 20–25 cmH_2O to decrease the risk of overdistension of non-dependent regions.

Electrical impedance tomography (EIT) is a non-invasive technique giving dynamic information on regional ventilation that can be embarked in modern ventilators. Regional hypoventilated lung units ("Silent spaces") correspond to both collapsed areas in the dependent territories, and distended areas in the non-dependent regions. Using this technique, PEEP is set to minimize the percentage of total silent spaces.

We describe a case series of patients suffering from 2019 coronavirus disease (COVID-19)-related ARDS in whom we compared PEEP settings based on $PEEP/FiO_2$ tables, P_L/ FiO2 table, and EIT.

METHODS

In March 2021, we enrolled some mechanically ventilated patients who were admitted to our Intensive Care Unit (ICU) because of a COVID-19-related moderate-to-severe ARDS. The diagnosis of COVID-19 relied upon positive result on polymerase chain reaction of sputum or nasal swab. The Ethic Committee of our University Hospital approved this study with a waiver of informed consent because of the use of routine procedures, as well as the use of de-identified data.

All patients were ventilated in volume control mode [tidal volume (Vt): 6–7 ml/kg ideal body weight (IBW)], with FiO_2 set to achieve peripheral oxygen saturation (SpO_2) between 92 and 95%, and respiratory rate (RR) set to reach $PaCO_2$ between 38 and 45 mmHg. Transpulmonary pressures were measured with the use of an esophageal balloon catheter (Nutrivent; Sidam, Mirandola, Italy) after its correct positioning has been verified through passive chest compression during occlusion. As part of our routine monitoring, patients were also equipped with a 32-electrode soft-textile EIT belt (Sentec; Therwil, Switzerland), which was directly connected to the ventilator (ELISA 800 VIT, Lowenstein Medical; Kronberg, Germany). Some maneuvers were performed in supine position after 24–48 h of mechanical ventilation while the patients were still sedated (midazolam and sufentanyl) and paralyzed (cisatracurium or atracurium). Respiratory mechanics variables were recorded after 10 min at different PEEP levels while all the other parameters (FiO_2, Vt, RR, flow rates, etc.) remained unchanged.

Positive end-expiratory pressure (PEEP) was first set according to the lower, then, to the higher $PEEP/FiO_2$ ALVEOLI table (2). Next, PEEP as based upon end-expiratory P_L/FiO_2 table, was applied (3). Finally, an automated decremental PEEP trial was performed under EIT monitoring (Best-PEEP-Tool, Lowenstein Medical): PEEP was set at 24 cmH_2O (corresponding to the maximum PEEP in the $PEEP/FiO_2$ table) and was reduced by 2 cmH_2O every 10 inspirations until 6 cm H_2O, with a 3-s end-expiratory hold between decremental steps. For each PEEP values, percentages of relatively collapsed and overdistended lung regions were given by the EIT, and the "best" PEEP ($PEEP_{EIT}$) was considered as the lowest level associated with the lowest total percentage of the lung silent spaces (collapsed + distended).

Data are presented as median (interquartile range) and are compared using Wilcoxon signed-rank test. Bias and limits of agreement between different approaches were calculated with the Bland-Altman approach. Statistical analyses were performed by GraphPad software (La Jolla, CA, USA) with two-tailed $p < 0.05$ deemed as significant.

RESULTS

Seventeen patients (15 men, 2 women) were enrolled. Median age was 65 (62–71) years, and body mass index was 31.1 (28.5–33.0). The ARDS was severe in 6 and moderate in 11 patients, while the PaO_2/FiO_2 was 136 (103–155), Vt 6.6 (6.2–7.0) mL/kg IBW, and RR 24 (22–27), respectively. Twelve patients were under high-flow oxygen therapy for a median of 1 (1, 2) day before intubation. All patients, except for one, were discharged alive.

Positive end-expiratory pressure derived from EIT ($PEEP_{EIT}$), corresponding to the lowest level of PEEP achieving the lowest percentage of total silent spaces (distended + collapsed), was significantly different from the other PEEP values. It was higher than the lower $PEEP/FiO_2$ table, and lower than the higher $PEEP/FiO_2$ or P_L/FiO_2 tables (**Table 1**). The Bland-Altman analysis showed that $PEEP_{EIT}$ was 1.3 cm H_2O higher than the lower $PEEP/FiO_2$ table with limits of agreement from −8.5 to 11.2 cm H_2O. By contrast, $PEEP_{EIT}$ was 5 and 4 cm H_2O lower, respectively, than higher $PEEP/FiO_2$ and P_L/FiO_2 tables, with again wide limits of agreement (**Figure 1**).

In terms of respiratory mechanics, $PEEP_{EIT}$ was associated with lower plateau pressure, mechanical power, transpulmonary pressures, and with a higher static compliance (Crs) than higher $PEEP/FiO_2$ or P_L/FiO_2 tables (**Table 1**). Driving pressures were not significantly different.

A better distribution of ventilation was achieved with $PEEP_{EIT}$: lung collapse was lower with $PEEP_{EIT}$ than with lower $PEEP/FiO_2$ table (9 vs. 13%; $p = 0.04$), while lung distension was reduced as compared to higher $PEEP/FiO_2$ and P_L/FiO_2 tables (6 vs. 20 and 13%, respectively; $p < 0.01$) (**Figure 1**).

DISCUSSION

Personalized PEEP guided by EIT, with the aim to minimize relative alveolar distention and collapse, was different than PEEP based upon $PEEP/FiO_2$ or P_L/FiO_2 tables. Although in terms of respiratory mechanics, $PEEP_{EIT}$ did not differ from lower $PEEP/FiO_2$ table. There were very important individual variations as witnessed by the wide range of limit agreement in Bland-Altman analyses. Therefore, each patient exhibited different lung properties that cannot be ascertained by using global mechanics parameter such as driving or transpulmonary pressures, compliance, or pressure-volume curves. This may explain the negative results of important clinical trials, which compared low vs. high PEEP in ARDS patients (2, 4).

TABLE 1 | Effect of positive end-expiratory pressure (PEEP) settings on respiratory mechanics.

Variable	Lower PaO_2/FiO_2 table	Higher PaO_2/FiO_2 table	P_L/FiO_2 table	$PEEP_{EIT}$
PEEP (cm H_2O)	10 (10 to 14)	17 (16 to 20)	15 (14 to 20)	13 (12 to 14)*#
P_{PLAT} (cm H_2O)	23 (20 to 26)	33 (28 to 38)	29 (24 to 37)	25 (22 to 27)#
Driving Pressure (cm H_2O)	12 (10 to 14)	14 (12 to 18)	13 (11 to 16)	12 (11 to 13)
C_{RS} (mL/cm H_2O)	39 (34 to 48)	30 (24 to 37)	35 (26 to 43)	38 (34 to 45)#
Mechanical Power (J/min)	25.1 (22.7 to 34.3)	34.4 (28.0 to 43.6)	34.1 (26.0 to 40.7)	28.4 (24.4 to 32.0)#
Inspiratory Transpulmonary pressure (cm H_2O)	6.6 (4.3 to 13.5)	17.5 (9.9 to 21.6)	14.7 (9.4 to 18.7)	11.5 (6.4 to 14.3)#
Expiratory Transpulmonary pressure (cm H_2O)	−0.3 (−2.8 to 3.6)	5.0 (2.0 to 8.0)	4.0 (1.5 to 6.5)	1.3 (0.1 to 2.0)#
Silent spaces (%)	18 (10 to 26)	30 (13 to 48)	23 (17 to 35)	16 (9 to 23)#

*$p < 0.05$ $PEEP_{EIT}$ vs. Lower PaO_2/FiO_2 table.
#$p < 0.05$ $PEEP_{EIT}$ vs. Higher PaO_2/FiO_2 and P_L/FiO_2 tables.

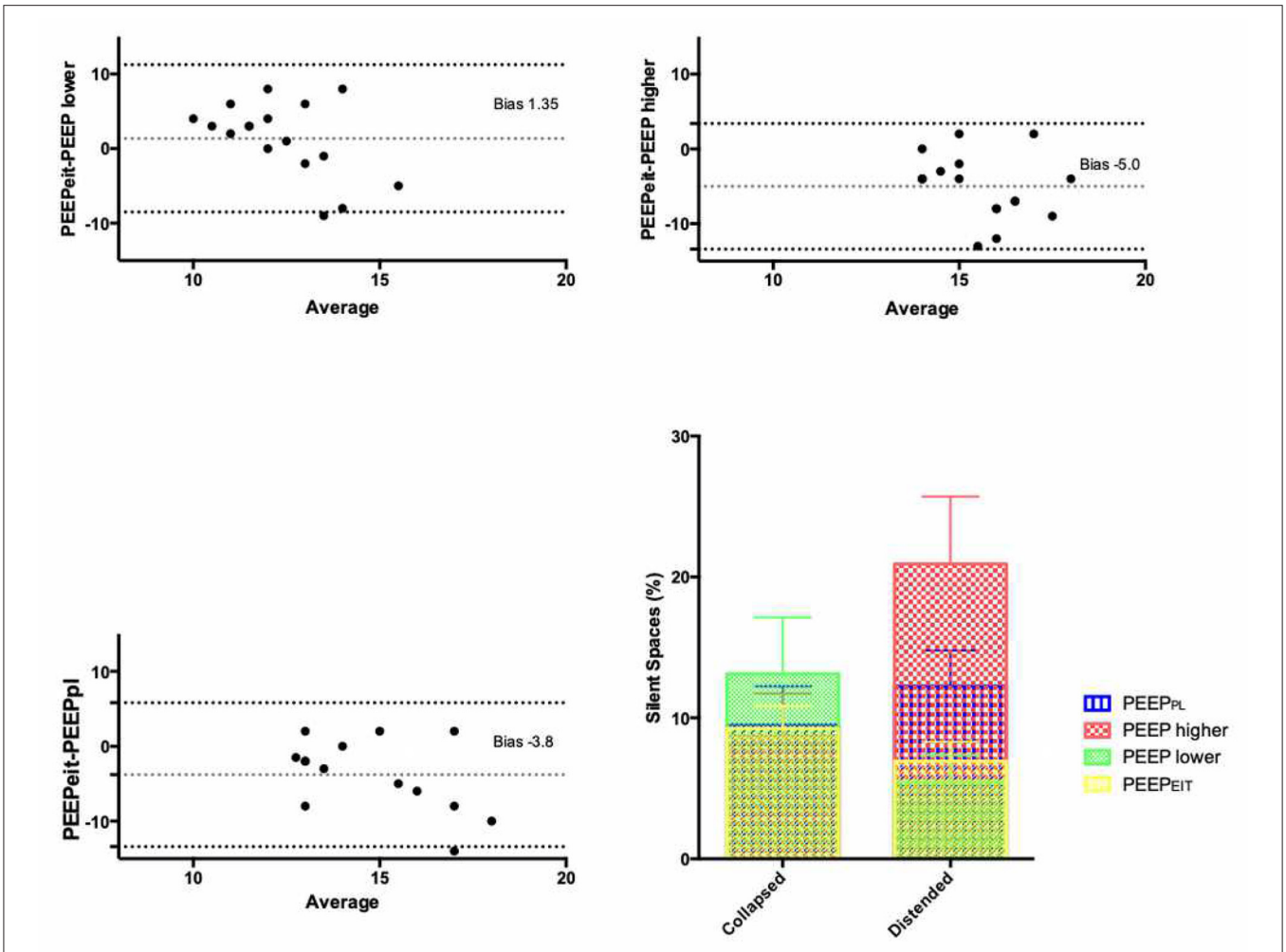

FIGURE 1 | Bland-Altman plots evaluating agreement between PEEP derived from EIT ($PEEP_{EIT}$) and positive end-expiratory pressure (PEEP) values derived from lower and higher PEEP/FiO_2 tables and P_L/FiO_2 table. Dotted lines: bias and its 95% confidence interval. Lower right panel: percentages of collapsed and distended lung regions measured by electrical impedance tomography (EIT) under different PEEP settings. Percentage of collapse was lower with $PEEP_{EIT}$ than with lower PEEP/FiO_2 table ($p = 0.04$), while percentage of distended areas was reduced as compared to higher PEEP/FiO_2 and P_L/FiO_2 tables ($p < 0.01$).

Several other recent studies evaluated EIT-guided PEEP titration. Van der Zee et al. (5) and Sella et al. (6) have compared $PEEP_{EIT}$ vs. PEEP/FiO_2 tables in each of the 15 cases of COVID-19-related ARDS patients. In both studies, PEEP values differed with important individual variations. Interestingly, $PEEP_{EIT}$ was lower (12 cmH_2O) in the Sella study than in the

Van der Zee's (21 cm H_2O). This highlights the huge variability between patients with ARDS, depending on weight, age, sex, or duration of mechanical ventilation.

When comparing $PEEP_{EIT}$ and P_L/FiO_2 table, Scaramuzzo et al. (7), in 20 patients under non-COVID-19 ARDS, found no correlation between the values given by the 2 techniques. As in our study, $PEEP_{EIT}$ achieved a more homogenous distribution of ventilation.

Our work has several limitations. First, we only included patients with COVID-19. Whether these patients behaved similarly to those suffering from non-COVID-19 ARDS in terms of respiratory mechanics is still matter of debate. Second, most of our patients were over-weighted. Hence, this may have contributed to the low agreement between techniques. Finally, only 17 patients have been enrolled, precluding any generalization. However, each patient was its own control, and we just wanted to underline the poor agreement between routinely used techniques at the patient level.

The use of EIT allows for a personalized PEEP titration with the aim to minimize the total amount of pulmonary silent spaces. Whether this approach could translate in outcome improvement remains to be investigated.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comité d'éthique du CHRU de Nancy. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SG designed the study, collected and analyzed data, and wrote the manuscript. MC, GC, and AC collected and analyzed data. All authors read and approved the manuscript.

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

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ORIGINAL RESEARCH
published: 03 January 2022
doi: 10.3389/fmed.2021.780005

Sex Differences in Use of Low Tidal Volume Ventilation in COVID-19—Insights From the PRoVENT–COVID Study

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

Received: *20 September 2021*
Accepted: *30 November 2021*
Published: *03 January 2022*

Citation:
Swart P, Nijbroek SGLH, Paulus F, Neto AS and Schultz MJ (2022) Sex Differences in Use of Low Tidal Volume Ventilation in COVID-19—Insights From the PRoVENT–COVID Study. Front. Med. 8:780005. doi: 10.3389/fmed.2021.780005

The purpose of this study was to compare and understand differences in the use of low tidal volume ventilation (LTVV) between females and males with acute respiratory distress syndrome (ARDS) related to coronavirus disease 2019 (COVID-19). This is a *post-hoc* analysis of an observational study in invasively ventilated patients with ARDS related to COVID-19 in 22 ICUs in the Netherlands. The primary endpoint was the use of LTVV, defined as having received a median tidal volume (V_T) ≤6 ml/kg predicted body weight (PBW) during controlled ventilation. A mediation analysis was used to investigate the impact of anthropometric factors, next to the impact of sex *per se*. The analysis included 934 patients, 251 females and 683 males. All the patients had ARDS, and there were no differences in ARDS severity between the sexes. On the first day of ventilation, females received ventilation with a higher median V_T compared with males [6.8 (interquartile range (IQR) 6.0–7.6 vs. 6.3 (IQR 5.8–6.9) ml/kg PBW; $p < 0.001$]. Consequently, females received LTVV less often than males (23 vs. 34%; $p = 0.003$). The difference in the use of LTVV became smaller but persisted over the next days (27 vs. 36%; $p = 0.046$ at day 2 and 28 vs. 38%; $p = 0.030$ at day 3). The difference in the use LTVV was significantly mediated by sex *per se* [average direct effect of the female sex, 7.5% (95% CI, 1.7–13.3%); $p = 0.011$] and by differences in the body height [average causal mediation effect, −17.5% (−21.5 to −13.5%); $p < 0.001$], but not by the differences in actual body weight [average causal mediation effect, 0.2% (−0.8 to 1.2%); $p = 0.715$]. In conclusion, in this cohort of patients with ARDS related to COVID-19, females received LTVV less often than males in the first days of invasive ventilation. The difference in the use of LTVV was mainly driven by an anthropometric factor, namely, body height. Use of LTVV may improve by paying attention to correct titration of V_T, which should be based on PBW, which is a function of body height.

Keywords: lung protective ventilation, low tidal volume ventilation (LTVV), sex, gender, COVID-19, intensive care unit, critical care, mechanical ventilation

INTRODUCTION

Coronavirus disease 2019 (COVID-19) pandemic continues to have a relentless impact on the healthcare systems worldwide. Critical care systems are overloaded as many patients with COVID-19 develop acute respiratory failure requiring admission to a hospital for supplementary oxygen. A substantial proportion of these patients need admission to an intensive care unit (ICU) for ventilatory support (1, 2). Lung–protective ventilation, including the use of a low tidal volume (V_T), is recommended in patients with acute respiratory distress syndrome (ARDS) (3, 4) and there is growing evidence that the use of low-V_T ventilation (LTVV) also benefits patients with ARDS related to COVID-19 (5, 6).

Differences between females and males with regard to the use of LTVV have been described in surgery patients during general anesthesia (7–12) as well as critically ill patients in the ICU—and irrespective of the presence of ARDS (13–16, 44). It is uncertain if the sex difference in the use of LTVV also exists in patients with COVID-19. Use of LTVV might be limited in these patients because, due to the large numbers of patients requiring respiratory support, ventilation may need to be provided by healthcare professionals with much less experience in invasive ventilation, and thus also in the use of LTVV—it is uncertain whether this translates into sex differences.

To compare ventilation management with respect to LTVV in females vs. males, we reassessed the database of a conveniently-sized national multicenter study named "PRactice of VENTilation in patients with COVID-19" (PRoVENT–COVID) (5), a study that focused on ventilator settings and ventilation parameters in the first 4 calendar days of ventilation. Next to the hypothesis that the use of LTVV differs between the sexes, we also tested the hypothesis that differences in LTVV use are driven by anthropometric differences, i.e., differences in height and weight between the sexes, more than by sex *per se*.

MATERIALS AND METHODS

Design, Setting, and Participants

Secondary analysis of the database from the PRoVENT–COVID study, an investigator-initiated, national, multicenter, observational study in 22 ICUs in the Netherlands in the first 3 months of the national outbreak (5).

The protocol of the study of PRoVENT–COVID was approved by the institutional review boards of each participating hospital—need for individual patient informed consent was waived seen the observational design of the investigation. The PRoVENT–COVID study was registered at clinicaltrial.gov under the identifier NCT04346342.

Consecutive patients aged 18 years or older were enrolled if admitted to an ICU in one of the participating hospitals and having had received invasive ventilation for acute respiratory failure due to COVID-19, which had to be confirmed by RT–PCR. The PRoVENT–COVID study excluded SARS–CoV−2 infected patients that received ventilation for other reasons than COVID-19, e.g., patients that received ventilation for post-operative ventilation.

Data Collection and Analysis

Demographics, home medication, comorbidities, and disease severity scores were collected at baseline. The Berlin definition for ARDS was used to determine whether a patient had ARDS, and for ARDS severity (17).

Detailed information regarding ventilation management was captured in the first 4 calendar days of invasive ventilation at fixed time points every 8 h. Pulmonary and extrapulmonary events were captured up to hospital discharge, with a maximum of 28 days. Outcomes, such as intubation and life status, were collected till day 90.

We used the following equations:

$$V_T \text{ normalized to predicted body weight (PBW) } (V_{T,PBW}) \text{ [ml/kg]} = \text{absolute } V_T \text{ (ml)/PBW (kg) (18);} \quad (1)$$

$$\text{PBW in females (kg)} = 45.5 + 0.91^{*}(\text{height [cm]} - 152.4); \quad (2a)$$

$$\text{and PBW in males (kg)} = 50.0 + 0.91^{*}(\text{height [cm]} - 152.4); \quad (2b)$$

$$V_T \text{ normalized to actual body weight (ABW) } (V_{T,ABW}) \text{ [ml/kg]} = \text{absolute } V_T \text{ (ml)/ABW (kg)} \quad (3)$$

$$\text{driving pressure } (\Delta P) \text{ [cm } H_2O] = \text{peak pressure (Ppeak) [cm } H_2O] - \text{PEEP [cm } H_2O]; \text{ and}$$
$$\text{respiratory system compliance (Crs) [ml/cm } H_2O] = \text{Absolute } V_T \text{ (ml)/}\Delta P\text{[cm } H_2O] \quad (4)$$

Study Endpoints

The primary endpoint was the use of LTVV in the first 4 calendar days of invasive ventilation. Secondary endpoints were other key ventilation parameters, including absolute V_T, $V_{T,ABW}$ and $V_{T,PBW}$, PEEP, ΔP, and Crs.

Power Calculation

The PRoVENT–COVID study contains a conveniently sized cohort of patients. We did not perform a formal power calculation; the sample size was based on the number of patients available in the database. With 1,000 patients, the study has >80% power to detect an absolute difference ranging from 9 and 15% in the use of LTVV considering a use rate of 50% in the female patients as shown previously (16).

Statistical Analysis

No assumptions were made for missing data. As the first calendar day was a flexible day that lasted from the moment of intubation and start of ventilation in the participating ICU and in theory could last from 1 min to 23 h and 59 min, we merged the first and second calendar day, which was then named "day 1." The following calendar days were named "day 2" and "day 3." As the ventilation strategy and settings may vary substantially in the first

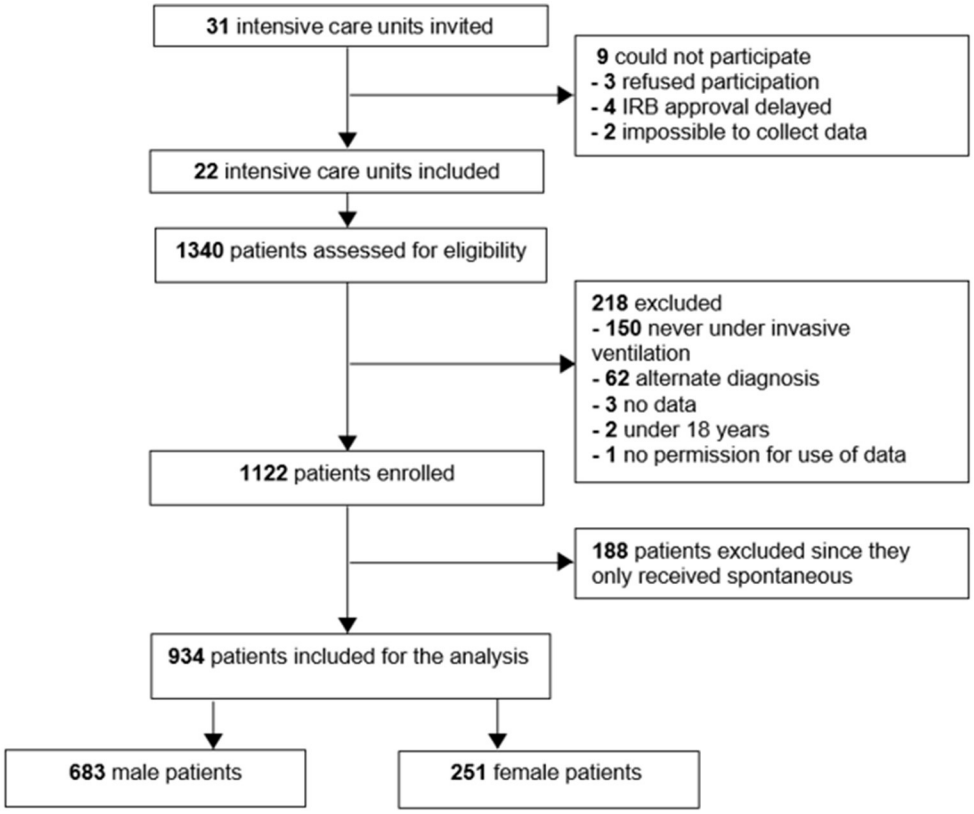

FIGURE 1 | Study flowchart.

hour of intubation, we also ignored the first available V_T, i.e., collected within 1 h of intubation.

Data are reported as numbers and proportions for categorical variables, and as medians with interquartile ranges (IQRs) for continuous variables. In addition, we also provided the 90% range for V_T. For baseline characteristics, the sexes were compared using the Fisher exact test for categorical variables, and the Wilcoxon rank-sum test for continuous variables. In all the analyses, males are used as the reference.

Ventilation parameters per day are presented in cumulative distribution plots, and in line graphs with error bars. In the distribution plots, vertical dotted lines represent the ideal cutoff for each parameter, and horizontal dotted lines the respective proportion of patients reaching each cutoff. All the ventilatory variables were aggregated per day and reported as such. For this, we calculated the mean of each ventilatory parameter per patient per day. In the tables, continuous variables were reported as medians of the means per each patient.

Patients were classified as having received LTVV, if the mean $V_{T,PBW}$ was $\leq$6 ml/kg during the controlled ventilation. For day 1, we ignored the breath in the first hour of ventilation, as this breath could have not been adjusted to achieve LTVV, e.g., in patients who started ventilation in the emergency department. Breaths collected under pressure support ventilation were also ignored, as were a breath that was collected at the moment spontaneous breathing activity was likely. This was the case if the measured (total) RR exceeded the set RR >2 breaths per min.

To further assess if sex is associated with differences in V_T an unadjusted mixed-effects linear regression model was used to extract the risk difference among the sexes. All analyses were performed using multilevel (patients nested in hospitals), mixed modeling with hospitals as a random effect to account for within-center clustering. Two *P*-values were reported in the graphs: (1) *P*-value for sex differences, reflecting the overall test for difference between sex across the days; and (2) *p*-values for the sex × day interaction, evaluating if change over time differed between the sexes.

The proportions of patients having had received LTVV are described and visualized in pie charts. An unadjusted mixed-effect generalized linear model was used to extract the risk difference for LTVV use.

To investigate whether differences in the use of LTVV between females and males are mediated by body height and ABW, a mixed-effect mediation model was used. In the mediation analysis, we assessed the individual impact of body height and ABW as potential mediators for the difference in the use of LTVV between sex. Mediators are variables that are affected by group assignment and that subsequently can affect the outcome.

TABLE 1 | Baseline characteristics of patient.

	Overall	Females	Males	*p*
Number of patients	934	251	683	
Age, years	65.0 [57.0, 72.0]	64.0 [55.0, 71.5]	65.0 [57.0, 72.0]	0.177
Weight, kg	86.0 [77.3, 96.4]	80.0 [70.0, 90.0]	89.0 [80.0, 98.2]	<0.001
Height, cm	176.0 [170.0, 183.0]	165.0 [162.0, 170.0]	180.0 [174.0, 185.0]	<0.001
BMI, kg/m^2	27.8 [25.2, 30.9]	28.4 [25.9, 32.3]	27.6 [25.2, 30.1]	0.002
Intubation at admission	152 (16.3)	38 (15.1)	114 (16.7)	0.618
NIV before intubation	77 (9.2)	23 (10.0)	54 (8.9)	0.688
Duration of NIV	7.5 [2.0, 18.1]	5.0 [1.8, 11.5]	8.0 [2.2, 24.0]	0.327
CT before intubation	326 (36.2)	97 (40.8)	229 (34.6)	0.099
% affected lung parenchyma on CT				0.682
0%	14 (4.3)	4 (4.1)	10 (4.3)	
25%	103 (31.4)	27 (27.8)	76 (32.9)	
50%	99 (30.2)	35 (36.1)	64 (27.7)	
75%	93 (28.4)	26 (26.8)	67 (29.0)	
100%	19 (5.8)	5 (5.2)	14 (6.1)	
X-ray before intubation	485 (85.7)	122 (85.3)	363 (85.8)	0.891
Number of affected quadrants				0.335
1	38 (7.8)	7 (5.9)	31 (8.5)	
2	114 (23.5)	34 (28.6)	80 (21.9)	
3	135 (27.8)	35 (29.4)	100 (27.3)	
4	198 (40.8)	43 (36.1)	155 (42.3)	
Pneumothorax	4 (1.8)	2 (3.8)	2 (1.2)	0.238
SAPS II	36.0 [29.0, 43.5]	35.0 [31.0, 43.5]	36.0 [29.0, 43.2]	0.573
APACHE II	16.0 [14.0, 21.0]	15.0 [12.0, 20.0]	17.0 [14.0, 22.0]	0.039
APACHE IV	56.0 [45.0, 70.0]	57.0 [46.0, 69.2]	56.0 [44.0, 70.0]	0.460
SOFA	7.0 [6.0, 10.0]	7.0 [6.0, 9.2]	7.0 [6.0, 10.0]	0.160
ARDS severity				0.386
Mild	188 (20.4)	51 (20.7)	137 (20.3)	
Moderate	630 (68.4)	162 (65.9)	468 (69.3)	
Severe	103 (11.2)	33 (13.4)	70 (10.4)	
Co-existing disorders				
Arterial hypertension	310 (33.2)	72 (28.7)	238 (34.8)	0.085
Heart failure	37 (4.0)	7 (2.8)	30 (4.4)	0.345
Diabetes	214 (22.9)	56 (22.3)	158 (23.1)	0.861
Chronic kidney disease	39 (4.2)	10 (4.0)	29 (4.2)	1.000
Baseline creatinine, μmol/L*	77.0 [62.0, 98.5]	63.5 [51.8, 78.0]	82.0 [68.0, 105.0]	<0.001
Liver cirrhosis	3 (0.3)	2 (0.8)	1 (0.1)	0.178
COPD	72 (7.7)	20 (8.0)	52 (7.6)	0.890
Active hematological malignancy	13 (1.4)	3 (1.2)	10 (1.5)	1.000
Active solid tumor malignancy	26 (2.8)	10 (4.0)	16 (2.3)	0.182
Neuromuscular disease	4 (0.4)	2 (0.8)	2 (0.3)	0.294
Immunosuppression	20 (2.1)	5 (2.0)	15 (2.2)	1.000
Home medication				
Systemic corticosteroids	34 (3.6)	8 (3.2)	26 (3.8)	0.844
Inhalation corticosteroids	105 (11.2)	40 (15.9)	65 (9.5)	0.007
ACE inhibitor	155 (16.6)	37 (14.7)	118 (17.3)	0.374
ARB II	106 (11.3)	22 (8.8)	84 (12.3)	0.162
Beta blocker	171 (18.3)	37 (14.7)	134 (19.6)	0.104
Insulin	68 (7.3)	20 (8.0)	48 (7.0)	0.670
Metformin	148 (15.8)	33 (13.1)	115 (16.8)	0.189
Statin	284 (30.4)	62 (24.7)	222 (32.5)	0.025
Calcium channel blocker	165 (17.7)	41 (16.3)	124 (18.2)	0.562

Data are median (quartile 25%–quartile 75%) or no (%). Percentages may not total 100 because of rounding.

**Most recent measurement in 24 h before intubation, or at ICU admission under invasive ventilation.*

APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; ARDS, acute respiratory distress syndrome.

Therefore, mediators are on the causal pathway of the relation between group and outcome, at least partly explaining the effects of the group on the outcome. For the mediation models, the following estimates are described: (1) the total effect (estimates the total effect of sex on ventilation); (2) the average causal mediation effect [ACME, explains how much of the effect of sex on ventilation is explained by the mediator (height or weight)]; and (3) the average direct effect (ADE, explains how much of the effect of sex on ventilation is still explained by sex after considering the effect of the mediator). For this model, Quasi–Bayesian 95% CI were estimated after 10,000 simulations. The mediation models included day and centers as a random effects.

All the analyses were done in R version 4.0.2 and the significance level was set at 0.05.

RESULTS

Patients

Of 1,122 eligible patients, 188 patients did not receive controlled ventilation at any time point data were collected for this study, leaving us with 934 fully analyzable patients, 251 females and 683 males (**Figure 1**). Males had a higher median body height and also a higher median ABW. Aside from differences in baseline APACHE II scores, plasma creatinine, and use of statins and inhalation corticosteroids at home, there were no differences at baseline between the sexes (**Table 1**). Other severity scores and ARDS severity were comparable between females and males (**Table 1**). Compared with females, males had a higher mortality rate and a longer duration of ventilation (**Table 2**).

Ventilation Parameters

On day 1, females received a higher median $V_{T,PBW}$ than males [6.8 (IQR 6.0–7.6, 90% range 5.4–8.8) vs. 6.3 (IQR 5.8–6.9, 90% range 5.0–8.0) ml/kg PBW; $p < 0.001$; **Figures 2**, **3** and **Table 3**]. This sex difference became smaller at day 2 [6.4 (IQR 5.9–7.1, 9% range 5.0–8.4) vs. 6.3 (IQR 5.8–7.0, 90% range 5.0–7.9) ml/kg PBW; $p = 0.046$] and at day 3 [6.5 (IQR 6.0–7.1, 90% range 5.1–8.2) vs. 6.2 (IQR 5.6–6.9; 90% range 4.9–7.8) ml/kg PBW; $p = 0.001$; **Supplementary Figures 1, 2** and **Supplementary Tables 1, 2**]. On day 1, females received ventilation with a slightly lower median PEEP and a higher median ΔP (**Figures 2**, **3** and **Table 3**). These differences became smaller on days 2 and 3 (**Supplementary Figures 1, 2** and **Supplementary Tables 1, 2**). Median Crs was lower in females at all 3 days.

Use of LTVV

Low tidal volume ventilation was generally underused, with only a third of patients receiving ventilation with a median $V_{T,PBW}$ ≤6 ml/kg PBW–at day 1, females received LTVV less often than males (23 vs. 34%; $p = 0.003$; **Figure 4**). The sex difference in use

TABLE 2 | Outcome.

	Overall	Females	Males	*p*
Number of patients	934	251	683	
Ventilatory free days at 28 days	2.0 [0.0, 16.0]	9.0 [0.0, 18.0]	0.0 [0.0, 15.0]	0.001
Extubation	545 (58.8)	159 (63.3)	386 (57.1)	0.098
Duration of ventilation, days	14.0 [8.0, 23.0]	12.0 [7.0, 20.8]	15.0 [8.0, 24.0]	0.012
Duration of ventilation in survivors at day 28	16.0 [10.0, 28.0]	13.0 [9.0, 23.0]	17.0 [10.0, 29.0]	0.003
Tracheostomy	154 (16.6)	32 (12.8)	122 (18.1)	0.059
Reintubation	118 (12.8)	38 (15.3)	80 (11.9)	0.184
Pneumothorax	8 (0.9)	1 (0.4)	7 (1.1)	0.690
Thromboembolic complications*	266 (28.5)	65 (25.9)	201 (29.4)	0.326
Acute kidney injury**	421 (45.2)	100 (40.0)	321 (47.1)	0.054
Renal replacement therapy	173 (18.5)	35 (13.9)	138 (20.2)	0.029
ICU length of stay, days	15.0 [9.0, 27.0]	14.0 [9.0, 24.0]	16.0 [9.0, 27.5]	0.094
In survivors, days	18.0 [11.0, 30.0]	16.0 [10.0, 27.0]	18.0 [11.0, 31.0]	0.067
Hospital length of stay, days	24.0 [14.0, 37.0]	22.0 [14.0, 36.0]	24.0 [14.0, 39.0]	0.408
In survivors, days	29.5 [20.0, 44.0]	27.0 [20.0, 39.0]	30.0 [20.0, 46.0]	0.062
ICU mortality	301 (33.0)	66 (27.2)	235 (35.2)	0.026
Hospital mortality	310 (36.1)	67 (29.9)	243 (38.3)	0.029
d7 mortality	97 (10.5)	27 (10.9)	70 (10.3)	0.809
d28 mortality	266 (28.9)	60 (24.6)	206 (30.5)	0.084
d90 mortality	323 (37.9)	70 (31.1)	253 (40.3)	0.016

Data are median (quartile 25%–quartile 75%) or no (%). Percentages may not total 100 because of rounding.

**Pulmonary embolism was defined when confirmed by chest CT angiography or when highly suspicious according to clinical assessment and treated accordingly by the attending the physician.*

***Acute kidney injury was defined when one of the following criteria was met at any point within 28 days after intubation: (1) a 1.5-fold increase of creatinine compared with baseline; and/or (2) an absolute creatinine increase of 26.5 μmol/L compared with baseline; and/or (3) a urinary output <0.5 ml/kg per h for more than 6 h.*

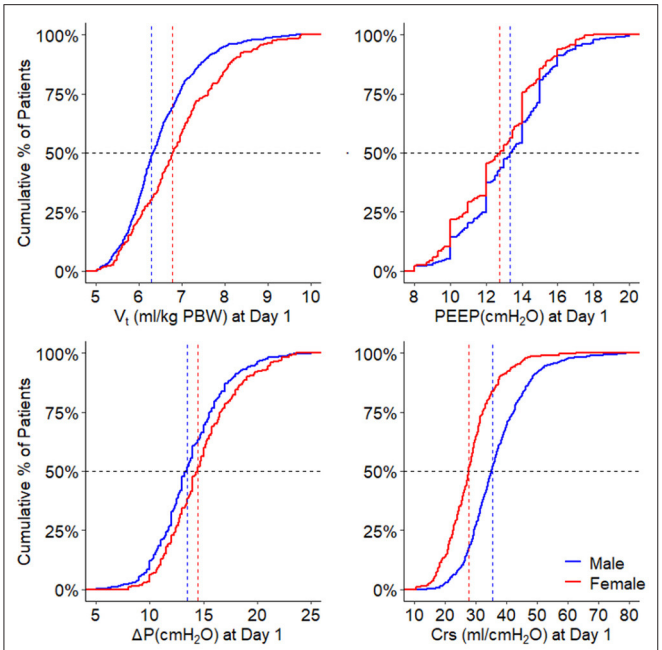

FIGURE 2 | Ventilation parameters during the first day. Cumulative frequency distribution of tidal volume, PEEP, driving pressure, and respiratory system compliance. Vertical dotted lines represent the median on the first calendar day of ventilation for each variable, and horizontal dotted lines show the respective proportion of patients reaching each cutoff. V_T, tidal volume; PEEP, positive end expiratory pressure; ΔP, driving pressure; Crs, respiratory system compliance; PBW, predicted body weight. The *p*-value for the sex reflects the overall test for difference between sex over the days, the *p*-value for the sex × year interaction evaluates if change over time differed by sex.

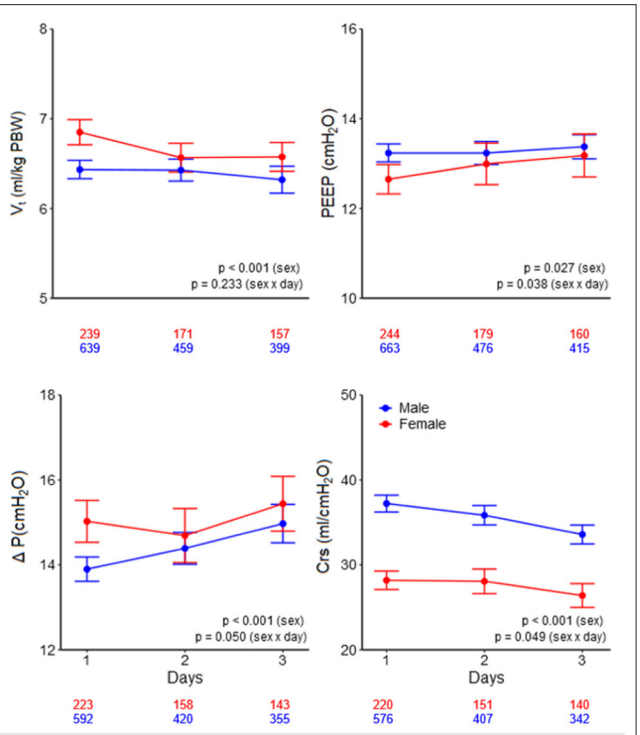

FIGURE 3 | Ventilatory variables over the days. Line graphs with error bars of tidal volume, PEEP, driving pressure, and respiratory system compliance. The numbers under the x-axis indicate the number of patients. V_T, tidal volume; PEEP, positive end-expiratory pressure; ΔP, driving pressure; Crs, respiratory system compliance; PBW, predicted body weight. The *p*-value for the sex reflects the overall test for difference between sex over the days, the *p*-value for the sex × year interaction evaluates if change over time differed by sex.

of LTVV persisted at day 2 (27 vs. 36%; $p = 0.046$) and at day 3 (28 vs. 38%; $p = 0.030$; **Figure 4** and **Supplementary Tables 1, 2**).

Mediation Analysis

The difference in the use of LTVV between females and males was significantly mediated by sex [average causal mediation effect 7.5% (95% CI 1.7–13.3%); $p = 0.011$] but more by body height [average causal mediation effect −17.5% (95% CI −21.5 to −13.5%); $p < 0.001$; **Table 4**]. The difference was also significantly mediated by ABW in the model that only used this factor [average causal mediation effect −1.7% (95% CI −2.7 to −1.0); $p < 0.001$], but not in a model that also used body height, meaning that the difference in the use of LTVV was mainly mediated by differences in height, and not by weight.

DISCUSSION

The results of this analysis of a large cohort of critically ill patients with ARDS related to COVID-19 who received invasive ventilation in the ICU during the first wave of the national outbreak in the Netherlands can be summarized as follows: (1) females were at a higher risk of not receiving LTVV at all 4 days of ventilation; (2) PEEP was lower and ΔP was higher, but only at day 1; and (3) females had a lower Crs, a difference that did not change over the days. In addition, the mediation analysis suggests that (4) differences are partly explained by sex *per se*; (5) but are mostly explained by the differences in body height.

Our study has several strengths. The PRoVENT–COVID study is one of the largest multicenter studies that collected ventilator data at several time points per day, allowing a better insight into ventilation practice, and differences herein between females and males. This study involved more than one-third of all invasively ventilated patients with ARDS related to COVID-19 in the first wave of the outbreak in the Netherlands. Furthermore, we enrolled patients in 22 centers included university hospitals, non-university teaching as well as non-teaching hospitals, accounting for around one-fourth of the ICUs in the Netherlands. This all increases the generalizability of the findings. The design of PRoVENT–COVID assured completeness of data collection and the short timeframe within which data were gathered, avoiding the effect of practice changes over time. At last, we followed the analysis plan strictly and used sophisticated mediation analysis to determine which factors determine the sex difference in the use of LTVV.

The differences in V_T between females and males may seem small, especially when focusing on the median V_T, PBW. However, the 90% range clearly shows that V_T differs between the sexes–for instance, 16% of female patients received ventilation with a $V_{T,PBW}$ >8 ml/kg, while only 5% of male patients received

TABLE 3 | Ventilatory variables during the first day.

	Overall	Females	Males	*p*
Number of patients	908*	244	664	
V_T, Absolute, mL	451.0 [406.1, 500.0]	396.5 [343.8, 440.5]	468.5 [427.2, 514.8]	<0.001
V_T, mL/kg ABW	5.2 [4.6, 5.9]	4.9 [4.2, 5.8]	5.3 [4.6, 6.0]	<0.001
90% range	3.4–7.1	3.3–7.0	3.8–7.2	
V_T, mL/kg PBW	6.4 [5.9, 7.1]	6.8 [6.0, 7.6]	6.3 [5.8, 6.9]	<0.001
90% range	5.1–8.4	5.4–8.8	5.0–8.0	
V_T, PBW ≤6 mL/kg, %	272 (31.0)	56 (23.4)	216 (33.8)	0.003
V_T, PBW ≤8 mL/kg, %	808 (92.0)	202 (84.5)	606 (94.8)	<0.001
V_T, PBW ≤10 mL/kg, %	874 (99.5)	238 (99.6)	636 (99.5)	1.000
PEEP, cmH_2O	13.2 [11.3, 15.0]	12.7 [10.7, 14.0]	13.3 [11.7, 15.0]	0.002
Peak pressure, cmH_2O	27.0 [24.0, 30.0]	27.2 [24.7, 30.2]	27.0 [24.0, 30.0]	0.116
Driving pressure, cmH_2O	13.8 [12.0, 16.0]	14.5 [12.4, 16.9]	13.5 [11.8, 15.8]	<0.001
Mechanical power, J/min	18.9 [15.5, 22.9]	16.8 [14.0, 20.0]	19.8 [16.5, 23.7]	<0.001
Compliance, mL/ cmH_2O	32.9 [27.5, 40.1]	27.6 [22.6, 32.2]	35.2 [29.6, 42.7]	<0.001
Respiratory rate, bpm	22.0 [20.0, 24.2]	22.0 [20.0, 25.0]	22.0 [20.0, 24.0]	0.257
FiO_2, %	0.5 [0.4, 0.6]	0.5 [0.4, 0.6]	0.5 [0.4, 0.6]	0.505
SpO_2, %	95.0 [93.6, 96.4]	95.0 [93.5, 96.2]	95.0 [93.7, 96.5]	0.588
$etCO_2$, mmHg	37.5 [33.1, 42.4]	37.0 [32.4, 42.1]	37.5 [33.4, 42.6]	0.351
Heart rate, beats per min	81.0 [70.0, 93.0]	80.4 [71.0, 93.8]	81.1 [69.7, 93.0]	0.713
Mean arterial pressure, mmHg	76.4 [71.5, 82.3]	76.2 [71.9, 82.0]	76.5 [71.3, 82.5]	0.930
pH	7.4 [7.3, 7.4]	7.4 [7.3, 7.4]	7.4 [7.3, 7.4]	0.259
Lactate, mmol/L	1.2 [1.0, 1.5]	1.2 [1.0, 1.5]	1.2 [1.0, 1.5]	0.755
PaO_2	80.0 [72.9, 90.7]	79.8 [72.2, 91.1]	80.1 [73.0, 89.9]	0.823
P/F ratio	174.2 [142.9, 208.6]	172.7 [135.6, 210.0]	174.6 [145.0, 208.0]	0.549
$PaCO_2$, mmHg	45.1 [40.5, 51.2]	44.0 [40.0, 50.1]	45.4 [41.0, 51.8]	0.056
Prone positioning	325 (47.6)	95 (49.2)	230 (46.9)	0.610
Duration of prone positioning	15.0 [11.0, 22.0]	16.0 [11.0, 23.0]	14.0 [11.0, 20.0]	0.129
Minute ventilation	9.7 [8.5, 11.2]	8.6 [7.5, 9.7]	10.2 [8.9, 11.5]	<0.001
Ventilatory ratio	1.7 [1.4, 2.0]	1.7 [1.4, 2.1]	1.7 [1.4, 2.0]	0.030
Recruitment maneuver	16 (2.8)	4 (2.3)	12 (3.0)	0.787

Data are median (quartile 25%–quartile 75%) or no (%). Percentages may not total 100 because of rounding.

PEEP, positive end-expiratory pressure; FiO_2, fraction of inspired oxygen; SpO_2, oxygen saturation; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen.

**Of 934 patients who received controlled ventilation on at least one timepoint of data collection, 908 received controlled ventilation at day 1.*

ventilation with a $V_{T,PBW}$ above this upper threshold of what is generally accepted as safe. The use of a high V_T is associated with a higher mortality and morbidity in ICU patients (5, 6, 13–15, 19–21). An earlier analysis showed that a one SD increases in V_T, $_{PBW}$ meant an increase of 28% in 28-day mortality (5). The finding that females received ventilation with a higher median V_T than males in this cohort is in line with results from several investigations originating from before the COVID-19 pandemic (13–16, 44). It interesting to note that V_T, in both females and males, was lower than in those previous cohorts, suggesting a temporal trend toward the use of lower V_T in critically ill patients (16). Despite the improved use of LTVV, however, differences between females and males persist.

Several reports on ventilated in patients with COVID-19 show a higher mortality in male patients (5, 22–30). This was also found in the current cohort. Interestingly, another study reported that the mortality of severely ill premenopausal but not post-menopausal female patients with COVID-19 are lower than age-matched male patients (31). The LUNG SAFE study, before COVID-19, did not find sex differences in mortality, but in that cohort, females had a shorter duration of invasive ventilation and a lower length of ICU stay (15). The reasons why male patients with COVID-19 have higher mortality remains uncertain. Biological factors, hormone factors such as estrogen, and factors related to the activity of X-linked genes have been suggested (31–34) and also sociocultural factors could play a role (34). It could also be interesting to look into the possible benefit of inhalation corticosteroids. In the current cohort, female patients had a significantly higher usage of inhalation corticosteroids as home medication. A total of 2 randomized clinical trials showed that using intravenous corticosteroids could reduce mortality (35, 36). These findings are confirmed in a recent meta-analysis (37). However, it is important to point out the difference between administration, i.e., intravenous vs. inhalation, and setting, i.e., during hospital admission vs. home medication.

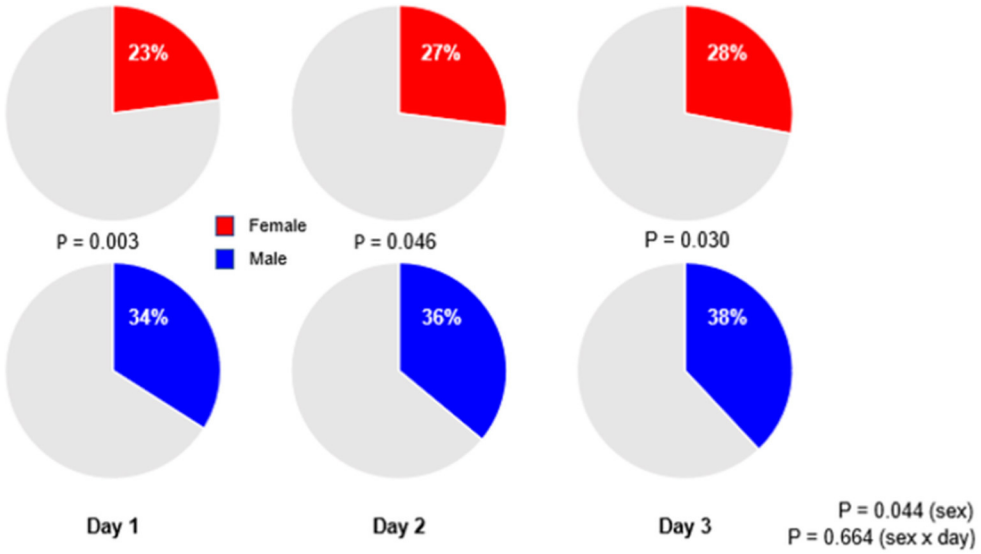

FIGURE 4 | Percentages of patients receiving low tidal volume ventilation. Significant *p*-value for the sex reflects the overall test for difference between sex over the days, while the *p*-value for the sex × year interaction evaluates if change over time differed by sex.

TABLE 4 | Mediation analysis.

	Adjusted absolute difference (95% CI)[a]	*p-value*
Univariable mediation model		
Body height as mediator		
Total effect of sex	−10.0 (−14.3 to −6.0)	<0.001
Average causal mediation effect of body height	−16.0 (−19.0 to −13.0)	<0.001
Average direct effect of female sex	6.0 (1.0 to 11.0)	0.018
Body weight as mediator		
Total effect of sex	−10.0 (−14.3 to −6.0)	<0.001
Average causal mediation effect of body weight	−1.7 (−2.7 to −1.0)	<0.001
Average direct effect of female sex	−8.4 (−12.7 to −4.0)	<0.001
Body height and weight as mediators*		
Total effect of sex	−9.8 (−13.6 to −6.0)	<0.001
Average causal mediation effect of body height	−17.5 (−21.5 to −13.5)	<0.001
Average causal mediation effect of body weight	0.2 (−0.8 to 1.2)	0.715
Average direct effect of female sex	7.5 (1.7 to 13.3)	0.011

[a]*All estimated were generated after 10,000 simulations.*
**CI estimated from robust clustered standard errors.*

The outcome advantage of female patients, however, should not withhold ICU doctors and nurses from using a correct V_T, seen the advantage of LTVV that has been found in pre-COVID-19 studies and in COVID-19 studies. In fact, this could increase the outcome differences between females and males.

Several studies in patients with non-COVID-19 have shown sex differences in important aspects of care in critically ill patients (7, 38–41). For instance—among patients with sepsis or shock, females are less likely to receive deep venous thrombosis prophylaxis or invasive ventilation, but are more likely to receive red blood cell transfusions (40). On the contrary, males receive "more intense" care, including placement of the central catheters for infusion of vasoactive medication (38) and invasive ventilation (38, 39). It is uncertain if similar differences, i.e., in non-ventilatory care, exist in patients with COVID-19 as well.

Of note, while $V_{T,PWB}$ was higher in the female patients, $V_{T,ABW}$ was higher in the male patients. It should be noticed, however, that the male patients had a significantly higher body mass index (BMI) compared with the females.

Next to the finding that female patients are ventilated with higher $V_{T,PBW}$, it is seen that PEEP was lower and ΔP was higher. These differences were rather small, and probably, therefore, less meaningful, and were only present at day 1. There was a remarkable difference in median Crs between the sexes. This finding is in line with the results of the earlier studies in patients with ARDS before COVID-19 (15, 42). The difference in Crs might be explained by differences in height (42). Further research may reveal associations between other anthropometric factors and Crs.

The findings of the mediation analysis are in line with findings of the previous studies in patients in the ICU (16) and in the operating room (12). In contrary to previous findings, we see that differences are only partly explained by sex *per se*. The actual body weight mediated the sex inequality in the use of LTVV in a model as a single factor, but not in the model using also body height.

Our findings point out the importance of using reliable methods to measure the height of the patients.

This analysis has some limitations; first, we only collected data during the first 4 calendar days of ventilation, and we cannot exclude the possibility that ventilation practices beyond these days remain different. Seen the observational nature of the study, we could not control for the unmeasured confounders. Also, the knowledge that ventilation data were being captured could have interfered with daily practice. The selection of ICUs was based on the personal contacts, which could have resulted in an overrepresentation of ICUs with more experience in lung-protective ventilation, including the use of LTVV, and the willingness to participate could have led to selection bias. Another limitation is that because this study was a national study, its worldwide generalizability is uncertain. Finally, the PRoVENT–COVID study did not collect the type of oxygen support before intubation. Early application of HFNC (high-flow nasal cannula) in the mild stage of ARDS may reduce mortality in the elderly patients with severe COVID-19 pneumonia (43). Further research should look into the influence of HFNC and should consider grouping the patients by age to see the impact of age on the use of LTVV in general and in female patients.

CONCLUSION

In this cohort of patients with ARDS related to COVID-19 who required invasive ventilation in the first wave of the national outbreak in the Netherlands, females received LTVV less often than males. Alike in the previous studies, in this cohort, the difference in the use of LTVV was driven by the anthropometric factors more than by sex *per se*. This information could be helpful in the proper titration of V_T in critically ill patients with COVID-19 and beyond.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

PS, MS, and FP were involved in the conceptualization, methodology, and worked with drafting of the manuscript. Acquisition, analysis, or interpretation of data was done by all the authors. Critical revision of the manuscript for important intellectual content by all the other authors. Statistical analysis was done by PS and AN. Administrative, technical, or material support was done by MS. MS, FP, and AN supervised the work.

FUNDING

This work was supported by Amsterdam University Medical Centers, Location Academic Medical Center, Amsterdam, the Netherlands.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.780005/full#supplementary-material

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Conflict of Interest: AN reports personal fees from Dräger, outside of the submitted work. MS reports personal fees from the Hamilton Medical, outside of the submitted work.

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

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ORIGINAL RESEARCH
published: 09 February 2022
doi: 10.3389/fmed.2022.717477

Impact of Succinylcholine vs. Rocuronium on Apnea Duration for Rapid Sequence Induction: A Prospective Cohort Study

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OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

Received: 31 May 2021
Accepted: 17 January 2022
Published: 09 February 2022

Citation:
Tang L, Zhao X, Li S, Huang L, Li J, Chen L and Huang S (2022) Impact of Succinylcholine vs. Rocuronium on Apnea Duration for Rapid Sequence Induction: A Prospective Cohort Study. Front. Med. 9:717477. doi: 10.3389/fmed.2022.717477

Objective: The present study aimed to evaluate the impact of 1.5 mg/kg succinylcholine or 1.2 mg/kg rocuronium, vs. 1.0 mg/kg succinylcholine on apnea duration in patients underwent rapid sequence induction (RSI).

Methods: This prospective cohort study was conducted in the Department of Anesthesiology in Shanghai General Hospital from July 2020 to November 2020. Apnea duration was defined as the time from apnea prompted by the $P_{ET}CO_2$ waveform to the time the point of oxygen saturation declined to 90% (T90) and 95% (T95) after succinylcholine or rocuronium administration. The primary outcome included T90 and T95 changes in 1.5 mg/kg vs. 1.0 mg/kg succinylcholine groups and 1.5 mg/kg succinylcholine vs. 1.2 mg/kg rocuronium groups.

Results: A total of 265 participants were subjected for analysis. The succinylcholine (1.0 mg/kg) group had a significantly longer T90 (50.72, 95% confidence interval [CI, 7.60, 94.38], $P = 0.015$) and T95 (48.09, 95% CI [7.11, 89.07], $P = 0.012$) than the succinylcholine (1.5 mg/kg) group. In addition, significantly longer T90 (56.84, 95% CI [16.24, 97.44], $P = 0.003$) and T95 (50.57, 95% CI [12.58, 88.57], $P = 0.003$) were observed in the rocuronium (1.2 mg/kg) group than those in the succinylcholine (1.5 mg/kg) group. No severe side events were observed during the operation.

Conclusion: Rocuronium and the lower dose of succinylcholine may be recommended to patients underwent RSI.

Keywords: rapid sequence induction intubation, succinylcholine, rocuronium, apnea duration, oxygen saturation

INTRODUCTION

Rapid sequence induction (RSI) is a special technique of anesthetic induction designed to reduce the risk of aspiration of secretions of any kind, e.g., regurgitated or vomited gastric contents. This is done by shortening the normal sequence of intubation procedures and omitting certain steps to minimize the time between loss of consciousness and swallowing reflexes until the airway is secured by tracheal intubation (1). In particular, RSI involves not using mask ventilation, at least for adults.

Neuromuscular blockade agents (NMBAs) are used to facilitate endotracheal intubation (2). Succinylcholine is a short-acting depolarizing NMBA that is the most commonly conventionally used NMBA in RSI because of its fast onset and short duration (3). Unfortunately, it can have serious side effects (4, 5). Rocuronium, a steroidal non-depolarizing NMBA, is an alternative to succinylcholine due to its fast onset (6, 7). However, the 1.0–1.2 mg/kg dose recommended for RSI has too long a duration of action that fatal hypoxia is imminent if the airway is difficult, especially if intubation and mask ventilation fail simultaneously. This disadvantage of rocuronium is not eliminated by the very rapid reversal with sugammadex (8), because this drug is often not available fast enough in emergency situations (9). Therefore, the selection of succinylcholine or rocuronium in RSI should be carefully considered and tailored to the specifics of each patient and their clinical indications and medical conditions.

Apnea caused from not using mask ventilation, however, includes the risk of hypoxemia. Therefore, "non-hypoxic apnea," defined as duration of apnea with SpO2 > 90%, is relevant to patient safety (10). Previous studies focused mainly on increasing oxygen storage to prolong non-hypoxic apnea duration (10, 11), whereas few studies have been performed on approaches to decrease oxygen consumption. Two aspects should be considered in the assessment of the optimal dose of succinylcholine and rocuronium in RSI: prolonging the non-hypoxic apnea duration (without additional oxygen consumption) and shortening the apnea interval (fast onset and good intubation conditions). Succinylcholine may lead to increased dose-dependent oxygen consumption (12). Our previous study showed that in obese patients the non-hypoxic apnea duration in the treatment with 1.5 mg/kg succinylcholine was shorter than that in the treatment with 0.9 mg/kg rocuronium (13), we assumed that fasciculation may be a potential cause of the shorter non-hypoxic apnea. However, poor intubation conditions and repeated intubation may also increase oxygen consumption. Succinylcholine is superior to rocuronium in terms of muscle relaxation effects in both good intubation conditions and clinically acceptable intubation conditions at quantities of 2–3 times the ED95 dose (6). Similar onset times and intubation conditions were achieved at doses higher than 3 times the ED95 dose (1.0 mg/kg−1.5 mg/kg succinylcholine and 1.0 mg/kg−1.2 mg/kg rocuronium) (7, 14–16). Therefore, the optimal doses of succinylcholine and rocuronium for application in RSI are still inconclusive.

Therefore, the aim of the present study was to compare the non-hypoxic apnea duration of the administration of 1.5 mg/kg succinylcholine, 1.0 mg/kg succinylcholine, and 1.2 mg/kg rocuronium during RSI.

MATERIALS AND METHODS

Study Design

This prospective cohort study was conducted in the Department of Anesthesiology in Shanghai General Hospital from July 2020 to November 2020. This study was approved by the Ethics Committee of Shanghai General Hospital ([2020]54) and was registered in the Chinese Clinical Trial Registration Center (http://www.chictr.org.cn/index.aspx) with the registration number ChiCTR2000034769. Written informed consent was obtained from all individual participant.

Participants

Patients who underwent elective surgery requiring RSI were enrolled. The following inclusion criteria were used: (1) American Society of Anesthesiologists (ASA) physical status I or II and (2) Age between 18 and 65 years. The exclusion criteria were as follows: (1) Unwilling to provide written informed consent; (2) Pregnancy; (3) Patients with a history of difficulty in intubation or failed intubation; (4) Obstructive sleep apnea syndrome; (5) A history of respiratory tract infection within a month; (6) Smoking cessation <2 months before surgery; (7) History of alcohol or drug abuse; (8) Cerebrovascular disease and increased intracranial pressure; (9) Drugs antagonists of rocuronium (such as phenytoin, carbamazepine, or protease inhibitors). In case one of the following conditions was present, the observation was to be suspended and the participant withdrawn from the study: (1) After preoxygenation, the end-tidal oxygen concentration was <90%; (2) Coughing during tracheal intubation; (3) Failed tracheal intubation twice times or more; (4) Recovery from spontaneous breathing before mechanical ventilation; (5) Severe allergic reactions; (6) Patients with circulatory fluctuations that were difficult to correct after 5 min of using vasoactive drugs. The participants were not compensated for their study participation.

Grouping and Masking

General anesthesia drugs and treatment strategies were selected based on clinical needs. The choice of a muscle relaxant was jointly decided by the anesthetist and the participants. As an observational exploratory study, no blindness was applied.

Typical Procedures

All subjects fasted for more than 8 h before surgery. After entering the operation room, a 20G indwelling vein cannula was placed in the median vein of the left antecubital fossa, and 10 mL/kg of sodium lactate Ringer's solution was infused to substitute for the fasting-induced fluid deficit. Then, 2% local lidocaine anesthesia was administered for the puncture and the placement of the left radial artery. Next, a pressure sensor was connected to the patient to measure the direct arterial pressure and perform blood gas analysis. If the left radial artery puncture and placement failed, the right forearm was used to measure the non-invasive blood pressure with a measurement interval of 1 min. Further, the subjects were connected to a GE CARESCAPE Monitor B650 (GE Healthcare Finland OY, Helsinki, Finland) to monitor the heart rate (HR), mean arterial pressure (MAP), finger pulse oxygen saturation (SpO_2), bispectral index (BIS) and nasopharyngeal temperature (Temp). The subject lied in the supine position and was kept warm using a medical insulation blanket. The oxygen flow rate used was 10 L/min; the oxygen concentration reached was 100%. The airway pressure-limiting valve of the anesthesia machine was fully opened, the breathing circuit was pre-filled, and the subject was instructed to breathe calmly under a closed mask for 3 min.

Then, an intravenous injection of fentanyl 3 μg/kg and propofol 2 mg/kg was administered. After the eyelash reflex disappeared and the subject ceased respond to the patting call, the muscle relaxant was administered (following the decision previously made by the anesthetist and the participants). Before the spontaneous breathing disappeared, the subject was to fasten the mask to avoid inhaling air; the mandible had to be unsupported before intubation, and any manual or mechanical ventilation was not to be applied. Fifty seconds after the administration of the muscle relaxant, the mask was removed, and a video laryngoscope (UETDC-K3) was utilized to perform a laryngoscopy to expose the glottis. Next, 60 s after the administration of the muscle relaxant, endotracheal intubation was conducted (7.5-mm cuffed tracheal tube for men and 7-mm cuffed tracheal tube for women). The insertion depth of the tracheal tube was 1 cm after the cuff was fully inserted into the glottis. After the tracheal intubation, a fiberoptic bronchoscope (UESCOPETIC-I1) was used to check whether the tracheal tube position is correct. The tracheal tube was opened in the air, without mechanical ventilation, and the end-expiratory carbon dioxide output was observed to monitor the recovery of spontaneous breathing. After tracheal intubation, to prevent the recovery of spontaneous breathing, intravenous bolus of rocuronium (0.6 mg/kg) was given to maintain muscle relaxation in the succinylcholine (1.5

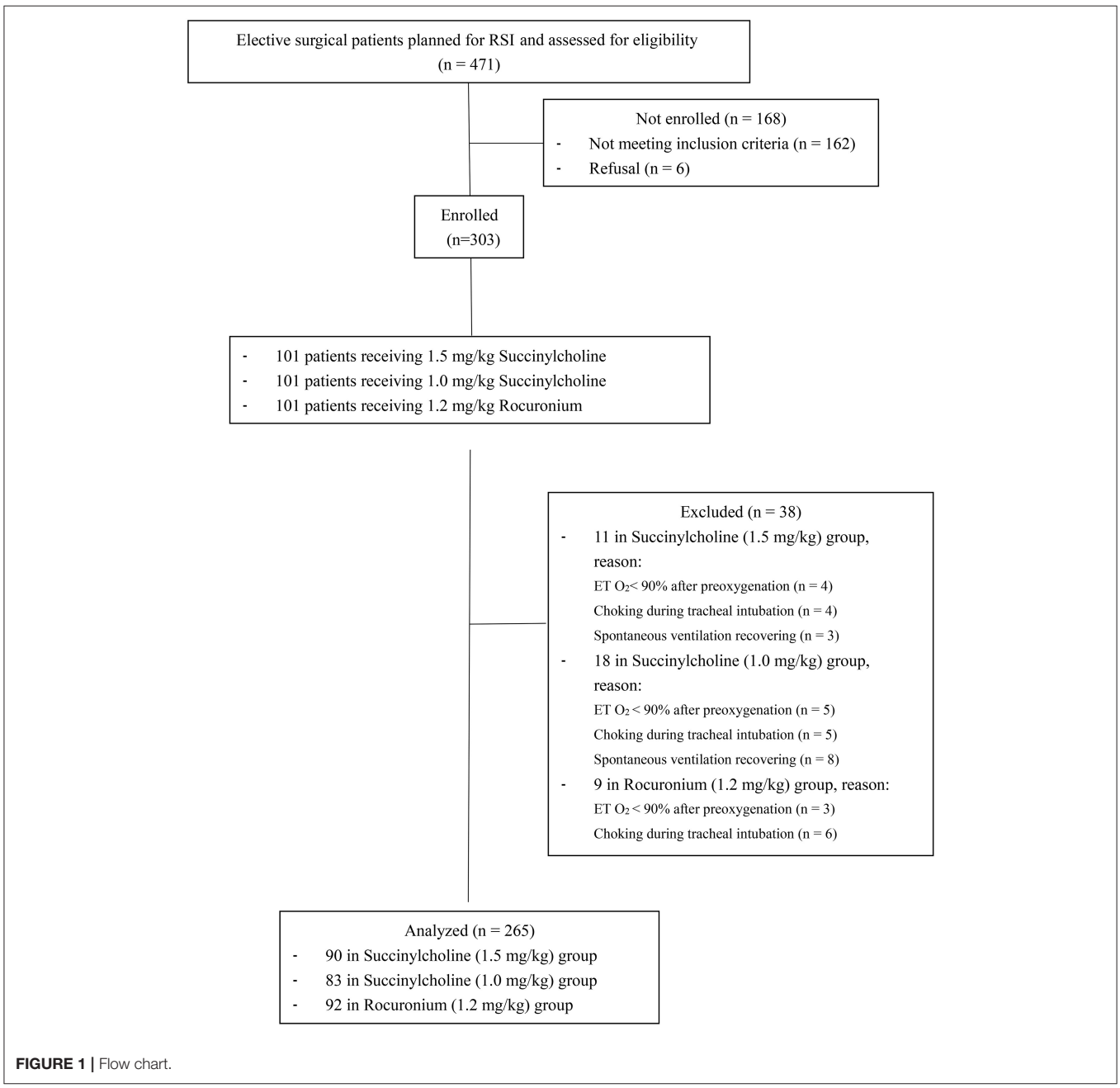

FIGURE 1 | Flow chart.

mg/kg) and succinylcholine bromide (1.0 mg/kg) groups. To prevent consciousness restoration during anesthesia, propofol was intravenously injected at a rate of 5 mg /kg/h (Willi's Ark CONCERT-III infusion pump). In case BIS was >60, intravenous injection of 20 mg of propofol was applied. When SpO_2 dropped to 90%, the tracheal tube was immediately connected to the anesthesia machine (GE Carestation 620) for mechanically controlled mechanical ventilation (parameter settings: oxygen concentration 100%, oxygen flow 1 L/min, tidal volume 8 mL/kg, frequency 16 beats/min, inhale-to-exhale ratio 1:2).

During the anesthesia, the hemodynamic parameters were monitored in real time. If HR > 110 beats/min, intravenous bolus of 1 mg of esmolol was administrated; if HR < 50 beats/min, an intravenous bolus injection of atropine 0.5 mg was given. If SBP > 170 mmHg, intravenous bolus injection of 1 mg perdipine was administered, and if SBP < 80 mmHg or MAP dropped more than 25% of the baseline value, 50 μg oxypinephrine was applied as an intravenous bolus injection.

Outcomes

The primary outcome was the non-hypoxic apnea duration. That is, the time interval between $P_{ET}CO_2$ waveform area prompts apnea to oxygen saturation declined to 95% (T95) and 90% (T90) of 1.5 mg/kg succinylcholine vs. 1.0 mg/kg succinylcholine groups, and 1.5 mg/kg succinylcholine vs. 1.2 mg/kg rocuronium groups.

Prespecified secondary outcomes included the T95 and T90 of the 1.0 mg/kg succinylcholine and 1.2 mg/kg rocuronium groups and adverse events. The exploratory outcomes included the exploration of factors that correlated with T90, and the variation of blood gas analysis, BIS, temperature, HR, MAP, SpO_2, ETO_2, and $P_{ET}CO_2$.

Any adverse reactions, such as laryngospasm, bronchospasm, and masseter spasm, or muscle rigidity during intubation, were recorded during the surgery operation. Any adverse events found were followed up before improvement or discharge.

Data Collection and Definition

The data collected included gender, age, ASA classification, preoperative hemoglobin (Hb), hematocrit (Hct), weight, height, body-mass index (BMI, kg/m^2), smoking history, Mallampati score, T95, T90, duration of muscle fibrillation (TF, the time from the onset of muscle fibrillation to the disappearance of muscle fibrillation after intravenous injection of muscle relaxants), classification of the degree of muscle fibrillation, and the conditions of tracheal intubation. In addition, the laryngoscope exposure classification, number of intubation attempts, HR, MAP, SpO_2, Temp, BIS, ETO_2, as well as for at room entry, 3 min after oxygen inhalation, 30 s after muscle relaxant administration, 50 s after muscle relaxant administration, 2 min after intubation, SpO_2 reduction to 95%, SpO_2 decrease to 90%, SpO_2 increase to 96%. Moreover, blood gas analysis was performed of pH, pO_2, pCO_2, cLac at room entry, 3 min after oxygen inhalation, and SpO2 decrease to 90%.

Muscle fibrillation was classified using the scale scores described in a previous report (17): 0 = No muscle tremor; 1 = Mild: slight muscle tremor in eyes, neck, face, or fingers, no limb movement; 2 = Moderate: moderate muscle tremor or obvious limb movement on both sides; 3 = Severe: severe or continuous and extensive muscle fibrillation. Endotracheal intubation condition was evaluated by Copenhagen score (18): 1 = excellent; 2 = good, and 3 = poor. Laryngoscope exposure classification (Cormack-Lehane classification) was defined as follows: 1 = the glottis was mostly visible; 2 = only the posterior union of the glottis could be seen, but not the glottis; 3 = only the epiglottis was visible; 4 = no glottal epiglottis could be seen. We used the World Health Organization classification for BMI: <18.5 (underweight), 18.5–24.9 (normal range), 25–29.9 (overweight), and >30 (obesity).

Sample Size Calculation

Preliminary analysis revealed that T90 in the succinylcholine (1.5 mg/kg), succinylcholine (1.0 mg/kg), and rocuronium (1.2 mg/kg) groups was 475.9 ± 64.7, 534.7 ± 64.7, and 528.7 ± 52.5, respectively. Therefore, an estimated sample size of 91

TABLE 1 | Clinical characteristics.

	Succinylcholine (1.5 mg/kg) (*n* = 90)	Rocuronium (1.2 mg/kg) (*n* = 92)	Succinylcholine (1.0 mg/kg) (*n* = 83)
Age, median (IQR)	39 (32, 52)	41 (32, 51)	43 (33, 52)
Gender			
Male	31 (34.4%)	43 (46.7%)	24 (28.9%)
Female	59 (65.6%)	49 (53.3%)	59 (71.1%)
Hemoglobin (g/L)	135 ± 13	137 ± 13	134 ± 11
Hematocrit	0.41 ± 0.04	0.41 ± 0.04	0.41 ± 0.03
Body weight (kg), median (IQR)	60 (54, 69)	65 (55, 72)	61 (54, 67)
Height (m)	1.63 ± 0.08	1.66 ± 0.09	1.63 ± 0.08
BMI (kg/m^2)	23.3 ± 3.0	23.4 ± 3.0	23.0 ± 2.8
<18.5	3 (3.3%)	3 (3.2%)	3 (3.61%)
18.5–24.9	65 (72.2%)	61 (66.3%)	62 (74.7%)
25–29.9	21 (23.3%)	27 (29.4%)	16 (19.3%)
≥30.0	1 (1.1%)	1 (1.1%)	2 (2.4%)
ASA			
1	70 (77.8%)	69 (75.0%)	63 (75.9%)
2	20 (22.2%)	23 (25.0%)	20 (24.1%)
Mallampati			
1	25 (27.8%)	27 (28.3%)	24 (28.9%)
2	47 (52.2%)	52 (56.5%)	46 (55.4%)
3	18 (20.0%)	13 (14.1%)	13 (15.7%)
Smoking No	87 (96.7%)	82 (89.1%)	70 (84.3%)
Yes	3 (3.3%)	10 (10.9%)	13 (15.7%)
Medical history None	70 (77.8%)	69 (75%)	63 (75.9%)
High blood pressure	11 (12.2%)	8 (8.7%)	6 (7.2%)
Diabetic mellitus	4 (4.4%)	5 (5.4%)	8 (9.6%)
Hypothyroidism	3 (23.1%)	6 (6.5%)	4 (4.8%)
Hepatitis B	2 (2.2%)	4 (4.3%)	2 (3.0%)

BMI, body-mass index; IQR, interquartile range.

TABLE 2 | Non-hypoxic apnea duration.

	Succinylcholine (1.5 mg/kg) ($n = 90$)	Rocuronium (1.2 mg/kg) ($n = 92$)	Succinylcholine (1.0 mg/kg) ($n = 83$)	
T90 (s)	404 (310, 511)	487 (385, 578)	446 (385, 551)	
T95 (s)	354 (267, 450)	420 (333, 513)	392 (337, 493)	
Primary outcome				
	Rocuronium vs. Succinylcholine (1.5 mg/kg)	**P**	**Succinylcholine (1.0 mg/kg) vs. Succinylcholine (1.5 mg/kg)**	**P**
T90 Change (95% CI)	56.84 s (16.24, 97.44)	0.003	50.72 s (7.06, 94.38)	0.015
T95 Change (95% CI)	50.57 s (12.58, 88.57)	0.003	48.09 s (7.11, 89.07)	0.012
Secondery outcome				
	Rocuronium vs. Succinylcholine (1.0 mg/kg)	**P**		
T90 Change (95% CI)	6.12 s (−34.58, 46.82)	0.48		
T95 Change (95% CI)	2.48 s (−35.74, 40.70)	0.54		

T90, oxygen saturation declined to 90%; T95, oxygen saturation declined to 95%. CI, confidence interval.

patients per group could provide 80% power to detect a between-group difference, assuming a two-sided significance level of 2.5%. Considering a loss of follow-up of 10%, a number of 101 subjects per group are required.

Statistical Analysis

Continuous variables that follow normal distribution was expressed with mean ± Standard deviation (SD), otherwise presented as median and interquartile range (IQR). Categorical variables were displayed using number and percentages. For multiple demographic characteristics comparison, nonparametric test was applied for continuous variables that not conformed to normal distribution. The comparison between the 1.5 mg/kg succinylcholine vs. 1.0 mg/kg succinylcholine and 1.5 mg/kg succinylcholine vs. 1.2 mg/kg rocuronium groups were analyzed using student *t* test. Two-way repeated measurement ANOVA was used to detect the effects of treatment and time interaction on HR and MAP. In addition, categorical variable comparison was conducted using Chi-square or Fisher exact tests. Pearson correlation analysis was employed to assess the correlation between T90 and the interested variables. All data were analyzed using SPSS 22.0 (IBM Corp., Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

Patient and Public Involvement

Not applicable.

RESULTS

A total of 471 patients were assessed for eligibility, of which 162 failed to meet the inclusion criteria, and 6 refused to participate. Of the enrolled 303 patients, 38 were excluded because of incomplete data for T90 and T95. Therefore, a total number of 265 subjects were analyzed: 90 cases in the 1.5 mg/kg succinylcholine, 83 in the 1.0 mg/kg succinylcholine, and 92 in the 1.2 mg/kg rocuronium groups (**Figure 1**). The demographic data are presented in **Table 1**.

TABLE 3 | Adverse events.

	Succinylcholine (1.5 mg/kg) ($n = 90$)	Rocuronium (1.2 mg/kg) ($n = 92$)	Succinylcholine (1.0 mg/kg) ($n = 83$)
Overall	23	13	19
Type of adverse events			
Sore throat	17	13	14
Myalgia	10	0	6
Degree of adverse events			
Mild	23	13	19
Severe	0	0	0

T90 in the 1.2 mg/kg rocuronium group was significantly longer (56.84 [95% CI 16.24–97.44], $P = 0.003$) than that in the 1.5 mg/kg succinylcholine group. Additionally, T90 in the 1.0 mg/kg succinylcholine group was statistically significantly longer (50.72 [95% CI 7.06–94.38], $P = 0.015$) than that in the 1.5 mg/kg succinylcholine group. Compared with the 1.5 mg/kg succinylcholine group, the 1.2 mg/kg rocuronium group had a significant longer T95 (50.57 [95% CI 12.58–88.57], $P = 0.003$). When compared with the succinylcholine (1.5 mg/kg) group, the succinylcholine (1.0 mg/kg) exhibited a significant longer T90 (48.09 [95% CI 7.11–89.07], $P = 0.012$).

For secondary outcome comparison, the T90 (6.12 [95% CI −34.58–46.82], $P = 0.48$) and T95 (2.48 [95% CI 35.74–40.70], $P = 0.54$) values were comparable between the 1.0 mg/kg succinylcholine and 1.2 mg/kg rocuronium groups (**Table 2**). No severe adverse events were observed during the surgery and during follow-up in all groups. A total number of 23, 13, and 19 mild adverse reactions occurred in the 1.5 mg/kg succinylcholine, 1.2 mg/kg rocuronium, and 1.0 mg/kg succinylcholine groups, respectively. Among them, sore throat and myalgia were the most common side effects (**Table 3**).

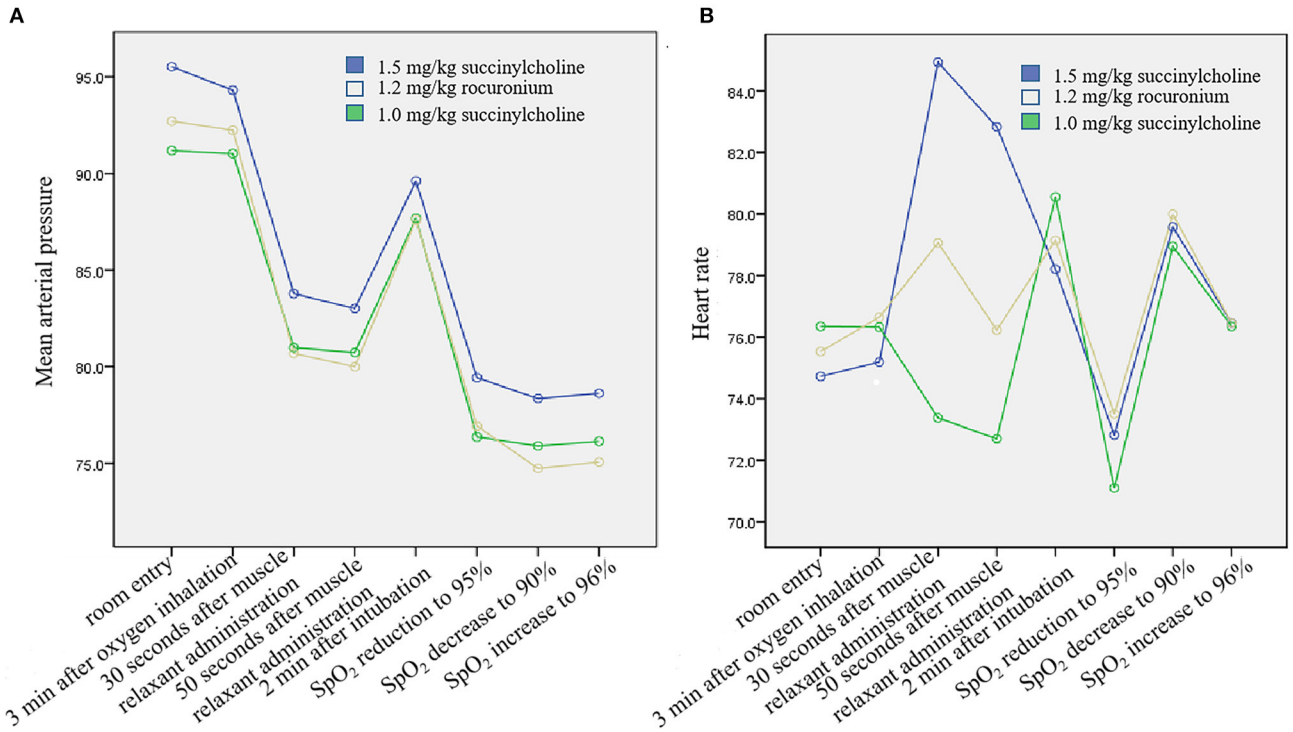

FIGURE 2 | Mean arterial pressure and heart rate variation. **(A)** Mean arterial pressure. Two-way repeated measurement ANOVA suggested that time and treatment interaction was comparable ($P = 0.279$). **(B)** Heart rate. Two-way repeated measurement ANOVA suggested that time and treatment interaction showed statistical significance among the groups ($P < 0.001$), though no clinical significance was observed.

One incubation attempt was successfully performed in all patients. Tracheal intubation evaluation revealed that the incubation conditions, C-L classification, and incubation number were comparable among the groups. The time for muscle fibrillation was comparable between the 1.5 mg/kg and 1.0 mg/kg succinylcholine groups ($P = 0.73$) (**Supplementary Table 1**). The degrees of muscle fibrillation in these two groups were also similar ($P = 0.11$) (**Supplementary Table 2**).

Moreover, the variation ratio of MAP and HR were within 30% at each time point (**Figures 2A,B**). In addition, the BIS variation among the three groups showed no clinical significance (**Supplementary Table 3**). The temperature during RSI was relatively stable, ranging from 36.0 °C to 37.1 °C.

Blood gas analysis showed a significantly different pH between room entry and 3 min after oxygen inhalation ($P < 0.01$) among the groups, despite no clinical significance. pO_2 at 3 min after oxygen inhalation time point was highest in the 1.0 mg/kg succinylcholine group ($P = 0.005$). The pCO_2 and cLac values significantly differed among the groups at room entry, 3 min after oxygen inhalation, and SpO_2 decrease to 90% time points (all $P < 0.01$) (**Table 4**). The SpO_2 in room entry and the minimum SpO_2 time points were comparable among the groups (all $P > 0.05$). In addition, ETO_2 was comparable among the groups, and $P_{ET}CO_2$ at 3 min after oxygen inhalation ($P = 0.013$) and SpO_2 increase to 96% time points ($P = 0.002$) were significantly differed (**Supplementary Table 4**).

Correlation analysis was used to explore the potential factors that might affect T90. As depicted in **Supplementary Table 5**, BMI, age, and hemoglobin were significantly correlated with T90 (all $P < 0.001$). Gender, smoking, muscle fibrillation time period, and muscle fibrillation degree were not correlated with T90.

DISCUSSION

In the present study, compared with 1.5 mg/kg succinylcholine group, both 1.0 mg/kg succinylcholine and 1.2 mg/kg rocuronium groups had significantly longer T90 and T95. These findings may provide evidence that lower dose succinylcholine and 1.2 mg/kg rocuronium may be feasible in clinical practice.

RSI is a critical medical measure that facilitates intubation. The selection of neuromuscular relaxants has been extensively studied, but there is no consensus. One of the highest risks of RSI comes from hypoxemia and reducing hypoxemia risk should be considered in the choice of muscle relaxants. Nevertheless, the available evidence on non-hypoxic apnea duration is limited. A meta-analysis showed that succinylcholine was superior to rocuronium in achieving excellent clinically acceptable intubation conditions (6). However, no statistical difference in the intubation conditions achieved was found between rocuronium and succinylcholine (19). In terms of non-hypoxic apnea duration, it was suggested that 1.0 mg/kg succinylcholine and 1.2 mg/kg rocuronium were superior to 1.5 mg/ kg succinylcholine in T90 and T95. These findings suggested

TABLE 4 | Blood gas analysis.

	Succinylcholine (1.5 mg/kg) ($n = 90$)	Rocuronium (1.2 mg/kg) ($n = 92$)	Succinylcholine (1.0 mg/kg) ($n = 83$)	P
pH				
Room entry	7.40 (7.39, 7.42)	7.42 (7.40, 7.43)	7.41 (7.40, 7.43)	0.002
3 min after oxygen inhalation	7.40 (7.38, 7.42)	7.42 (7.40, 7.43)	7.41 (7.39, 7.42)	0.005
SpO_2 decrease to 90%	7.30 (7.28, 7.33)	7.30 (7.28, 7.31)	7.31 (7.29, 7.32)	0.24
pO_2 (mmHg)				
Room entry	86 (85, 88)	85 (82, 87)	86 (84, 87)	0.051
3 min after oxygen inhalation	457 (413, 493)	445 (401, 482)	479 (432, 517)	0.005
SpO_2 decrease to 90%	63 (62, 65)	63 (62, 65)	63 (62, 65)	0.83
pCO_2 (mmHg)				
Room entry	36.1 (34.7, 38.2)	37.4 (36.6, 38.5)	36.8 (35.4, 38.8)	0.003
3 min after oxygen inhalation	35.6 (32.7, 37.7)	39.15 (36.7, 41.6)	38.1 (35.7, 40.9)	<0.001
SpO_2 decrease to 90%	52.8 (47.4, 57.7)	55.9 (51.4, 59.5)	57.2 (53.5, 62.4)	<0.001
cLac (mmol/L)				
Room entry	0.9 (0.8, 1.0)	1.0 (0.9, 1.2)	0.9 (0.7, 1.1)	<0.001
3 min after oxygen inhalation	0.9 (0.8, 1.1)	1.1 (1, 1.2)	0.9 (0.8, 1.1)	<0.001
SpO_2 decrease to 90%	1.0 (0.9, 1.1)	1.1 (1, 1.2)	1.0 (0.8, 1.1)	<0.001

that the administration of 1.0 mg/kg succinylcholine may be safer than higher doses. We noted that apneic oxygenation during the apnea period in RSI did not prevent desaturation as compared with conventional care measures in cardiac or traumatic arrest patients (20).

In the present study, the T95 and T90 in the 1.0 mg/kg succinylcholine and 1.2 mg/kg rocuronium groups were significantly longer than that in the 1.5 mg/kg succinylcholine group. In a previous study, Taha et al. reported that the T95 value in 1.5 mg/kg rocuronium-treated patients was 378 (370–393), which was lower than that in the present study. This discrepancy may be attributed to the differences in the fentanyl dose, start time points, and sample sizes (21). Our previous study compared the time of oxygen saturation decline to 92% (T92) in 0.9 mg/kg rocuronium- and 1.5 mg/kg succinylcholine-treated obese patients, in which rocuronium showed a significantly longer T92 (13), which in agreement with the present study.

Succinylcholine can trigger muscle fibrillation and increase muscle fibrillation-related metabolism. In this study, the degree and duration in the 1.5 mg/kg succinylcholine and 1.0 mg/kg succinylcholine groups were comparable, which may be explained with the supply of oxygen by myoglobin, which minimized its effect on systemic oxygen reservation (22). Moreover, the heart rate was significantly accelerated in the 1.5 mg/kg succinylcholine group, whereas mild effect was observed in the 1.0 mg/kg succinylcholine and 1.2 mg/kg rocuronium groups. Previous study suggested that succinylcholine increased anaerobic metabolism and disturbed the tissue oxygen supply and demand balance, and that high-dose succinylcholine elevated the risk of hemoglobin desaturation (12). In animal experiments, continuous infusion of succinylcholine augmented oxygen consumption (23). These previous results together with our findings suggest that a high dose of succinylcholine during RSI may need to be avoided.

This study is not without limitations. Although there were no significant differences in the intubation conditions, due to the observational nature of the study, we could not conclude whether they showed comparable effects. Additionally, elder adults and obese patients, as well as such with lung-related diseases were not included, which limited the representativeness of the conclusion. We noted that gender and height significantly differed among the three groups, and whether these two parameters affect oxygenation desaturation needs further investigation. Moreover, patients failed to complete RSI, coughing during intubation, or spontaneous breathing before mechanical ventilation were excluded for analysis, which may introduce selection bias, so the interpretation of results should be cautious.

CONCLUSION

In conclusion, this study revealed that a relatively low dose of succinylcholine and rocuronium led to a longer non-hypoxic apnea duration. Therefore, 1.0 mg/kg succinylcholine or 1.2 mg/kg rocuronium may be recommended for RSI to satisfy the required intubation conditions. Further large-scale randomized control studies are needed to validate these findings.

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

The studies involving human participants were reviewed and approved by Shanghai General Hospital. The patients/participants provided their written informed consent

to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

LT and XZ conceived and coordinated the study, designed, performed and analyzed the experiments, and wrote the paper. SL, LH, JL, LC, and SH carried out the data collection, data analysis, and revised the paper. All authors reviewed the results and approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.717477/full#supplementary-material

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frontiers in Medicine

ORIGINAL RESEARCH
published: 16 February 2022
doi: 10.3389/fmed.2022.751636

Neuromuscular Electrical Stimulation in Patients With Severe COVID-19 Associated With Sepsis and Septic Shock

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OPEN ACCESS

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Specialty section:
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

Received: *17 August 2021*
Accepted: *11 January 2022*
Published: *16 February 2022*

Citation:
Righetti RF, Grams ST, Costa WNdS, Saraiva LT, Salles ICDd and Yamaguti WP (2022) Neuromuscular Electrical Stimulation in Patients With Severe COVID-19 Associated With Sepsis and Septic Shock. Front. Med. 9:751636. doi: 10.3389/fmed.2022.751636

Background: Neuromuscular electrical stimulation (NMES) can be applied to critically ill patients. However, its results on muscle strength and functionality in patients with COVID-19 are unknown.

Objective: Evaluate the effects of intervention with NMES on muscle mass and functionality of patients with severe COVID-19 associated with sepsis and septic shock.

Methods: Seven patients with COVID-19 associated with sepsis or septic shock were selected, but only 5 patients completed all days of the intervention with NMES. The intervention was performed by a single physiotherapist on 7 consecutive days in a daily session of 40 min. The outcome measures were the femoris cross-sectional area; thickness of the anterior compartment of the quadriceps muscle; rectus femoris echogenicity; International Classification of Functioning, Disability, and Health (ICF)-muscle strength; PFIT-s, DEMMI, and the SOMS; feasibility, and safety. The patients were evaluated on days 1, 5, and 8.

Results: The rectus femoris cross-sectional area decreased significantly from days 1 to 8, but showed maintenance of the thickness of the anterior compartment of the quadriceps muscle from days 1 to 8. The MRC score increased significantly from days 1 to 5 and kept this improvement until day 8. All patients showed an increase in the MRC score and reduction of the ICF-muscle strength, meaning improved muscle strength from days 1 to 8. The PFIT-s increased significantly from days 1 to 5 and improved until day 8 compared to day 5. DEMMI and SOMS score increased significantly on day 8 compared to days 1 and 5.

Conclusion: Rehabilitation with NMES showed improvement in muscle strength and functionality of patients in this study with a potential protective effect on muscle mass loss in patients with critical COVID-19 associated with sepsis and septic shock. This study is the first report of the potential effects of neuromuscular electrical stimulation in patients with severe COVID-19 associated with sepsis and septic shock.

Keywords: COVID-19, sepsis, physiotherapy, neuromuscular electrical stimulation, muscle mass

INTRODUCTION

The Coronavirus disease 2019 (COVID-19) is caused by novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (1). The virus spread rapidly through the world population and several hospitals have produced guidelines for the respiratory management of these patients (2, 3). Most patients have a mild form of the disease, but 5% of patients present severe lung injury and required intensive care (4). These patients may develop ICU-acquired weakness (5).

Early mobilization in the intensive care unit (ICU) is proven to be effective in preventing muscle atrophy and functional disability. However, it is not necessarily applicable to all patients (6). Therefore, neuromuscular electrical stimulation (NMES) has been used as an additional rehabilitation strategy for critically ill patients (7). Studies using electrical muscle stimulation in septic patients have conflicting results depending on the titred stimulation frequency used. These studies showed that low stimulation frequency electrical stimulation was ineffective to preserve muscle mass (8) and high stimulation frequency electrical stimulation was able to increase strength (9). Carraro et al. (10) suggest that frail persons post-COVID-19 infection with muscle weakness or persons in prolonged inactivity for pandemic-related restriction may benefit from the full-body exercise program associated with NMES. However, these effects are unknown in patients in the acute phase of the disease with severe COVID-19.

The present study aims to describe our clinical protocol in the treatment with neuromuscular electrical stimulation of patients with COVID-19 associated with sepsis and septic shock during their acute intensive care unit stay and to discuss intervention responses in skeletal muscle mass and functional performance.

METHODS

All participants signed the Informed Consent Term, previously approved by the Ethics Committee of the Hospital Sírio-Libanês (number 3,999,139). This case series was conducted at the adult intensive care units of Hospital Sírio-Libanês, São Paulo, Brazil, and all approved ethical protocols were followed.

Patients

Seven patients with COVID-19 associated with sepsis or septic shock with age $\geq$ 18 years were selected. Sepsis diagnosis was defined by the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (11). Furthermore, patients should have the capacity to walk independently before hospitalization classified by mean of the Expanded Disability Status Score (EDSS) $\leq$ 6 (12) and immobilization period without walking $\leq$7 days.

Candidate Patients for Neuromuscular Electrical Stimulation

The inclusion criteria for starting NMES to critically ill patients include body mass index (BMI) $\leq$ 35 kg/m^2; without skin lesions, cardiac pacemaker, infection or trauma in lower limbs, neuromuscular diseases, use of neuromuscular blockers, polyneuropathy, and imminent risk of death in less than 48 hours (Simplified Acute Physiology Score III - SAPS III $\leq$ 80). The exclusion criteria for intervention were infarction and/or need for mechanical cardiopulmonary bypass devices or the need for intra-aortic balloon during ICU hospitalization.

Clinical Assessment

In the ICU admission, patients were evaluated and classified to clinical severity according to the Simplified Acute Physiology Score III (SAPS III) (13) and the Sequential Organ Failure Assessment (SOFA) (14). In addition, we collected clinical and neurological parameters. SAPS III and SOFA assessments were performed by the medical team of the intensive care unit.

Outcome Measures

Muscle mass was assessed using ultrasonography. Patients were evaluated concerning rectus femoris cross-sectional area (cm^2), the thickness of the anterior compartment of the quadriceps muscle (rectus femoris and vastus intermedius) (cm), and rectus femoris echogenicity (pixels) (5). The transducer was positioned perpendicular to the longitudinal axis of the thigh in 80% of the distal distance between the anterosuperior iliac spine and the upper midpoint of the patella to obtain measurements of the rectus femoris cross-sectional area, and thickness of the anterior compartment of the quadriceps muscle (rectus femoris and vastus intermedius). The measurements were performed using B-mode ultrasound (Logiq e ultrasound, GE Healthcare, USA) (**Figure 1**).

Functionality was assessed by the International Classification of Functioning, Disability, and Health (ICF) using the muscle strength domains (b730) based on the Medical Research Council (MRC) score for global strength (5). The ICF scores used were: 0–58 to 60 (without significant changes); 1–48 to 57 (slight loss); 2–31 to 47 (moderate loss); 3–4 to 30 (severe loss); and 4–0 to 3 (maximum loss). The MRC score is a voluntary method and depends on the understanding and collaboration of the patients. For this reason, in the case of patients on mechanical ventilation, it was evaluated only after interrupting sedation (15). In addition, we assessed functionality by the Physical Function ICU Test-scored (PFIT-s), Morton Mobility Index (DEMMI), and the Surgical Intensive Care Unit Optimal Mobilization Score (SOMS).

PFIT-s examine the capacity of the patient in the sit-to-stand level of assistance; maximal marching on the spot duration and number of steps; and shoulder flexion strength, and knee extension strength. The PFIT-s score ranges from 0 (unable to perform activities) to 10 (high physical functioning) (16). DEMMI is composed of 15 hierarchical mobility activities (bed-based, chair-based, static balance, walking-related, and dynamic balance). The total score is converted with Rasch Analysis with a score range from 0 (poor mobility) to 100 (high levels of independent mobility) (16). PFIT-s and DEMMI depend on the understanding and collaboration of the patients, and it was performed after interrupting the sedation. The SOMS score ranges from 0 (indicating that no mobilization should be considered since deemed to be futile, as for patients in a terminal unstable clinical condition such as those with intracranial

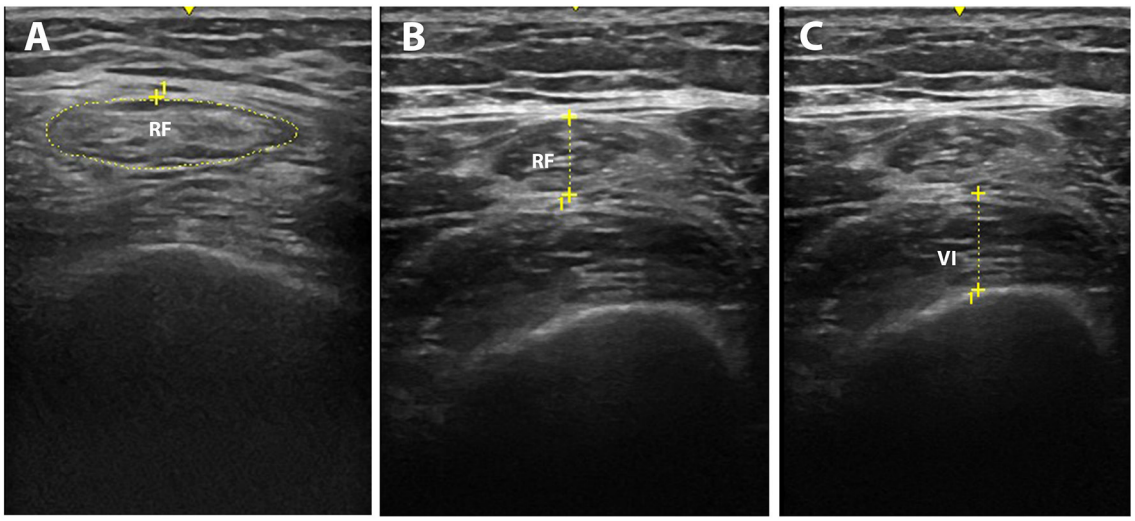

FIGURE 1 | Representative muscle ultrasound image methods: rectus femoris cross-section area **(A)**, the thickness of the anterior compartment of the quadriceps muscle [rectus femoris **(B)** and vastus intermedius **(C)**].

hypertension or severe systemic hemodynamic and respiratory insufficiency) to 4 (patients able to ambulate) (17).

The rectus femoris cross-sectional area (cm^2), the thickness of the anterior compartment of the quadriceps muscle, ICF-muscle strength, PFIT-s, DEMMI, and SOMS were evaluated on days 1, 5, and 8 of start intervention with neuromuscular electrical stimulation. All measurements were performed by the same physiotherapist on days 1, 5, and 8 and was blind to the interventions that were applied to the patients.

Neuromuscular Electrical Stimulation

The NMES was performed after interrupting the neuromuscular blocker with the patient in the supine position in the ICU bed with 30–60 degrees of the hips and knees joint flexion. The ICU bed itself was used to achieve the positioning of the patient necessary for intervention with NMES. Two pairs of self-adhesive electrodes (size 9 × 5 cm, SPES Medica Brazil Ltda, São Paulo, Brazil) were positioned distally over the motor area of vastus medialis and vastus lateralis muscles, and the other two were placed 5 cm below the inguinal region. The location of the electrodes was marked on the skin with a surgical marking pen to ensure application in the same location on subsequent days. This position of the NMES electrodes is capable of stimulating the motor points of the quadriceps muscles (18).

The parameters used were stimulation frequency of 100 Hz, a stimulation pulse width of 350 μs, a ramp-up time of 1 s, time on of 4 s, ramp-dow of the stimulation of the 1 s, and time off of 12 s. The stimulation pulse width was performed with charge-balanced biphasic pulses and trapezoidal waves. In awake patients, the intensity was established with the maximum muscle contraction tolerated by the patient. In sedated patients, it NMES was adjusted with 50% above the minimum necessary to generate a visible contraction (8). The stimulation frequency was based on Rodriguez et al. (9) that showed that the high stimulation frequency electrical stimulation presented a preventive effect in the progression of muscle weakness in patients having severe sepsis requiring mechanical ventilation. During the intervention with NMES, no voluntary muscle movement was requested.

The treatment with NMES was interrupted if the patient presented cardiorespiratory instability, high fever (above 39°C), development of muscle fatigue, pain above 7 on the Visual Analog Scale (VAS), or pain above 2 on the Pain Assessment in Advanced Dementia (PAINAD) scale (19).

The application of NMES was carried out by the same physiotherapist on 7 consecutive days in a daily session of 40 minutes. For the treatment, we used the NMES device (Neurodyn II; IBRAMED; Amparo; São Paulo; Brazil). The physiotherapist involved in the NMES intervention did not participate in the outcome assessment and was blind to the results.

Feasibility and Safety

Feasibility was determined based on adherence and safety was evaluated based on the incidence of adverse events. Adverse events were considered: hemodynamic instability, respiratory instability, skin injury, and bruises.

Statistical Analysis

Data were assessed for normality using the Shapiro-Wilk test. Parametric variables are presented as mean and standard error. Categorical data are presented as the absolute (n) and relative frequency (%). Change in the muscle mass and functional capacity was assessed by repeated measure analysis of variance. Statistical significance was indicated by a $P < 0.05$.

RESULTS

Seven patients attended the NMES sessions. One patient stopped the treatment of NMES and one patient died on day 8 (patients 4 and 6); therefore, data for these patients were not included in the outcomes of all patients; only their data are displayed in the

TABLE 1 | Characteristics of patients with COVID-19 associated with sepsis and septic shock during ICU and hospital stay.

Demographic characteristics and clinical characteristics													
Patient	**Age (y)**	**Gender**	**BMI**	**SOFA**	**SAPS III**	**COVID-19 severity**	**Sedation**	**Vasoactive drug**	**Neuromuscular blocker**	**Hydrocortisone**	**IMV days**	**ICU stay**	**Hospital stay**
1	67	Female	28.9	8	67	Critical illness	Yes	Yes	Yes	Yes	6	11	24
2	65	Female	30.2	0	38	Critical illness	Yes	Yes	Yes	Yes	4	15	22
3	72	Male	30.9	7	57	Critical illness	Yes	Yes	Yes	Yes	8	12	27
4	61	Male	31.7	0	46	Critical illness	Yes	Yes	Yes	Yes	6	28	28
5	67	Male	32.6	5	50	Critical illness	No	No	No	Yes	0	9	14
6	75	Male	31.2	7	90	Critical illness	Yes	Yes	Yes	Yes	9	9	21
7	70	Male	25.8	3	55	Critical illness	No	No	No	Yes	0	3	11
Mean ± SD	68.1 ± 4.6	–	30.2 ± 2.3	4.2 ± 3.3	57.5 ± 16.9	–	–	–	–	–	4.7 ± 3.5	12.4 ± 7.7	21.0 ± 6.3

Neurologic characteristics and comorbidities													
Patient	**EDSS ≤6**	**RASS (D1/D5/D8)**	**Glasgow (D1/D5/D8)**	**CAM (D1/D5/D8)**	**Oxygen therapy**	**NIV**	**Hypertension**	**Diabetes mellitus**	**Obesity**	**Dyslipidemia**	**Anxiety**	**Hypothyroidism**	**COPD**
1	Yes	−2/0/0	•/15/15	–/–/–	Yes	Yes	No	No	Yes	No	No	Yes	No
2	Yes	1/0/0	•/15/15	–/–/–	Yes	Yes	Yes	No	Yes	No	No	No	No
3	Yes	1/0/0	•/15/15	+/–/–	Yes	No	No	No	No	Yes	No	Yes	No
4	Yes	−4/0/•	•/15/•	–/–/•	Yes	No	No	No	No	No	No	No	No
5	Yes	0/0/0	15/15/15	–/–/–	Yes	No	Yes	Yes	Yes	Yes	No	No	No
6	Yes	−5/−5/•	•/•/•	–/–/•	Yes	Yes	Yes	No	Yes	Yes	No	No	No
7	Yes	0/0/0	15/15/15	–/–/–	Yes	Yes	Yes	No	No	No	No	No	Yes

BMI, body mass index; CAM, Confusion Assessment Method; COPD, chronic obstructive pulmonary disease; EDSS, Expanded Disability Status Score; ICU, intensive care unit; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation; RASS, Richmond Agitation Sedation Scale; SAPS III, Simplified Acute Physiology Score III; SOFA, Sequential Organ Failure Assessment; •, not applicable.

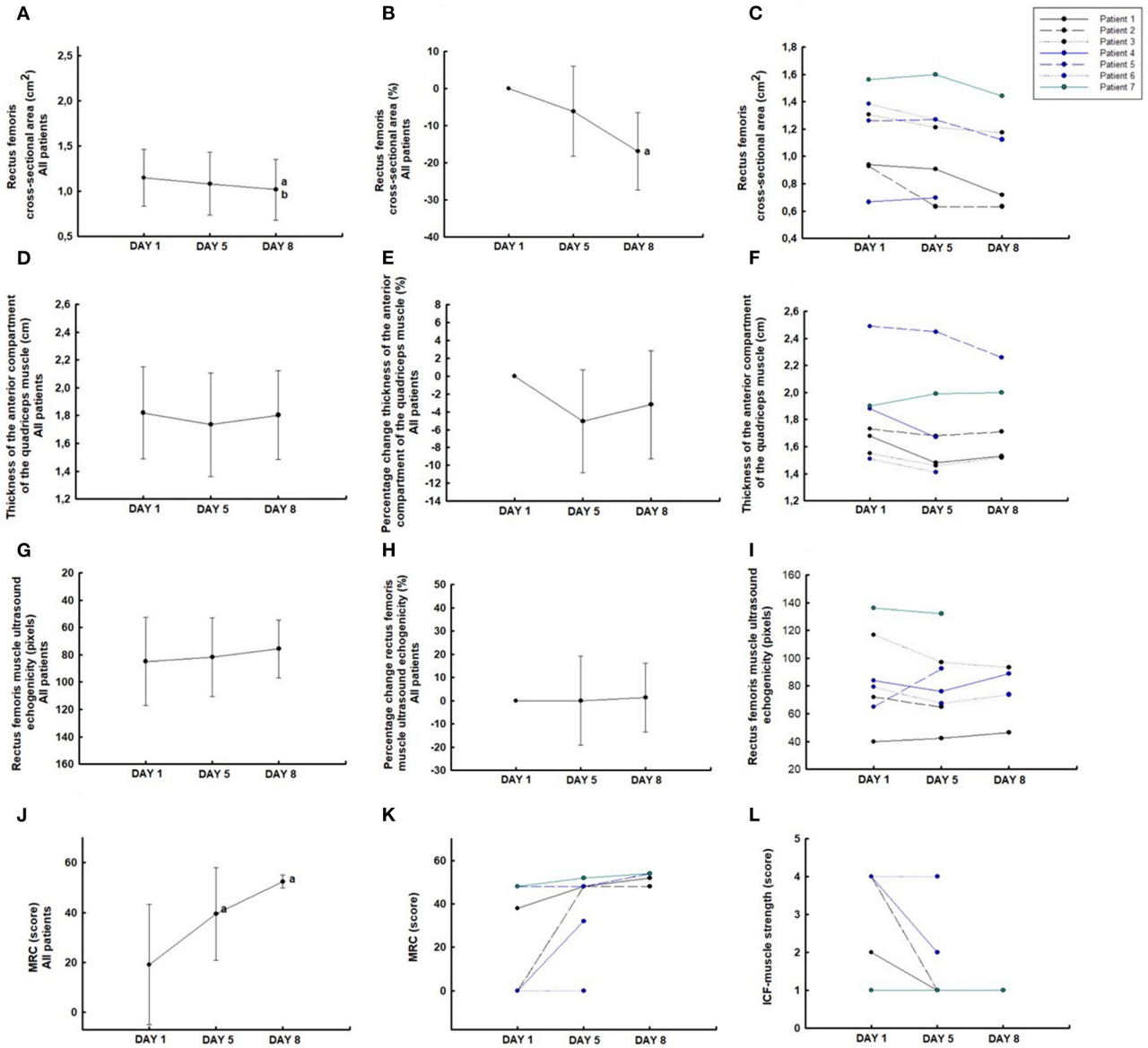

FIGURE 2 | Ultrasound muscle assessement of the rectus femoris cross-section área **(A–C)**; the thickness of the anterior compartment of the quadriceps muscle (rectus femoris and vastus intermedius) **(D–F)**; rectus femoris echogenicity **(G–I)**; MRC score **(J,K)**; and International Classification of Functioning, Disability, and Health (ICF)-muscle strength **(L)**. $^{a}P < 0.05$ compared to day 1; $^{b}P < 0.05$ compared to day 5.

individual patient values graph. The demographic characteristics of the patients are shown in **Table 1**.

Muscle Mass Outcomes

The rectus femoris cross-sectional area decreased significantly (−16.9% [95% CI, −29.8 to −3.9]; $P < 0.05$) from days 1 to 8 (**Figures 2A–C**), but showed maintenance of the thickness of the anterior compartment of the quadriceps muscle (−3.20% [95% CI, −10.6 to 4.2]; $P = 0.3$) from days 1 to 8 (**Figures 2D–F**). These patients showed a reduction of 2.1% [95% CI, −3.7 to −0.5] per day in the rectus femoris cross-sectional area and 0.3% [95% CI, −1.3 to 0.5] per day in the thickness of the anterior compartment of the quadriceps muscle during 8 days. Furthermore, patients showed maintenance of the echogenicity (1.3% [95% CI, −17.1 to 19.7%]; $P = 0.8$) from days 1 to 8 with an increase of 0.16% per day (**Figures 2G–I**).

Peripheral Muscle Strength and Functional Outcomes

The MRC score increased significantly from days 1 to 5 ($P < 0.05$) and kept this improvement until day 8 ($P = 0.5$) (**Figure 2J**). In the five patients evaluated, all (100%) showed an increase in the MRC score (**Figure 2K**) and reduction of the ICF-muscle strength, meaning improved muscle strength from days 1 to 8

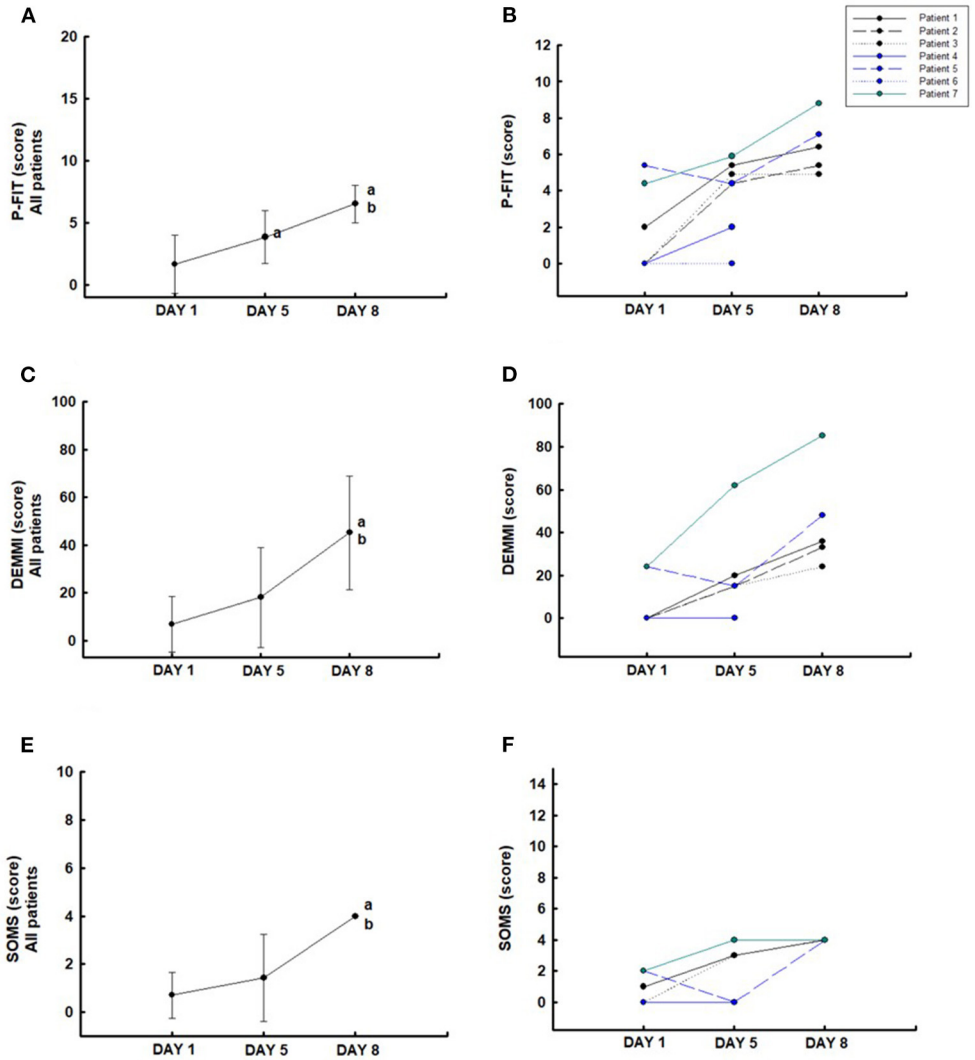

FIGURE 3 | Functionality: Physical Function ICU Test-scored (PFIT-s) **(A,B)**, Morton Mobility Index (DEMMI) **(C,D)**, and the Surgical Intensive Care Unit Optimal Mobilization Score (SOMS) **(E,F)**. [a]$P < 0.05$ compared to day 1; [b]$P < 0.05$ compared to day 5.

(**Figure 2L**). Four (80%) patients evaluated showed an increase in the MRC score and one (20%) maintained the MRC score values from days 5 to 8. Three patients (60%) showed a decrease in the ICF-muscle strength from days 1 to 5 and these values were maintained on day 8. Two patients (40%) maintained the ICF-muscle strength on days 5 and 8 compared with the baseline values (day 1).

The PFIT-s increased significantly from days 1 to 5 and improved until day 8 compared to day 5 ($P < 0.05$) (**Figure 3A**). All patients (100%) showed an increase in the PFIT-s on day 5 compared to day 1 and improvement on day 8 compared to day 5 (**Figure 3B**). DEMMI (**Figure 3C**) and SOMS (**Figure 3E**) scores increased significantly on day 8 compared to days 1 and 5 ($P < 0.05$). In the five patients evaluated, the individual data present that all (100%) patients showed an increase in the DEMMI (**Figure 3D**) and SOMS (**Figure 3F**) scores on days 5 and 8 compared with the baseline values (day 1).

Feasibility and Safety

No adverse events were reported during the case series. Five patients completed the assessments and intervention. One patient interrupted the NMES intervention but did not claim intolerance during the application, and one patient died due to worsening pulmonary and respiratory conditions. None of the NMES intervention sessions were interrupted by pain.

DISCUSSION

Patients with COVID-19 associated with sepsis and septic shock treated with NMES presented a reduction of 16.9% in the rectus

femoris cross-sectional area, but with no significant reduction in the thickness of the anterior compartment of the quadriceps muscle (3.2%) and no significant increase of rectus femoris echogenicity on day 8 (1.3%). The magnitude of these alterations was 2.1, 0.3, and 0.16% per day, respectively. We emphasize that these reported values in the present case series are smaller than those found compared to another study conducted at the same hospital and research group that evaluated severe COVID-19 patients without NMES intervention. This study showed a reduction of 30.1% in the rectus femoris cross-sectional area, 18.6% in the thickness of the anterior compartment of the quadriceps muscle, and increase of 16.8% in the echogenicity on day 10 with themagnitude of these alterations being about 3.7, 2.1, and 1.68% per day, respectively (5).

The ability of electrical muscle stimulation to improve or maintain strength, muscle mass, and functionality in ICU patients with sepsis is controversial. However, the results seem to be related to the type of stimulation frequency involved in muscle stimulation. Rodriguez et al. (9) used high stimulation frequency in the neuromuscular electrical stimulation and showed a preventive effect in the progression of muscle weakness in patients having severe sepsis requiring mechanical ventilation. On the other hand, when Poulsen et al. (8) used low stimulation frequency in the patients with septic shock admitted to the ICU, and showed that loss of muscle mass was unaffected by electrical muscle stimulation. Our results corroborate with the Rodriguez et al. (9) study and enhance the possible benefit of using high stimulation frequency for muscle electrical stimulation.

The effect of electrical muscle stimulation on muscle mass and strength can be explained by several factors. Nuhr et al. (20) and Hambrecht et al. (21) showed that NMES induces an increase in oxidative capacity with the transition from fast to slow fiber types associated with a decrease in anaerobic enzymes levels. All physiological muscle changes found with the use of electrical muscle stimulation in critically ill patients suggest that the origin is a systemic effect on microcirculation (22). Vanderthommen et al. (23) showed that in the identical levels of workload (10% of the quadriceps maximum isometric voluntary torque), the muscle reaches higher values in blood flow and oxygen consumption during NMES compared with voluntary muscle contractions. Moreover, a single session of NMES is sufficient to stimulate the increased levels of mRNA for IGF binding protein-4 (84%), MyoD (83%), myogenin (∼3-fold), cyclin D1 (50%), and p21-Waf1 (16-fold), which are indicative of the initiation of myogenic processes in skeletal muscle. In the same study, an additional NMES session (a total of 14 min spread over 2 days), was sufficient to induce an increase in the concentration of total skeletal muscle ribonucleic acid (RNA) (24), most likely representing an increase in muscle protein synthesis. These results indicate that molecular adaptations of skeletal muscle to loading respond in a very short time.

Neuromuscular blocking agents cause skeletal muscle relaxation by blocking the transmission of impulses at the neuromuscular junction (25). NMES evokes a muscle contraction by activating intramuscular branches of the nerve to the muscle and not the muscle fibers directly (26) and selected brain regions in a dose-response manner (27). The use of neuromuscular blocking agents during NMES intervention may interfere with the performance of muscle contraction. However, neuromuscular blockers present a recovery time of 8–40 min after their interruption (28). Therefore, we performed NMES intervention after interrupting the neuromuscular blocking agents.

Sedation is commonly used in patients admitted to the intensive care unit (29). Dirkes et al. (30) showed that NMES represents an effective and feasible interventional strategy to prevent skeletal muscle atrophy in a fully sedated patient with critically ill. In the same study, the non-stimulated leg showed substantial type 1 and type 2 muscle fiber atrophy (a 16 ± 9 and $24 \pm 7\%$ decline in muscle fiber; respectively). In contrast, no atrophy was observed in the muscle fibers collected from the stimulated leg. Although sedation does not interfere with NMES intervention, it can compromise functional assessments. Therefore, in the present study, the MRC score, P-FITs, and DEMMI evaluations were performed only after sedation withdrawal.

The limitation of this study is that it is a single-center study design and there is no control group to compare the efficacy. In addition, the number of cases is small and it is unclear whether the results can be generalized. Mateo et al. (31) used functional electrical stimulation associated with cycling in patients post-hospitalization in the ICU for a critical form of COVID-19. However, the present case series is the first report of the effects of neuromuscular electrical stimulation intervention in patients with severe COVID-19 in the acute phase of the disease associated with sepsis and septic shock. Randomized clinical trials with more patients reporting the efficacy of electrical stimulation using NMES in patients with COVID-19 associated with sepsis and septic shock are needed to confirm our findings.

CONCLUSION

Rehabilitation with NMES showed improvement in muscle strength and functionality of patients in this case series with a potential protective effect on muscle mass loss in patients with critical COVID-19 associated with sepsis and septic shock.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Hospital Sírio-Libanês (number 3,999,139). The patients/participants

provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SG, WC, LS, IS, and WY: study design. SG, WC, and LS: data collection. RR and WY: data analysis and draft manuscript. RR, SG, WC, LS, IS, and WY: manuscript review. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

The authors thank the Fundação de Amparo à Pesquisa do Estado de São Paulo FAPESP, number 18/16832-9) and Hospital Sírio-Libanês.

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frontiers | Frontiers in Medicine

TYPE Opinion
PUBLISHED 16 August 2022
DOI 10.3389/fmed.2022.917369

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

RECEIVED 27 April 2022
ACCEPTED 05 July 2022
PUBLISHED 16 August 2022

CITATION
Liu L (2022) Methods of liberation from mechanical ventilation: Which one is best? *Front. Med.* 9:917369. doi: 10.3389/fmed.2022.917369

Methods of liberation from mechanical ventilation: Which one is best?

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KEYWORDS

weaning from mechanical ventilation, automatic tube compensation, pressure support ventilation, proportional assist ventilation, neurally adjusted ventilatory assist

Methods of liberation from mechanical ventilation: Which one is best?

As an essential life-saving intervention, mechanical ventilation is also associated with complications which result to higher medical costs and mortality (1, 2). Therefore, it was essential to liberate patients from mechanical ventilation efficacy and safety for the shortest possible duration. Despite many studies comparing the safety and effectiveness of different methods for weaning have been published, many controversial questions remain concerning the best method for this process. Given that studies to date have not investigated the comparative of all available modes of weaning simultaneously, a network meta-analysis may help evaluate the relative effectiveness between all modes from both direct and mixed-treatment comparisons (3).

There were two network meta-analysis focuses on the best weaning methods published in this research topic of acute respiratory distress syndrome and mechanical ventilation. Although the study selection criteria were not identical, 12 randomized controlled trials (RCTs) were overlapped in the two studies. The study by Yi et al. including 24 RCTs showed that automatic tube compensation (ATC) obtained superior weaning success compared to T-piece and pressure support ventilation (PSV). Another study by Jhou et al. including 39 RCTs compared the efficacy among 7 modes of weaning and provided evidence that proportional assist ventilation (PAV) has a high probability of being the most effective ventilation mode regarding a higher rate of weaning success, a lower reintubation, and mortality rate. The features of pivotal clinical trials included in the meta-analysis are presented in the Table 1 (4–10). The reliability of these findings should be interpreted cautiously for several reasons. First, these findings were generated from single-center trials with limited sample size. Second, the difficulty of weaning (simple weaning, difficult weaning, and prolonged weaning) and duration of mechanical ventilation vary across studies, which has potential influence on the results of weaning outcome and may introduce a potential bias. Third, the variety of sedation and ventilation setting prior to or during liberation process also impact the clinical efficacy and introduce a potential bias. Further multicenter studies considering different clinical vignettes and respiratory physiology patterns are warranted to gain full insight into the real role of various weaning methods.

TABLE 1 Features of pivotal clinical studies.

References	Population	Interventions		Strength	Weakness
		Control group	Experimental group		
Esteban et al. (4)	484 ICU patients	T-piece; T-piece for a maximum of 2 h	PSV Pressure support of 7 cm H_2O and PEEP $\leq$ 5 cm H_2O	• Multicenter randomized design • The result supported SBT with pressure support or T-tube are suitable methods for extubation	• patients received longer mechanical ventilation before the SBT • the imbalances of patients after randomization
Chittawatanarat et al. (5)	520 SICU postoperative patients	T-piece, with an oxygenation setting of 10–15 L/min	PSV: inspiratory pressure 5–7 cm H_2O, PEEP 5 cm H_2O	• The randomized control trial • Surgical patient	• unblinded study design • prolong ventilator use
Subirà et al. (6)	1,153 ICU patients	T–piece for 2 h	PSV: 30-min with pressure support 8 cm H_2O and zero PEEP	• Multicenter randomized design • Large sample size • The results supported the use of a shorter, less demanding strategy of 30 min of pressure support ventilation for SBT	• unblinded study design • non-protocolized extubation strategies
Xirouchaki et al. (7)	208 ICU patients	PAV+: the initial percentage of assist was set to 60–80%a/	VCV/PCV to PSV: PSV: the inspiratory pressure was set to 20–25 cm H_2O (including $PEEP_E$)	• The result supports PAV+ may be used as a mode of support in critically ill patients	• single center • lack information on weaning time • unblinded study design
Botha et al. (8)	50 ICU patients	PAV+: 70% support and weaned to 30% support by decrements of 10% as tolerated	PSV: Start with pressure support level required and weaned to 10 cm H_2O as tolerated	• Appropriate number of patients enrolled • First RCT with PAV+ with a study period longer than 48 h • Well study protocol	• poor generalizability
Cohen et al. (9)	99 ICU patients	PSV to ATC; ATC: ventilator circuit with flow-triggering (2 L/min) and CPAP of 5 cm H_2O, with inspiratory ATC set at 100%	PSV to CPAP; CPAP: ventilator circuit with flow triggering (2 L/min) and CPAP of 5 cm H_2O	• The largest single-center study to assess the use of commercially available ATC	• No formally assess the technical performance of ATC
Taniguchi et al. (10)	70 ICU patients	SmartCare	PSV; Pressure 5–7 cm H_2O and PEEP 5 cm H_2O	• The result confirmed the efficiency of respiratory physiotherapy–driven weaning protocol	• small sample size • poor generalizability • the effectiveness of SmartCare^{TM} performance during weaning phase of invasive MV

ICU, intensive care unit; PSV, pressure support ventilation; SICU, surgical intensive care unit, PAV, proportional assist ventilation; VCV, voulme control ventilation; PCV, pressure control ventilation; ATC, automatic tube compensation; CPAP, continuous positive airway pressure; MV, mechanical ventialtion.

Nonetheless, these findings promote pondering deeply over the criteria for the ideal method of ventilator liberation. PSV is the most commonly used mode of weaning in recent decades. In PSV mode, the PS can decrease the work of breathing imposed by the endotracheal tube (11). Short duration of PSV with a low level of assistance was also recommended by the most recent guidelines performed as initial spontaneous breathing trial rather than T-piece or CPAP (12). The network meta-analysis also showed that PSV increased the rate of weaning success when compared with T-piece. However, PSV can only provide a constant positive pressure which may not match the patient's respiratory demand. Of note, Yi et al. found that PAV was superior to PSV regarding weaning success, and Jhou et al. found that ATC was also superior to PSV. A sizeable effect with patient-ventilator asynchrony and over-assistance during PSV weaning might be a possible explanation (13). PAV, which delivered

positive pressure ventilation in proportion to instantaneous inspiratory effort, was associated with less patient ventilator asynchrony and lower risk of over-assistance (14). Nevertheless, PAV is relatively complex; indeed, the settings need knowing or estimating the patient's compliance and resistance (15). ATC, which delivered dynamic positive pressure automatically to compensate for the resistance of artificial airway, can improve synchronization between patient and ventilator, and avoided over-assistance (16, 17). However, ATC cannot increase lung ventilation heterogeneity as compared to low PS and PEEP (18). Nonetheless, unloading the respiratory muscle without over-assistance and better patient-ventilator interaction might be essential to the ideal method of weaning.

Neurally adjusted ventilatory assist (NAVA) mode uses the electrical activity of the diaphragm to control the ventilator and delivers pressure support in proportion to patients' neural effort. It has been demonstrated that NAVA improved patient-ventilator interaction and reduced inappropriate ventilator assist when compared with PSV (19, 20). Despite limited real-world experience, NAVA might be ideally suitable for the weaning process. Several studies have shown that NAVA improves the weaning outcome when compared with PSV, especially for patients difficult to wean (13, 21, 22). However, RCTs, comparing the safety and effectiveness between NAVA and other weaning modes, such as PAV and ATC, are absent.

Although, there is still controversy about the best method of liberation from mechanical ventilation, new mode in line with respiratory physiology might be a light at the end of the tunnel.

Author contributions

LL wrote the original version and revised the Editorial.

Funding

This study was supported by Key Research and Development Plan of Jiangsu Province (BE2020786) and 333 High Level Talents Training Project in the sixth phase in Jiangsu.

Conflict of interest

The author declares 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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