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Short-term mortality in COVID-19 patients ventilated with low and high PEEP: a retrospective observational study

Mortalidade a curto prazo em pacientes COVID-19 ventilados com PEEP baixa e alta: um estudo observacional retrospectivo

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Abstract

Background: During invasive mechanical ventilation (IMV), positive end-expiratory pressure (PEEP) is generally used to improve oxygenation, but it can also provide variable effects that contribute to lung injury. Although some studies have addressed the influence of PEEP on mortality, this has been poorly investigated in COVID-19 patients. **Aim:** To investigate whether initial ventilation with low or high levels of PEEP influences short-term mortality in invasively ventilated COVID-19 patients. **Methods:** Retrospective study including invasively ventilated COVID-19 patients hospitalized between April 2020 and July 2021. Demographic, clinical, and ventilatory variables were obtained from electronic medical records. Ventilator settings and parameters were assessed at fixed time points during the first 48 hours of IMV. Low and high PEEP were considered when < 10 cmH_2O and ≥ 10 cmH_2O, respectively. The primary outcome was 28-day mortality after endotracheal intubation. **Results:** Of 183 patients, 55 (30%) and 128 (70%) were ventilated with low and high PEEP, respectively. Kaplan-Meier analysis showed that the high PEEP group had lower 28-day mortality when compared with the low PEEP group ($P < 0.001$). After multivariate Cox regression analysis adjusting for potential confounders, the high PEEP group had a hazard ratio of 0.44 (95% CI of 0.28 to 0.70) for 28-day mortality, indicating a 56% lower risk of death compared with the low PEEP group. **Conclusion:** The use of PEEP ≥ 10 cmH_2O was associated with higher short-term survival in this cohort of mechanically ventilated COVID-19 patients.

Keywords: Acute Respiratory Distress Syndrome; COVID-19; Mechanical Ventilation; Mortality; Positive End-Expiratory Pressure.

Resumo

Introdução: Durante a ventilação mecânica invasiva (VMI), a pressão positiva expiratória final (PEEP) é geralmente utilizada para melhorar a oxigenação, mas também pode apresentar efeitos variáveis que contribuem para lesão pulmonar. Embora alguns estudos tenham abordado a influência da PEEP na mortalidade, isso foi pouco investigado em pacientes COVID-19. **Objetivo:** Investigar se a ventilação inicial com níveis baixos ou altos de PEEP influencia a mortalidade a curto prazo em pacientes COVID-19 em ventilação invasiva. **Métodos:** Estudo retrospectivo incluindo pacientes COVID-19 em VMI hospitalizados entre abril de 2020 e julho de 2021. Variáveis demográficas, clínicas e ventilatórias foram obtidas de prontuários eletrônicos. Configurações e parâmetros do ventilador foram avaliados em momentos fixos nas primeiras 48 horas de VMI. PEEP baixa e alta foram consideradas quando < 10 cmH_2O e ≥ 10 cmH_2O, respectivamente. O desfecho primário foi a mortalidade em 28 dias após a intubação endotraqueal. **Resultados:** Dos 183 pacientes, 55 (30%) e 128 (70%) foram ventilados com PEEP baixa e alta, respectivamente. A análise de Kaplan-Meier mostrou que o grupo PEEP alta teve menor mortalidade em 28 dias quando comparado ao grupo PEEP baixa ($P < 0,001$). Após análise de regressão multivariada de Cox ajustando para potenciais confundidores, o grupo PEEP alta apresentou *hazard ratio* de 0,44 (IC 95% de 0,28 a 0,70) para mortalidade em 28 dias, indicando um risco de morte 56% menor comparado ao grupo PEEP baixa. **Conclusão:** O uso de PEEP ≥ 10 cmH_2O foi associado a maior sobrevida em curto prazo nesta coorte de pacientes COVID-19 ventilados mecanicamente.

Palavras-chave: Síndrome do Desconforto Respiratório Agudo; COVID-19; Ventilação Mecânica; Mortalidade; Pressão Positiva Expiratória Final.

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INTRODUCTION

Patients with severe COVID-19 frequently develop acute respiratory failure (ARF), resulting from the interplay of multiple complex pathophysiological mechanisms, including diffuse alveolar damage, microvascular thrombosis with perfusion abnormalities, loss of normal pulmonary vascular regulation, and hyperinflammatory and immune-mediated tissue injury[1]. In such cases, patients often require ICU admission and invasive mechanical ventilation (IMV) as part of the management of COVID-19-related ARF.

During IMV, positive end-expiratory pressure (PEEP) is a key adjustable parameter used to improve oxygenation, prevent alveolar collapse, and reduce the risk of atelectrauma[2]. However, PEEP can also become a double-edged sword, as an inadequately selected level tends to promote harmful effects. While excessive PEEP leads to lung overdistension, insufficient PEEP results in cyclic alveolar recruitment-derecruitment[2,3]. Both conditions contribute to ventilation-induced lung injury (VILI), which can be inflicted early and result in a poor prognosis for the patient[2,4].

Considering these variable effects, some studies have investigated whether different PEEP levels would impact relevant clinical outcomes, such as mortality. Results of most recent high-quality meta-analyses showed that low-PEEP versus high-PEEP ventilation strategies did not influence mortality in patients with and without acute respiratory distress syndrome (ARDS)[5,6]. However, such findings were only observed in non-COVID-19 populations, and PEEP effects in COVID-19 patients have been poorly investigated. Although a previous study showed that PEEP does not influence mortality in COVID-19 patients[7], other evidence suggests that a high PEEP strategy is associated with favorable outcomes, including lower mortality[8].

Given the limited evidence and conflicting findings, continuing the investigation into the influence of PEEP in the critically ill COVID-19 population is a necessity for clinical practice. This knowledge is also important because choosing an adequate PEEP is a cornerstone of the lung protective strategy, which is a standard of care in mechanically ventilated patients. Thus, this study aimed to investigate whether initial ventilation with high or low levels of PEEP influences short-term mortality in invasively ventilated COVID-19 patients. We hypothesized that PEEP does not impact mortality or that high PEEP may be associated with better outcomes.

METHODS

Study design and participants. This was a single-center, retrospective observational study including patients with acute respiratory failure due to COVID-19 who received IMV at the *Hospital Estadual de Bauru* (São Paulo, Brazil) from April 2020 to July 2021. *Hospital Estadual de Bauru* is a public tertiary hospital that was one of the main regional centers designated for severe cases of COVID-19. All patients admitted to the ICU received 24-hour care provided by physicians, nurses and physiotherapists. Inclusion criteria were: (i) patients of both sexes aged 18 years or older; (ii) laboratory-confirmed SARS-CoV-2 infection; (iii) intubation at the study hospital; (iv) receipt of IMV for at least 24 hours, and (v) diagnosis of ARDS according to the Berlin definition. Patients with negative or inconclusive molecular testing for SARS-CoV-2 and those who died before completing 24 hours of IMV were considered not eligible. After inclusion, patients were excluded from the final analysis if they had incomplete IMV data or were lost to follow-up. All study procedures were approved by the Research Ethics Committee at the Federal University of São Carlos (CAAE 51653521.5.0000.5504, approval number 5.046.372).

Clinical and ventilatory data. All data were extracted from electronic medical records. Demographic and clinical characteristics included age, sex, body mass index (BMI), comorbidities, time since first symptoms, and COVID-19 vaccine. Charlson comorbidity index and Simplified Acute Physiology Score 3 (SAPS 3) were calculated as previously described[9,10]. On the first calendar day of IMV, laboratory tests were checked to assess C-reactive protein, hemoglobin, leukocytes, lymphocytes, platelets, and creatinine. The first arterial blood gas analysis after starting IMV was checked to obtain pH, partial pressure of carbon dioxide ($PaCO_2$) and partial pressure of arterial oxygen (PaO_2). Oxygenation was determined by the ratio between partial pressure of arterial oxygen and fraction of inspired oxygen (PaO_2/FiO_2), and severity of ARDS was classified as mild (PaO_2/FiO_2 201-300), moderate (PaO_2/FiO_2 101-200) or severe ($PaO_2/FiO_2 \leq 100$)[11]. In the first 48 hours of IMV, we registered the use of adjuvant therapies, such as prone position, neuromuscular blockers, vasopressors, and corticosteroids. Ventilator settings and parameters were aggregate as the mean of measurements obtained in the first hour after intubation and thereafter every 8 hours during the first 48 hours of IMV. Plateau pressure was obtained after an inspiratory pause of 2-3 seconds[12] and in the absence of spontaneous breathing, which was confirmed by two criteria: (1) controlled ventilation mode, and (2) total respiratory rate not exceeding the set respiratory rate. Driving pressure was calculated as the difference between plateau pressure and PEEP. Static respiratory system compliance was calculated as tidal volume/driving pressure. Given the previous suggestions for initial standardized ventilator setting for ARDS[13-16], high and low PEEP was considered when ≥ 10 cmH_2O and < 10 cmH_2O, respectively. Due to the observational design, PEEP adjustment was not controlled and likely was not standardized to a single titration strategy. Nonetheless, the institutional protocol adhered to established ARDS ventilation guidelines[12], permitting both systematic approaches (e.g., PEEP/FiO_2 tables or decremental titration based on respiratory system compliance) and clinical judgment, taking into account oxygenation, respiratory mechanics, and hemodynamics. In addition, other predefined lung-protective ventilation goals included aiming to maintain a tidal volume of 4-8 ml/kg of predicted body weight, a plateau pressure < 30 cmH_2O, and FiO_2 adjusted to maintain SpO_2 between 92% and 96%[17].

Outcomes. The primary outcome was short-term mortality, defined as death within 28 days after endotracheal intubation. Secondary outcomes include extubation, tracheostomy, hemodialysis, ICU and hospital length of stay, and overall hospital mortality. Length of ICU and hospital stay were calculated using the admission and discharge dates among discharged patients.

Statistical analysis and sample size. Continuous variables were described as median and interquartile range (IQR 25 – 75%), while categorical variables were presented using absolute frequency and proportions. Intergroup comparisons were performed using the chi-square test, unpaired t-test, or Mann-Whitney U test. Kaplan-Meier analysis and univariate Cox regression were initially used to investigate the 28-day survival rate in the high and low PEEP groups. Multivariate Cox regression modelling was performed in steps. First, we controlled for age, sex, BMI, comorbidities, SAPS 3 score, use of vasopressors and neuromuscular blockers (models 1 and 2). In models 3 and 4, we added adjustments for arterial blood gas analysis variables (pH, $PaCO_2$ and PaO_2/FiO_2) and static compliance of the respiratory system, respectively. Proportionality of hazards was tested by visually examining survival curves and by checking residual plots for each independent variable. A P value < 0.05 was considered statistically significant, and all data analysis was performed using SPSS 20 (Chicago, Illinois, USA) and GraphPad Prism 5.0 (San Diego, California, USA). The sample size was determined using a pragmatic approach, according to the number of eligible patients identified within the study period, instead of being established through an a priori power analysis.

RESULTS

Of the 307 patients assessed for eligibility, 90 were excluded before inclusion due to negative or inconclusive molecular testing for SARS-CoV-2 (n = 88) or death within the first 24 hours of IMV (n = 2). Thus, 217 patients met the eligibility criteria and were included in the study. After inclusion, 34 patients were excluded from the final analysis due to incomplete IMV data (n = 33), defined as the absence of at least one key ventilatory parameter of interest (PEEP, plateau pressure, or tidal volume) on either of the two assessment days, or loss to follow-up (n = 1). Therefore, the final analyzed sample comprised 183 patients, who were ventilated with high PEEP (n = 128) or low PEEP (n = 55) (Figure 1).

Comparing both groups (Table 1), we found that the high PEEP group had a higher BMI and received neuromuscular blocking agents more frequently compared to the low PEEP group (P < 0.05). In addition, patients of the high PEEP group were ventilated with higher peak and plateau pressures, and also had higher respiratory system compliance (P < 0.05).

Analysis of the outcomes showed that the high PEEP group had more extubation, tracheostomy, and lower both 28-day and overall hospital mortality (P < 0.05). Kaplan-Meier survival analysis showed that patients ventilated with high PEEP had significantly lower 28-day mortality than those ventilated with low PEEP (Figure 2A). After multivariate Cox regression analysis adjusting for all covariates, the high PEEP group had a hazard ratio of 0.44 (95% confidence interval of 0.28 to 0.70) for 28-day mortality, indicating a 56% lower risk of death compared with patients ventilated with low PEEP (Figure 2B).

DISCUSSION

This study investigated whether initial ventilation with high or low levels of PEEP influences short-term mortality in invasively ventilated COVID-19 patients. After multivariate analysis adjusting for potential confounders, our main results showed that patients ventilated with high PEEP during the first 48 hours of IMV had lower 28-day mortality than those ventilated with low PEEP. Although the sample size was determined pragmatically, a post-hoc power analysis was deemed unnecessary given that the regression results were statistically significant and well supported by confidence intervals.

Intriguingly, our results differ from the most current Cochrane systematic review, which found moderate-certainty evidence showing that high levels compared to low levels of PEEP do not influence mortality in mechanically ventilated ARDS patients[5]. However, such finding should be carefully interpreted, as this review only included evidence from studies on patients with non-COVID-19-associated ARDS. Although the pathophysiology of COVID-19 and non-COVID-19-associated ARDS is substantially similar, some available data suggest specificities of severe COVID-19 lung disease[18]. This includes pulmonary vascular dysfunction and microangiopathy, higher dead space fraction, and altered hypoxic pulmonary vasoconstriction[18]. Such characteristics certainly contribute to the heterogeneity of lung injury in COVID-19-associated ARDS, which may also influence the response to PEEP[19].

On the other hand, studies evaluating ARDS subgroups have shown favorable results with high PEEP. For example, in a systematic review that analyzed ARDS patients who responded to increased PEEP by improved

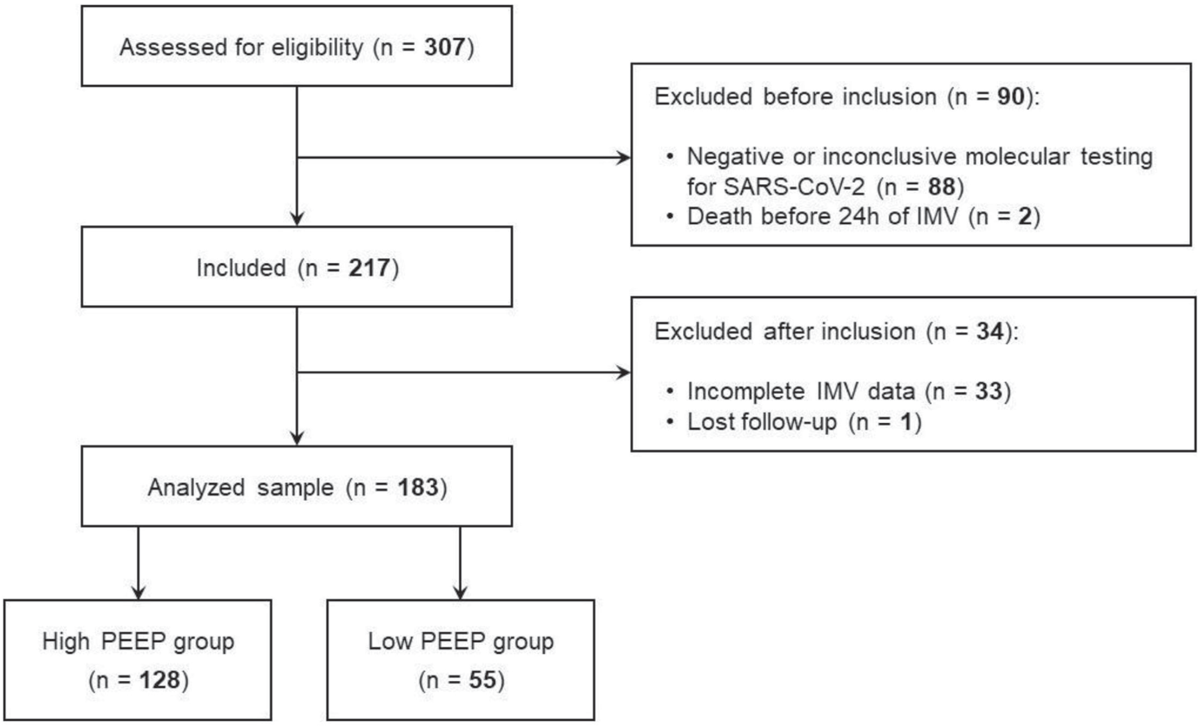

Figure 1. Flow diagram of the study population. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IMV, invasive mechanical ventilation; PEEP, positive end-expiratory pressure.

Source: prepared by the authors.

Table 1. Characteristics and 28-day mortality rate of the total group and subgroups of patients ventilated with high and low positive end-expiratory pressure (PEEP)

	Total (n = 183)	**High PEEP (n = 128)**	**Low PEEP (n = 55)**	***P*-value**
Demographic and clinical data				
Age, years	62 (52 -72)	62 (52 – 69)	65 (52 – 75)	0.100
Male sex, n (%)	100 (55)	71 (56)	29 (53)	0.733
Body mass index, kg/m^2	29 (25 – 33)	30 (27 – 34)	26 (22 – 29)	< 0.001
Charlson comorbidity index, score	2 (1 – 4)	2 (1 – 3)	3 (1 – 4)	0.255
Onset of symptoms, days	11 (8 – 14)	11 (8 – 14)	12 (9 – 16)	0.329
COVID-19 vaccine, n (%)	18 (10)	15 (12)	3 (6)	0.187
SAPS 3, score	60 (56 – 66)	60 (55 – 66)	61 (56 – 67)	0.217
Laboratory tests, at day 1 of IMV				
C-reactive protein, mg/l	157 (100 – 195)	157 (101 – 197)	155 (98 – 192)	0.852
Hemoglobin, g/dL	12.4 (11.3 – 13.6)	12.4 (11.4 – 13.6)	12.5 (10.4 – 13.3)	0.219
Leukocytes, 10^3/mm^3	12.1 (9.1 – 16.8)	12.0 (8.9 – 16.1)	13.3 (10.0 – 17.7)	0.195
Lymphocytes, 10^3/mm^3	0.76 (0.48 – 1.09)	0.76 (0.46 – 1.04)	0.77 (0.49 – 1.18)	0.498

Data are expressed as median (IQR 25 – 75%) or absolute frequency (%). SAPS 3: Simplified Acute Physiology Score; IMV: invasive mechanical ventilation; $PaCO_2$: partial pressure of carbon dioxide; PaO_2/FiO_2: ratio between partial pressure of arterial oxygen and fraction of inspired oxygen; ARDS: acute respiratory distress syndrome; PCV: pressure-controlled ventilation; VCV: volume-controlled ventilation; PEEP: positive end-expiratory pressure; PBW: predicted body weight; ICU: intensive care unit.

Source: prepared by the authors.

Table 1. Continued...

	Total (n = 183)	High PEEP (n = 128)	Low PEEP (n = 55)	*P*-value
Platelets, $10^3/mm^3$	245 (178 – 322)	248 (178 – 340)	242 (187 – 312)	0.734
Creatinine, mg/dl	1.0 (0.8 – 1.7)	1.0 (0.8 – 1.6)	1.1 (0.8 – 2.3)	0.920
Blood gas analysis, first after starting IMV				
pH	7.32 (7.25 – 7.38)	7.32 (7.25 – 7.37)	7.33 (7.26 – 7.40)	0.360
$PaCO_2$, mmHg	42 (36 – 49)	42 (36 – 49)	41 (32 – 48)	0.218
PaO_2/FiO_2	142 (103 – 180)	141 (104 – 182)	147 (101 – 179)	0.938
Mild ARDS, n (%)	44 (24)	31 (24)	13 (24)	0.912
Moderate ARDS, n (%)	109 (60)	77 (60)	32 (58)	
Severe ARDS, n (%)	30 (16)	20 (16)	10 (18)	
Adjunctive therapies, first 48 hours of IMV				
Vasopressors, n (%)	138 (75)	98 (77)	40 (73)	0.581
Neuromuscular blockers, n (%)	97 (53)	75 (59)	22 (40)	0.021
Prone position, n (%)	49 (27)	98 (77)	40 (73)	0.581
Corticosteroids, n (%)	162 (89)	113 (88)	49 (89)	0.875
IMV during the first 48 hours				
PCV/VCV, n (%)	149 (81)/34 (19)	105 (82)/23 (18)	44 (80)/11 (20)	0.746
Peak pressure, cmH_2O	29 (26 – 32)	29 (27 – 32)	26 (24 – 31)	0.009
Plateau pressure, cmH_2O	26 (24 – 28)	26 (24 – 29)	23 (22 – 27)	0.001
PEEP, cmH_2O	10 (9 – 11)	11 (10 – 12)	8 (8 – 9)	< 0.001
Total respiratory rate, breaths/min	24 (22 – 26)	24 (22 – 26)	24 (20 – 26)	0.203
Tidal volume, ml/kg of PBW	8.1 (7.3 – 9.0)	8.2 (7.4 – 9.1)	7.8 (7.2 – 8.8)	0.181
Driving pressure, cmH_2O	15 (14 – 17)	15 (13 – 17)	15 (13 – 18)	0.120
Static compliance, ml/cmH_2O	35 (29 – 42)	35 (29 – 43)	33 (29 – 35)	0.014
Outcomes				
Extubation, n (%)	49 (27)	41 (32)	8 (16)	0.014
Tracheostomy, n (%)	39 (21)	33 (26)	6 (11)	0.024
Hemodialysis, n (%)	59 (32)	38 (30)	21 (38)	0.260
ICU length of stay, days	24 (17 – 37)	23 (16 – 38)	24 (14 – 39)	0.921
Hospital length of stay, days	31 (26 – 47)	31 (26 – 48)	32 (18 – 44)	0.623
28-day mortality, n (%)	113 (62)	69 (54)	44 (80)	0.001
Hospital mortality, n (%)	134 (73)	87 (65)	47 (86)	0.014

Data are expressed as median (IQR 25 – 75%) or absolute frequency (%). SAPS 3: Simplified Acute Physiology Score; IMV: invasive mechanical ventilation; $PaCO_2$: partial pressure of carbon dioxide; PaO_2/FiO_2: ratio between partial pressure of arterial oxygen and fraction of inspired oxygen; ARDS: acute respiratory distress syndrome; PCV: pressure-controlled ventilation; VCV: volume-controlled ventilation; PEEP: positive end-expiratory pressure; PBW: predicted body weight; ICU: intensive care unit.

Source: prepared by the authors.

oxygenation, the results showed that high PEEP (> 10 cmH_2O) was associated with reduced ICU and hospital mortality[20]. Furthermore, another systematic review including only moderate to severe ARDS patients found that a high PEEP strategy without lung recruitment maneuver was associated with a lower risk of death when compared to patients ventilated with low PEEP[21]. Interestingly, these results corroborate our findings and this may be due to sample similarities, considering that our study also had a predominance of patients with moderate to severe ARDS (76%), who tend to have greater potential for lung recruitment and better response to PEEP compared to patients with mild ARDS[22]. At the same time, these evidences are also in line with the most current guideline that recommends a higher PEEP as opposed to a lower PEEP in this subgroup of patients[23].

To the best of our knowledge, only two observational studies have investigated the influence of PEEP on mortality in COVID-19 patients. In the first study, the authors retrospectively analyzed 933 patients and compared high-PEEP versus low-PEEP ventilation strategies, which were based on the high and low PEEP/FiO_2 tables of the ARDS Network[7]. The results showed that ventilation with high PEEP was associated with fewer ventilator-free days, higher incidence of acute kidney injury (AKI), and higher use of renal replacement therapy, but without influence on mortality[7]. On the other hand, the same research group conducted a second retrospective study with 790 COVID-19 patients and found opposite results, showing that a high PEEP/low FiO_2 strategy was associated with less AKI, shorter duration of ventilation and length of stay, and lower mortality compared to low PEEP/high FiO_2 strategy[8]. Speculatively, these divergent results were attributed to a different ARDS phenotype, suggesting that patients in the second study probably had more recruitable lung tissue, which tends to benefit more from high PEEP ventilation. Because these results corroborate our findings, we also believe that our sample was predominantly composed of patients with a higher potential for lung recruitment. Although we are not aware of the use of any bedside measure to assess lung recruitability (e.g., the recruitment-to-inflation ratio), most of our patients had poor respiratory-system compliance (median of 35 ml/cmH_2O), which is a characteristic associated with a higher percentage of potentially recruitable lung[22]. This may also explain the higher mortality in the low PEEP group, which had lower respiratory system compliance and was ventilated with low PEEP when probably the most appropriate strategy should have been ventilation with high PEEP to provide more protective lung ventilation.

During IMV management, PEEP is often used to improve oxygenation, but its inadequate titration can provide detrimental effects. While an excessive PEEP results in alveolar overdistension, increased dead space and V-Q mismatch, an insufficient PEEP leads to alveolar collapse, increased pulmonary shunt and impaired oxygenation[3]. For this reason, the best suggestion is that PEEP be individualized considering not only hemodynamics and oxygenation, but also using respiratory mechanics to find a PEEP that minimizes lung collapse and overdistension[3]. In our study, due to its observational design, PEEP adjustments were not controlled, and it was not possible to determine whether

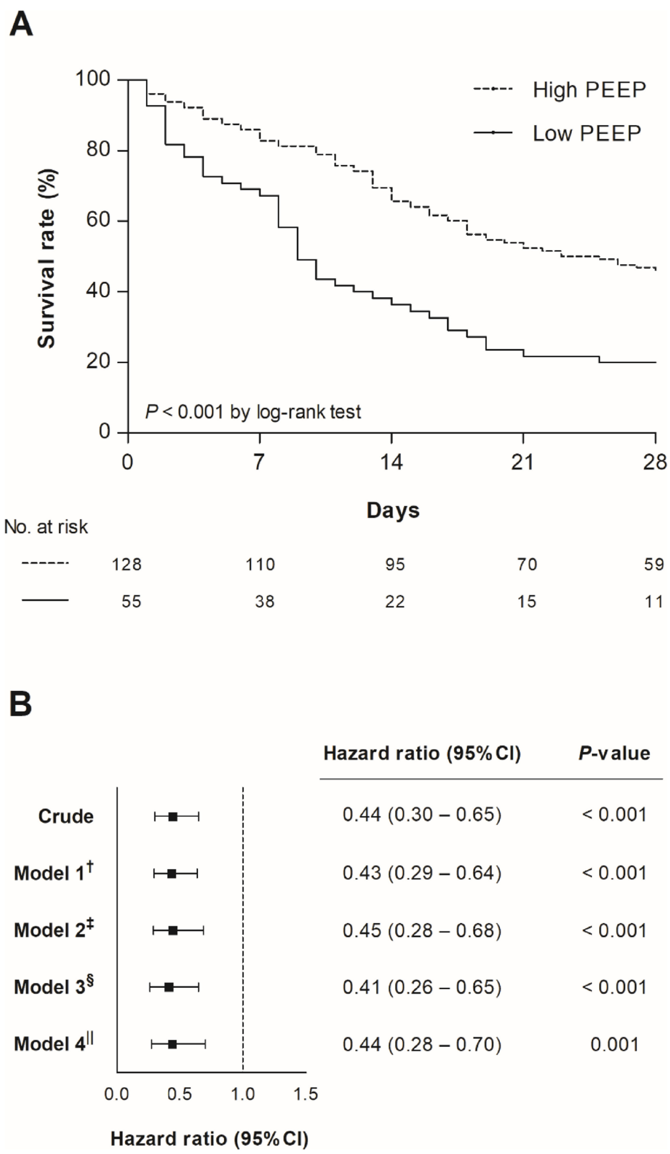

Figure 2. (A) Kaplan-Meier analysis comparing survival between patients that ventilated with high PEEP (≥ 10 cmH_2O) and low PEEP (< 10 cmH_2O). (B) Cox regression analysis showing crude and adjusted hazard ratios for the association between high PEEP (≥ 10 cmH_2O) and 28-day mortality.

Caption: †Model 1: adjusted by age and sex; ‡Model 2: adjusted for Model 1 + BMI, Charlson comorbidity index, SAPS 3, use of vasopressors and neuromuscular blockers; §Model 3: adjusted for Model 2 + arterial blood gas analysis variables (pH, $PaCO_2$ and PaO_2/FiO_2); ||Model 4: adjusted for Model 3 + static respiratory system compliance. CI: confidence interval; PEEP: positive end-expiratory pressure; BMI: body mass index; SAPS 3: Simplified Acute Physiology Score; IMV: invasive mechanical ventilation; $PaCO_2$: partial pressure of carbon dioxide; PaO_2/FiO_2: ratio between partial pressure of arterial oxygen and fraction of inspired oxygen.

Source: prepared by the authors.

titration was performed empirically or according to a systematic method (e.g., PEEP/FiO_2 tables, stress index, or decremental PEEP trial). However, we speculate that patients in the low PEEP group may have had more heterogeneous lungs, which could have led the clinical team to choose lower PEEP due to plateau pressures approaching the safety limit (27-30 cmH_2O)[23,24]. In this scenario, excess mortality might be more attributable to underlying lung heterogeneity rather than to low PEEP directly causing VILI. Although a sensitivity analysis using static compliance was performed, this measurement may have been influenced by the inspiratory pause time used to assess plateau pressure. While pauses of 2-3 seconds have been applied[12], previous evidence suggests that pauses ≥ 3 seconds can underestimate plateau pressure, particularly in patients with more heterogeneous lungs[25]. Consequently, the use of a longer inspiratory pause (3 s) may have led to an underestimation of lung heterogeneity, and this potential confounder might not have been fully accounted for in the multivariate Cox regression.

Additionally, we also consider that changes in clinical practice over the course of the study period may have affected PEEP selection. Early in the pandemic, healthcare professionals with limited experience were called upon to manage critically ill patients requiring IMV. These professionals likely relied on emerging literature, which at times provided conflicting suggestions on PEEP selection, as well as discussions of distinct COVID-19 phenotypes that might respond differently to PEEP[26]. In addition, different SARS-CoV-2 variants were circulating during this period, potentially resulting in variable patterns of pulmonary involvement and influencing the response to PEEP[27]. Although the study period extended into the early phase of vaccination in Brazil, with some vaccinated patients included, no differences were observed between subgroups.

Finally, we believe that setting a PEEP < 10 cmH_2O may have been insufficient in the low PEEP group. Consequently, lung damage may have occurred by three distinct mechanisms or a combination of them: (1) atelectrauma, since insufficient PEEP does not keep the alveoli open at the end of expiration, resulting in alveolar instability and cyclic derecruitment. Repeatedly, this phenomenon can lead to structural damage, inflammation, and changes in the permeability of the alveolar-capillary membrane, contributing to lung injury[28]; (2) regional overdistension, which may occur due to heterogeneity of COVID-19 lung disease. Although low PEEP may prevent some alveolar collapse, certain areas of the lung may remain collapsed while others are overdistended as a result of uneven pressure distribution. This may lead to inhomogeneous ventilation, and the combination of atelectrauma in collapsed regions and overdistension in preserved areas is a significant cause of lung injury[29]; and (3) inflammation and immune response, considering that insufficient PEEP can trigger an inflammatory response, releasing inflammatory mediators (cytokines and chemokines) that favor the recruitment of inflammatory cells and amplify local and systemic inflammation, contributing to pulmonary and multiorgan dysfunction[30]. Thus, the low PEEP group may have been exposed to a higher risk of VILI and its consequences, which would be determinant for poor outcomes and lower survival[2,4]. However, our findings derive from an observational design, and future randomized controlled trials should be conducted to further investigate PEEP effects on outcomes of invasively ventilated COVID-19 patients.

Study limitations. First, our study was carried out in a single center, which may limit the extrapolation of these results to other contexts. Second, patients in the low PEEP group used fewer neuromuscular blockers than patients in the high PEEP group. This may have resulted in a higher rate of patient-ventilator asynchrony, which is an event associated with higher mortality[31]. Unfortunately, we were unable to assess the asynchrony index, and despite adjusting the regression models for neuromuscular blocker use, we recognize that the occurrence of patient-ventilator asynchronies may have been an unmeasured underlying factor that influenced the outcome. Third, we could not identify why healthcare workers chose between high or low PEEP, which was the same limitation reported in other observational studies[7,8]. However, we speculate that PEEP was selected based on a set of conditions that included not only respiratory mechanics but also oxygenation parameters, responses to therapies such as prone position, and hemodynamic side effects. Fourth, we were also unable to detect whether lung recruitability was assessed or whether any individualized approach was used to titrate PEEP. In ARDS patients, although there is no consensus on the best strategy for adjusting an optimal PEEP, using some method is still better than a blind PEEP prescription[32]. Therefore, we do not know whether surviving patients benefited from any specific strategy for PEEP titration. Another possible limitation is that PEEP and other ventilatory parameters were evaluated only in the first 48 hours of IMV. Although this may seem like a short observation period, data from experimental studies suggest that this duration of mechanical ventilation is sufficient to generate VILI[33]. In addition, other large observational studies have also evaluated similar exposure times to identify ventilatory predictors of poor outcomes in mechanically ventilated COVID-19 patients[34-36]. Lastly, considering the observational nature of our study, a causal relationship between PEEP and mortality cannot be established, and the findings should be interpreted from an exploratory perspective, which may provide a statistical basis and rational support for further investigations.

CONCLUSION

In this cohort of mechanically ventilated COVID-19 patients, the use of PEEP ≥ 10 cmH_2O was associated with higher short-term survival. However, it remains unclear whether the use of PEEP < 10 cmH_2O contributed directly to VILI or whether patients receiving lower PEEP had more heterogeneous lungs and, consequently, a higher baseline risk of death. Moreover, our results do not rule out the importance of evaluating lung recruitability and adopting an individualized approach to determine the optimal PEEP level. Finally, high-quality randomized controlled trials are warranted to better clarify the impact of high versus low PEEP strategies on mortality and other clinically relevant outcomes in patients with COVID-19-associated ARDS.

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CONFLICT OF INTEREST

Dr. Renata Gonçalves Mendes, co-author of the paper, is a member of the BJR editorial board in the role of section editor.

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RESEARCH DATA AVAILABILITY

Research data is only available upon request.

ARTIFICIAL INTELLIGENCE USE STATEMENT

No AI tools were used in the preparation of this manuscript.

AUTHOR CONTRIBUTIONS

ADH: conceptualization, methodology, investigation, data curation, formal analysis, and writing – original draft. SNL: conceptualization, methodology, investigation, data curation, formal analysis, and writing – review & editing. VVC: methodology, investigation, data curation, and writing – review & editing. KSL: methodology, investigation, data curation, and writing – review & editing. LNSS: methodology, investigation, and writing – review & editing. CGLD: conceptualization, methodology, and writing – review & editing. RMM: conceptualization, methodology, supervision, and writing – review & editing. RGM: conceptualization, methodology, supervision, funding acquisition, project administration, and writing – review & editing.

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