BMC Pulmonary Medicine

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Prone position ventilation-induced oxygenation improvement as a valuable predictor of survival in patients with acute respiratory distress syndrome: a retrospective observational study

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Abstract

Background In patients with severe acute respiratory distress syndrome (ARDS), prolonged and inappropriate use of prone position ventilation (PPV) is a known risk factor for mortality. Hence, it is critical to monitor patients' response to PPV and accurately differentiate responders from non-responders at an early stage. The study aimed to investigate the relationship between oxygenation improvement after three rounds of PPV and survival rate in patients with pulmonary ARDS. Additionally, we sought to identify the earliest turning point for escalation from PPV to extracorporeal membrane oxygenation.

Methods We performed a retrospective observational study from 2015 to 2023. We included adult patients who received invasive mechanical ventilation, underwent at least three periods of at least 6 h of PPV after admission to the Intensive Care Unit, and meet the ARDS criteria. The study collected data on each PPV session, including changes in $PaCO_2$, PaO_2, pH, FiO_2, PaO_2:FiO_2 ratio, and clinical outcomes.

Results A total of 104 patients were enrolled in the study. The change in $PaCO_2$ from baseline to the third PPV session (P3) had the highest area under the receiver operating characteristic curve (AUC) of 0.70 (95% CI 0.60–0.80; $p < 0.001$) for predicting hospital mortality, with an optimal cut-off point of 3.15 (sensitivity 75.9%, specificity 56.0%). The percentage change in PaO_2:FiO_2 ratio from baseline to P3 also had significant AUC of 0.71 (95% CI 0.61–0.81; $p < 0.001$) for predicting hospital mortality, with an optimal cut-off value of 99.465 (sensitivity 79.6%, specificity 62.0%).

$PaCO_2$ responders were defined as those with an increase in $PaCO_2$ of ≤ 3.15% from baseline to P3, while PaO_2:FiO_2 responders were defined as those with an increase in PaO_2:FiO_2 ratio of ≥ 99.465% from baseline to P3. In the multivariable Cox analysis, PaO_2:FiO_2 responders had a significantly lower 60-day mortality risk (hazard ratio 0.369; 95% CI 0.171–0.798; $p = 0.011$).

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Conclusions The percentage change in PaO_2:FiO_2 ratio from baseline to P3 was a significant predictor of outcomes. The model fit and prediction accuracy were improved by including the variable of $PaCO_2$ responders.

Keywords Acute respiratory distress syndrome, Oxygenation, Prone position, Responders, Ventilation

Introduction

The overall mortality for patients with severe acute respiratory distress syndrome (ARDS) remains approximately 45% [1–3]. Moreover, over 15% of hospitalized patients with COVID-19 develop pulmonary ARDS, which is the primary cause of death in these patients [4–11]. Prone position ventilation (PPV) has been evaluated as a key strategy in managing severe ARDS patients [12, 13]. Studies have shown that 32.9% of patients with severe ARDS were treated with PPV [14], and this proportion was even higher in COVID-19 patients (77%) [15]. Early (within 36 h) and prolonged PPV can improve lung homogeneity, ventilation/perfusion ratios, and outcomes in patients with moderate to severe ARDS by reducing ventilator-associated lung injury (VALI) [16–18].

However, irrationally prolonged PPV has been identified as a risk factor for mortality in severe ARDS patients, as it may delay the initiation of extracorporeal membrane oxygenation (ECMO) [16, 19, 20]. Therefore, it is essential to monitor patients' responses to PPV treatment and accurately distinguish responders from non-responders early on. However, there are various definitions for prone positioning responders. Some studies have defined PPV responders as patients whose PaO_2/FiO_2 (P/F) improved by 20% or 53.5% after PPV, while others defined PPV responders as those with a decrease in $PaCO_2$ of ≥ 1 mmHg [21–27]. Existing studies have defined PPV responders and non-responders based solely on the changes in arterial blood gas after a single prone-positioning session. However, treatments targeting the etiology of ARDS may not take effect after the first PPV session. Therefore, predicting outcomes based solely on changes between baseline and the first PPV treatment may have limited clinical value. Furthermore, in clinical practice, PPV is often performed multiple times [28–30], even if oxygenation does not improve after previous sessions, as demonstrated in the PROSEVA trial [16]. Additionally, under the framework of lung-protective ventilation, PPV is often performed with low tidal volume ventilation, which can result in hypercapnia [31].

Therefore, it is desirable to use a composite measure of PPV efficacy and identify an early turning point for escalating from PPV to ECMO. The objective of our study was to explore the relationship between oxygenation improvement after three rounds of PPV and survival in patients with pulmonary ARDS, in order to support clinical decision-making on PPV during the COVID-19 pandemic.

Methods

Study design

We performed a retrospective observational study in the Intensive Care Unit (ICU) of the First Affiliated Hospital of Guangzhou Medical University, a tertiary-care referral hospital in China, between November 2015 and March 2023. The institution's Medical Ethics Committee waived the requirement for written informed consent and approved the study (ES-2023-K006-01). The study was reported adhering to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement guidelines [32].

Participants

To be eligible for inclusion in the study, patients had to be adults (≥ 18 years), receiving invasive mechanical ventilation, undergoing at least three PPV sessions after admission to the ICU, and meeting the criteria for ARDS as per the Berlin definition [33]. Exclusion criteria included patients who received PPV for less than 6 h each time, patients who underwent ECMO before or during the first three PPV attempts, patients with severe immunosuppression due to drug-induced immunosuppression for solid-organ transplantation or human immunodeficiency virus infection, pregnant women, and those with multiple organ failure.

Procedures and definitions

Lung-protective ventilation was applied to all ARDS patients throughout the study period following the guidelines [12, 34]. All other ventilator variable settings and the use of PPV were left to the discretion of the physicians, who adhered to the guidelines and the Berlin definition. Patients were placed in PPV for at least 6 h daily. Sedation, neuromuscular blocking agents, and analgesia were provided as required.

Arterial blood gas (ABG) analyses were performed at admission to the ICU. For patients requiring PPV, ABG analyses were performed at least 2 h after each PPV session. ABG ($PaCO_2$, PaO_2, pH) analyses were measured using a point-of-care blood gas analyzer (ABL800 FLEX, Radiometer, Denmark), and FiO_2 was recorded from the ventilator at the time of blood sampling for ABG

analyses. The P/F ratio was calculated using variables obtained after the completion of each PPV session.

Data collection and evaluation

Data were obtained from the nursing records and hospital electronic database records, and all individual data were anonymized. All medical records were independently reviewed by two researchers to determine the patients' demographics (age and gender), time from admission to ICU to the first PPV, Acute Physiology and Chronic Health Evaluation (APACHE) II, Sequential Organ Failure Assessment (SOFA), Richmond Agitation Sedation Scale (RASS), comorbidities, neuromuscular blocking agents use, arterial blood gases ($PaCO_2$, PaO_2, pH), FiO_2, P/F ratio, and clinical outcomes (ventilator-free days at 28 days, length of in-hospital stay, length of ICU stay, 28-day mortality, 60-day mortality, and hospital mortality). The primary outcome was all-cause hospital mortality. Secondary outcomes included 28-day hospital mortality and 60-day hospital mortality. Patients were followed until hospital discharge or death. We recorded each PPV section and subsequent changes in $PaCO_2$, PaO_2, pH, FiO_2, and P/F ratio. If these data were missing, we used data closest time point but never more than 16 h after the PPV session. Only the earlier ABG result remained in the final analysis if the patient had multiple ABG results at the same PPV section interval.

Statistical analysis

Given the retrospective exploratory nature of the study, formal sample size or power calculations were not conducted. Missing or questionable data values were interpolated or verified by cross-referencing with data extracted from original medical records.

Quantitative variables were presented as the mean ± standard deviation (SD) or median with interquartile range (IQR), depending on the normality of the distribution. Qualitative variables were expressed as frequencies (%), and compared using the Chi-square or Fisher exact test, as appropriate. Statistical significance among groups was determined by the ANOVA test when data met assumptions of normal distribution and equal variance. Otherwise, the Mann–Whitney U tests were applied.

Repeated blood sample results ($PaCO_2$, PaO_2, pH, FiO_2, and P/F ratio) from the baseline to each prone position were analyzed using linear mixed-effects models to account for the repeated measures structure of the dataset. Satterthwaite's method was used to estimate p values for the mixed-effects models, and the fixed effects parameters (times of prone position) were estimated using maximum likelihood estimation.

Receiver operating characteristic (ROC) curves were generated to determine the predictive value of the percentage PPV-induced changes in the P/F ratio and $PaCO_2$ between baseline and each PPV session for hospital mortality. The optimal cutoff values of ROC curves were identified through Youden's index, which maximizes the sum of sensitivity and specificity. The area under the curves (AUC), a quantitative measure of the model performance, was presented with 95% CI. A value of AUC close to 1 indicates better model performance.

The association between different variables and hospital mortality in patients who received PPV for ARDS was analyzed using multivariate logistic regression models. Variance inflation factors (VIFs) were assessed to test for the presence of multicollinearity. A stepwise forward–backward selection procedure was used with a stopping rule based on the minimum Bayesian Information Criterion (BIC). The goodness of fit was evaluated using the Hosmer–Lemeshow test. A nomogram plot was generated based on the multivariate logistic regression models. The model was internally validated using bootstrap resampling for 1000 iterations and bias-corrected.

We verified the proportional hazards assumption that risk functions for different values of covariates were proportional. Time-to-event data were analyzed using the Kaplan–Meier method and survival curves between two groups were compared via a Log-rank test. Hazard ratios (HRs) with 95% CIs were calculated using Cox proportional hazards models. Multivariate Cox regression also applies a stepwise forward–backward selection procedure for variable screening.

Statistical analyses were performed using R and the R-studio interface by independent statisticians (R version 4.3.1). If not specified, a two-sided P value < 0.05 was considered statistically significant.

Results

Patient characteristics

During the study period, 12,495 patients were admitted to our ICU. Of these, 893 (7.15%) met the Berlin criteria for ARDS and required invasive mechanical ventilation (IMV). After excluding patients who did not meet the inclusion criteria, 104 patients (79 male and 25 female) remained in the analysis. The median age of the included patients was 60 (IQR, 51–72) years and the mean APACHE II score of 22 ± 7. (Fig. 1) Fifty patients survived the hospital stay, and the overall 28-day mortality rate was 24.0%.

The characteristics of the patients were grouped by prognosis status and are presented in Table 1. There were no statistically significant differences among the groups in demographic characteristics, time from admission to ICU to the first PPV, sedation scores, or severity scores

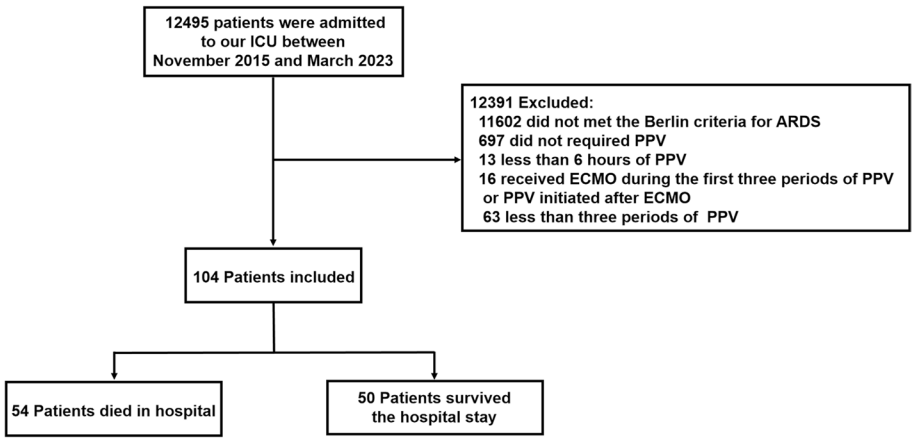

Fig. 1 Flow Diagram of the study population. ICU intensive care unit. ARDS acute respiratory distress syndrome. PPV prone position ventilation. ECMO Extracorporeal Membrane Oxygenation

Table 1 Characteristics of the patients at baseline

Characteristic	Total ($n=104$)	Survivors ($n=50$)	Non-survivors ($n=54$)	*p* value
Age, years	60.00 [51.00, 72.25]	60.00 [49.00, 72.00]	62.50 [53.25, 72.75]	0.376
Gender, male	79 (76.0)	38 (76.0)	41 (75.9)	> 0.999
Bacterial infection	60 (57.7)	32 (64)	28 (51.9)	0.238
APACHE II score (mean (SD))	21.88 (7.15)	21.98 (7.50)	21.80 (6.89)	0.897
SOFA score	9.00 [7.00, 11.00]	9.00 [6.25, 11.00]	8.00 [7.00, 11.00]	0.541
RASS (mean (SD))	-3.83 (0.53)	-3.80 (0.61)	-3.85 (0.45)	0.62
Neuromuscular blockade	67 (64.4)	31 (62.0)	36 (66.7)	0.684
Time from admission to ICU to the first PP	1.00 [0.00, 3.00]	1.00 [0.00, 3.00]	1.00 [0.00, 2.00]	0.962
Comorbidities				
Septic shock	65 (62.5)	26 (52.0)	39 (72.2)	0.043
Immunocompromised	54 (51.9)	17 (34.0)	37 (68.5)	0.001
Barotrauma	12 (11.5)	5 (10.0)	7 (13.0)	0.763
Severe pneumonia	101 (97.1)	47 (94)	54 (100)	0.108
COVID-19	23 (22.1)	11 (22.0)	12 (22.2)	> 0.999
Pre-prone ventilation parameters				
FiO_2	0.90 [0.70, 1.00]	0.90 [0.70, 1.00]	0.98 [0.71, 1.00]	0.444
Pre-prone blood gases				
pH	7.37 [7.32, 7.42]	7.37 [7.29, 7.42]	7.38 [7.34, 7.43]	0.177
$PaCO_2$, mm Hg	41.45 [36.50, 50.17]	42.85 [37.33, 53.63]	39.90 [35.65, 47.72]	0.161
PaO_2, mm Hg	79.85 [66.00, 102.00]	83.65 [66.12, 103.75]	77.50 [66.32, 100.12]	0.711
P/F ratio, mm Hg	93.93 [73.85, 141.75]	97.83 [83.48, 142.25]	89.67 [71.03, 136.92]	0.347

Data are reported as *n* (%), mean (SD), or median [1st–3rd quartile]

APACHE acute physiology and chronic health evaluation, *COVID-19* Coronavirus disease 2019, *FiO_2* fraction of inspired oxygen, *$PaCO_2$* arterial partial pressure of carbon dioxide, *PaO_2* arterial partial pressure of oxygen, *P/F ratio* PaO_2:FiO_2, *PP* prone position, *SD* standard deviation, *SOFA* sequential organ failure assessment, *RASS* Richmond Agitation Sedation Scale

at ICU admission. Barotrauma, bacterial infection, and severe pneumonia were similar between the groups. However, the non-survival group had a significantly higher percentage of immunocompromised patients (17 [34.0%] vs 37 [68.5%]; $p=0.001$).

The results of arterial blood gas analysis and ventilator settings at baseline did not show statistically significant

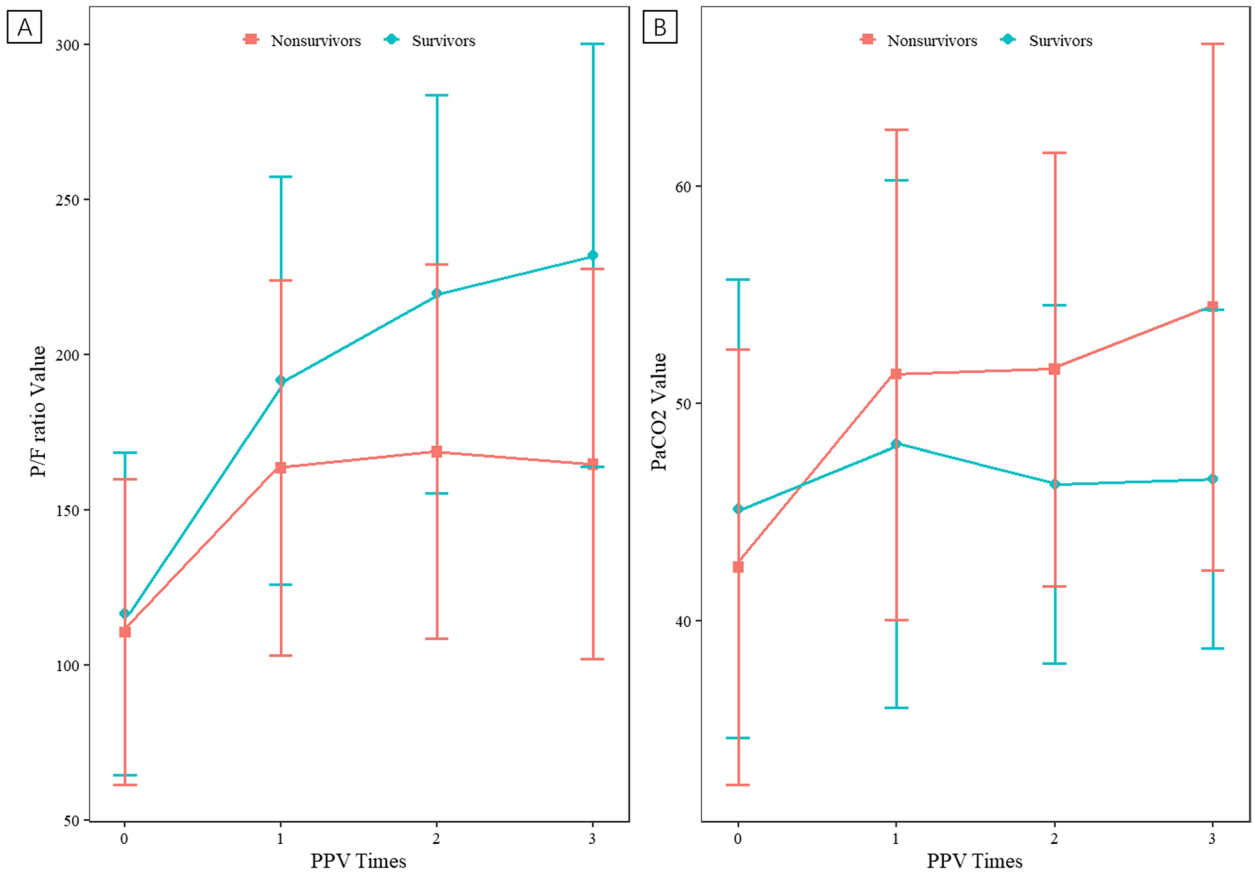

Fig. 2 Mean values of PaO_2:FiO_2 ratio at baseline and after each prone position ventilation session. Error bars indicate standard deviation. PaO_2:FiO_2 ratio was obtained at the following time points: ICU admission (baseline), after the first prone position ventilation session (time P1), after the second prone position ventilation session (time P2), and after the third prone position ventilation session (time P3)

differences between hospital survivors and non-survivors. At baseline, the median length of ICU stay and hospital stay were 28 days (17–43 days) and 35 days (23–57 days), respectively. The median P/F ratio was 93.9 mm Hg (73.9–141.8 mm Hg) and $PaCO_2$ was 41.5 mm Hg (36.5–50.2 mm Hg).

Oxygenation response to PPV sessions

During the three PPV sessions, neuromuscular blockades were used in 67 (64.4%) of the patients, showing no statistically significant differences between hospital survivors and non-survivors. The first PPV session resulted in a rise in the P/F ratio that persisted after the patient was repositioned back in the supine position in 87.5% of the cases. Following the first PPV session, the P/F ratio increased in 47 (94%) of survivors and 44 (81.5%) of non-survivors.

Among survivors, the P/F ratio increased from 117 ± 52 mm Hg at baseline to 192 ± 66 mm Hg at the first PPV (P1), to 220 ± 64 mm Hg at the second PPV (P2), and to 232 ± 68 mm Hg at the third PPV (P3). In non-survivors, the P/F ratio stepped up from 111 ± 49 mm Hg at baseline to 164 ± 60 mm Hg at P1, to 169 ± 60 mm Hg at P2, and then declined to 165 ± 63 mm Hg at P3.

The $PaCO_2$ among survivors increased from 45 ± 11 mm Hg at baseline to 48 ± 12 mm Hg at P1. However, three rounds of PPV yielded similar results (P2: 46 ± 8 mm Hg; P3:47 ± 8 mm Hg). In non-survivors, $PaCO_2$ kept increasing from baseline (42 ± 10 mm Hg), reaching 54 ± 12 mm Hg at P3. (Fig. 2 and Table 2).

No significant differences were found in $PaCO_2$ through the first PPV period between the survival and non-survival groups. However, $PaCO_2$ was found to be significantly different at P2 ($p = 0.004$) and P3 ($p < 0.001$). Between-group differences were significant in the P/F ratio for all PPV rounds ($p_{P1} = 0.025$; $p_{P2} < 0.001$; $p_{P3} < 0.001$). (Table 2) The results of analyzing repeated blood samples ($PaCO_2$ and P/F ratio) between each PPV group are presented in e-Table 1 and e-Table 2.

Table 2 Blood gases in survivors and non-survivors

	Survivors ($n=50$)	Non-survivors ($n=54$)	*p* value
pH			
ICU admission	7.35 (0.09)	7.38 (0.07)	0.084
PPV times 1	7.35 (0.08)	7.35 (0.07)	0.916
PPV times 2	7.39 (0.06)	7.37 (0.06)	0.03
PPV times 3	7.41 (0.06)	7.36 (0.07)	0.001
$PaCO_2$			
ICU admission	45.15 (10.56)	42.46 (10.03)	0.186
PPV times 1	48.13 (12.15)	51.32 (11.27)	0.168
PPV times 2	46.28 (8.24)	51.56 (9.98)	0.004
PPV times 3	46.52 (7.80)	54.42 (12.12)	< 0.001
PaO_2			
ICU admission	89.60 (32.68)	89.75 (36.73)	0.983
PPV times 1	120.49 (30.60)	116.08 (34.87)	0.496
PPV times 2	122.48 (31.35)	108.56 (28.27)	0.019
PPV times 3	117.87 (26.24)	101.38 (23.90)	0.001
FiO_2			
ICU admission	0.83 (0.20)	0.86 (0.18)	0.438
PPV times 1	0.66 (0.15)	0.75 (0.17)	0.008
PPV times 2	0.58 (0.13)	0.68 (0.14)	< 0.001
PPV times 3	0.53 (0.11)	0.66 (0.15)	< 0.001
P/F ratio			
ICU admission	116.50 (52.10)	110.55 (49.29)	0.55
PPV times 1	191.58 (65.66)	163.51 (60.46)	0.025
PPV times 2	219.57 (64.14)	168.68 (60.32)	< 0.001
PPV times 3	231.97 (68.17)	164.66 (62.87)	< 0.001

Data are reported as mean (SD)

PPV times 1: after the first prone position ventilation session; PPV times 2: after the second prone position ventilation session; PPV times 3: after the third prone position ventilation session

Abbreviations: FiO_2 fraction of inspired oxygen, *$PaCO_2$* arterial partial pressure of carbon dioxide, *PaO_2* arterial partial pressure of oxygen, *P/F ratio* PaO_2:FiO_2, *PPV* prone position ventilation, *SD* standard deviation

Predictive value of the changes in P/F ratio and $PaCO_2$ response

The AUC value for the percentage changes in the P/F ratio between baseline and the P3 round was significant for predicting the probability of hospital mortality (AUC 0.71, 95% CI 0.61–0.81; $p<0.001$). (e-Table 3) The optimal cut-off value for this was 99.465, with a sensitivity of 79.6%, a specificity of 62.0%, a positive predictive value of 69.4%, and a negative predictive value of 73.8%, as determined by using the maximum value of the Youden index. (e-Fig. 1) Patients were considered as P/F ratio responders if they had an increase in the P/F ratio of greater than or equal to 99.465% from baseline to the P3 round.

All AUC values for the changes in the $PaCO_2$ between baseline and different PPV times for predicting hospital mortality were significant ($p_{p1}=0.021$; $p_{p2}=0.003$; $p_{p3}<0.001$). The ROC analysis of the change in the $PaCO_2$ between baseline and time P3 had the highest AUC curve (AUC 0.70, 95% CI 0.60–0.80; $p<0.001$). (e-Table 3) The optimal cut-off point to predict hospital mortality was 3.15, with a sensitivity of 75.9%, a specificity of 56.0%, a positive predictive value of 65.8%, and a negative predictive value of 68.3%. (e-Fig. 2) Similarly, patients were considered as $PaCO_2$ responders if they had an increase in $PaCO_2$ of less than or equal to 3.15% from the baseline to time P3. A detailed description of the characteristics of patients in the different responder groups at baseline is provided in e-Table 4 and e-Table 5.

Clinical outcomes and predictors of mortality

All variables without multicollinearity were included in the multivariate logistic regression analysis. The stepwise regression analysis identified P/F ratio responders (OR, 0.207; 95% CI, 0.071–0.56), $PaCO_2$ responders (OR, 0.219; 95% CI, 0.073–0.61), age (OR, 1.047; 95% CI, 1.011–1.092), immunocompromised (OR, 6.49; 95% CI, 2.268–21.084), and septic shock (OR, 3.35; 95% CI, 1.196–10.19) as significantly associated with hospital mortality. (Table 3) We further constructed a nomogram incorporating these predictors in e-Fig. 3. Internal validation using bootstrapping with 1000 samples demonstrated the robustness of the predictive model (Brier value = 0.183; concordance index = 0.822).

During the 60-day follow-up, 48 patients (46.2%) died. Survival analysis comparing the P/F ratio of responders

Table 3 Regression analysis to evaluate the association between survival and covariates

Variables and parameters	aOR/ aHR	95% CI	*p* value
Multivariate logistic regression[a]			
P/F ratio responders	0.207	0.071–0.56	0.003
$PaCO_2$ responders	0.219	0.073–0.61	0.005
Age	1.047	1.011–1.092	0.018
Immunocompromised	6.49	2.268–21.084	0.001
Septic shock	3.35	1.196–10.19	0.025
Multivariate cox regression			
Model 1 (28 days)			
P/F ratio responders	0.229	0.076–0.686	0.009
Age	1.03	0.997–1.064	0.074
Model 2 (60 days)			
P/F ratio responders	0.369	0.171–0.798	0.011
Immunocompromised	2.005	1.058–3.799	0.033
age	1.017	0.994–1.042	0.156
Septic shock	1.693	0.867–3.305	0.123

Abbreviations: *aOR* adjusted odds ratio, *aHR* adjusted hazard ratio, *CI* confidence interval, *$PaCO_2$* arterial partial pressure of carbon dioxide, *P/F* PaO_2:FiO_2

[a] Hosmer–Lemeshow goodness-of-fit test, $p=0.235$; Brier value = 0.183; concordance index = 0.822

The assumptions of proportional hazards were satisfied ($p_{model1}=0.75$; $p_{model2}=0.326$)

and non-responders groups revealed a significantly difference in 60-day mortality ($p=0.001$ by log-rank test). In contrast, $PaCO_2$ responders did not show a statistically significant difference in 60-day mortality compared to the non-responders group ($p=0.052$ by log-rank test, Fig. 3). The survival analysis of 28-day mortality is presented in e-Fig. 4.

After adjusting for potential confounders in the multivariable Cox analysis, P/F ratio responders remained associated with a significantly lower 60-day mortality risk (adjusted hazard ratio (aHR) 0.369; 95% CI 0.171–0.798; $p=0.011$). (Table 3).

Discussion

Given that lung-protective ventilation strategies such as lung recruitment, PEEP titration, and prone ventilation have demonstrated differing effects on pulmonary ARDS compared to extrapulmonary ARDS [35], we included only patients with pulmonary ARDS in our study population. All patients were ventilated using a low tidal volume ventilation (LTVV) strategy and were actively stabilized hemodynamically. This study included only patients who received at least three consecutive sessions of PPV, with PPV being carried out approximately 36 h after meeting the criteria for moderate-to-severe ARDS. To our knowledge, this is the first study to investigate the impact of improved oxygenation after each PPV on clinical outcomes in patients with pulmonary ARDS who received at least three PPV sessions.

The key findings of this study were as follows: First, there was a significant difference in the P/F ratio between survivors and non-survivors during the first three PPV sessions. Second, a cut-off value of a 99.465% increase in P/F ratio from baseline to after the third PPV session was more effective in predicting ICU outcomes (AUC: 0.713) compared to the first and second PPV sessions. Similarly, a cut-off value of a 3.15% increase in $PaCO_2$ from baseline to after the third PPV session was also predictive of ICU outcomes (AUC: 0.703). Third, Survival analysis revealed that non-responders to the P/F ratio had higher 28-day and 60-day mortality rates.

Among the first three PPV sessions, the changes of both the P/F ratio and $PaCO_2$ between the baseline and the third PPV session demonstrated the best discrimination in predicting in-hospital mortality.

Previously, P/F ratio responders were defined as patients who experienced a 20% or 53.5% improvement in P/F ratio after the first PPV session [15, 23], or even based on the subjective judgments of caregivers. In our cohort, using the cut-off value of 99.465% for the change in oxygenation as a predictor of hospital mortality outperformed the two previously reported cut-off values for the change in oxygenation (based on Youden's index). (e-Table 7).

Consistent with prior studies, PPV increases oxygenation in most patients with ARDS [36–38]. The effect of PPV's improving oxygenation persists even after patients are returned to the supine position [39, 40]. Additionally, multiple PPV sessions can further improve oxygenation [41, 42]. However, improved oxygenation alone does not always translate to improved survival [26, 27]. In pulmonary ARDS, the mechanisms underlying oxygenation improvement after PPV treatment are diverse, with improved lung homogeneity like playing the most important role. Although oxygenation may improve after the first PPV session, the etiological treatment for ARDS may not begin to work at the same time. Therefore, evaluating the patients' response to PPV treatment based solely on the status of oxygenation after the first PPV session may be risky. Implementing substantial changes in management strategies of ARDS patients, such as escalating to ECMO support or prolonging the PPV, based solely on the status of oxygenation after the first PPV session may introduce a high risk of complications.

Theoretically, monitoring changes in $PaCO_2$ may be more relevant than monitoring changes in P/F ratio for predicting the response to prone position (PP) in patients with ARDS [43]. Patients with ARDS have a better prognosis with decreased $PaCO_2$ after the PP, suggesting an improvement in the efficiency of alveolar ventilation [27]. Additionally, this study demonstrated that $PaCO_2$ responders predict improved outcomes in patients with ARDS. Pelosi et al. suggested that during PPV, the bed surface impedes the expansion of the anterior and abdominal chest walls, resulting in a decrease in chest wall compliance. In contrast, lung compliance and respiratory system compliance increase when the patient is transferred to the supine position [44, 45]. Langer et al. observed a significant increase in respiratory rate settings after prone positioning and a tendency to lead to an increase in minute ventilation. Therefore, a variation in the ventilatory ratio must be chosen to differentiate between CO_2 responders and non-responders and thus reflect changes in dead space [15]. Petit et al. observed through CT that patients with more normal ventilation lung tissue in ventral and medial-ventral regions and a lower dorsal tidal volume/overall tidal volume ratio were more likely to have improved static lung compliance after prone positioning [46, 47].

Elevated $PaCO_2$ after PPV might lead to further aggravated hypercapnia. Severe hypercapnia or a rapid rise in $PaCO_2$ could cause myocardial depression, increase pulmonary vascular resistance leading to increased right heart insufficiency [48], increase the risk of inpatient death in patients with cerebral injury [49], as well as

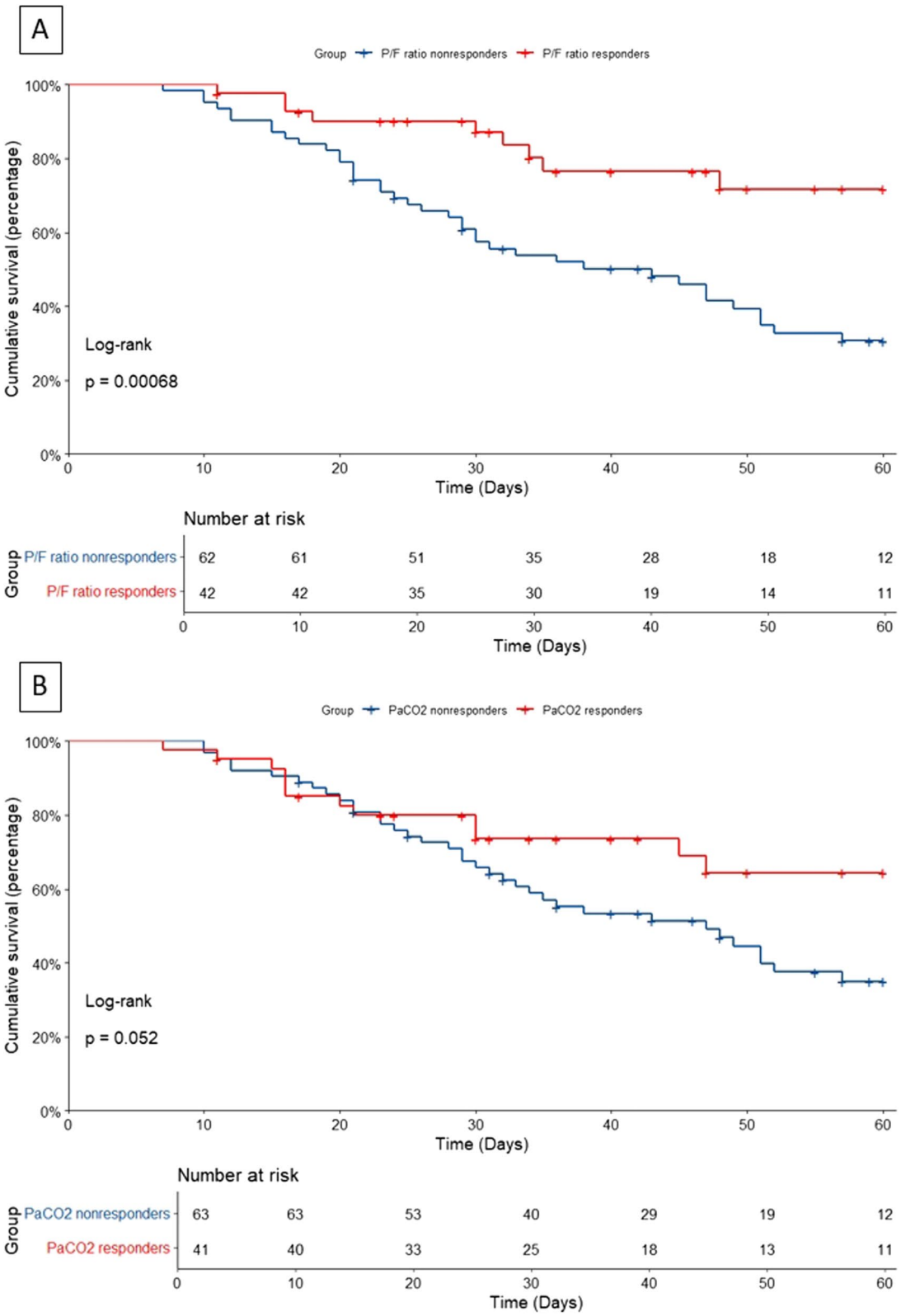

Fig. 3 Kaplan–Meier Survival Curves for 60-day Probability of Survival in Patients with Pulmonary ARDS. A, PaO_2:FiO_2 responders/ nonresponders; B, $PaCO_2$ responders/nonresponders. P/F ratio responders were defined as patients showing an increase in the PaO_2:FiO_2 ratio of greater than or equal to 99.465% from the baseline to time P3. $PaCO_2$ responders were defined as patients showing an increase in the $PaCO_2$ of less than or equal to 3.15% from the baseline to time P3

aggravate kidney injury and lung injury, which is detrimental to the patient's prognosis [31, 50, 51].

If the improvement in lung compliance counteracts the adverse factors that lead to increased chest wall compliance after PP, $PaCO_2$ may not continue to rise. Although the study did not monitor changes in the patients' chest wall elastic resistance, during which ventilatory parameters such as tidal volume, respiratory rate, inspiratory time, and PEEP do not make adjustments, we observed varying degrees of elevated $PaCO_2$ in both groups after PPV. After the third PP, $PaCO_2$ was significantly higher in the non-survivor group than in the survival group, reflecting the failure of PPV to increase alveolar ventilation as well as improve intrapulmonary heterogeneity. This indirectly suggests to clinicians that the etiology of the patient's lungs may be poorly reversible and that poorly controlled hypercapnia affects the patient's prognosis.

Certainly, elevated $PaCO_2$ after PPV might be associated with maintaining the same LTVV ventilation parameters, alternatively associated with not retitrating the optimal PEEP [52] and retaining deep sedation leading to reduced respiratory drive [53].

This study has several notable strengths. We investigated the improvement in oxygenation after three PPV sessions and its association with the survival of patients with pulmonary ARDS, which differs from previous studies. Using the optimal cut-off value, a nomogram model was constructed that incorporated five variables to predict the effect of PPV and all-cause in-hospital mortality with high efficiency and practical bedside application. This may serve to rationalize clinical decision-making regarding assisted ventilation strategies and avoid delays in escalating the therapeutic approach from PPV to ECMO. Our models for the third PPV achieved high predictive accuracy (AUC: 0.85). Substituting the data of the first or second PPV into the model also demonstrated high predictive accuracy (AUC_{P1}: 0.79; AUC_{P2}: 0.80), suggesting that our model had better generalization ability (e-Fig. 5).

Study limitations

Some limitations were present in this study. First, we only evaluated 104 patients due to a high quantity of unsuitable samples. Second, this was a single-center study, but the robustness of our final model was demonstrated by extensive internal validation. In addition, although the imputed data only accounted for 13.9%, it cannot be denied that it may have affected the outcome to some extent, which is a common limitation in studies based on retrospective data. Furthermore, the indicators included in the study were all blood gas indicators and were not combined with lung imaging and respiratory mechanics to evaluate the dynamic changes in lung recruitment.

Conclusion

Significant differences were observed in the P/F ratio during all periods of PPV between the survival and non-survival groups in patients with pulmonary ARDS in the ICU. The percentage changes in the P/F ratio from baseline to the third PPV session were significant predictors of the outcome. The inclusion of the variable $PaCO_2$ responders improved the model's fit and prediction accuracy.

Abbreviations

ABG	Arterial blood gas
APACHE II	Acute Physiology and Chronic Health Evaluation II
ARDS	Acute Respiratory Distress Syndrome
AUC	Area under the curves
CI	Confidence interval
COVID-19	Coronavirus disease 2019
ECMO	Extracorporeal Membrane Oxygenation
FiO_2	Fraction of inspired oxygen
HR	Hazard ratios
ICU	Intensive care unit
IQR	Interquartile range
LTVV	Low tidal volume ventilation
ORs	Odds ratios
PPV	Prone position ventilation
$PaCO_2$	Arterial partial pressure of carbon dioxide
PaO_2	Arterial partial pressure of oxygen
P/F ratio	PaO_2/FiO_2
RASS	Richmond Agitation Sedation Scale
RCT	Randomized Controlled Trial
ROC	Receiver operating characteristic
SD	Standard deviation
SE	Standard Error of Mean
SOFA	Sequential Organ Failure Assessment
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
Sum Sq	Sum of squares
VIF	Variance inflation factors

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-024-03349-3.

Supplementary Material 1.

Acknowledgements

We thank LetPub (www.letpub.com.cn) for its linguistic assistance during the preparation of this manuscript.

Authors' contributions

Study conception/design: YX. Data acquisition: QD, ZJ, BZ, JZ. Data analysis and interpretation: HL, MJ. Article writing: all authors. HL, QD, YX, WY were major contributor in writing the manuscript. All authors read and approved the final manuscript. YX is guarantor.

Funding

This study was supported by the Guangzhou Science and Technology Planning Project (No. 202102010353), Zhongnanshan Medical Foundation of Guangdong Province (No. ZNSA-2020003), Guangzhou Institute of Respiratory Health/ 2019 Clinical Independent Exploration Project of National Clinical Research Center of the First Hospital of Guangzhou Medical University (No.

2019GIRHZ10), and the Project of Cultivating High-level Clinical Research launched by the Guangzhou Medical University (02–408-2304-19099XM).

Data availability
The data that support the findings of this study are available from the corresponding author(Email: xuyuanda@sina.com) but restrictions apply to the availability of these data, which were used under licence for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request.

Declarations

Ethics approval and consent to participate
The institution's Medical Ethics Committee (the First Affiliated Hospital of Guangzhou Medical University, China) approved the study protocol and waived the need for informed consent. (ES-2023-K006-01).

Consent for publication
Consent for publication has been obtained.

Competing interests
The authors declare no competing interests.

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Received: 6 March 2024 Accepted: 17 October 2024
Published online: 20 November 2024

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