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Association between partial pressure of arterial carbon dioxide and survival to hospital discharge among patients diagnosed with sepsis in the emergency department

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Abstract

Objective—The objective of this study was to test the association between the partial pressure of arterial carbon dioxide (PaCO₂) and survival to hospital discharge among mechanically ventilated patients diagnosed with sepsis in the emergency department (ED).

Design—Retrospective cohort study of a single center trial registry.

Setting—Academic medical center.

Patients—Mechanically ventilated ED patients. Inclusion criteria: age ≥ 18, diagnosed with sepsis in the ED, and mechanical ventilation initiated in the ED.

Interventions—Arterial blood gases obtained after initiation of mechanical ventilation were analyzed. The primary outcome was survival to hospital discharge. We tested the association

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Contributors: BMF and BWR conceived the study. ITF and BMF were responsible for acquisition and quality of the data. BWR did the analysis. All authors were involved in interpretation of the data and participated in writing and revision of the manuscript. BMF and BWR wrote the first and final draft.

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between PaCO₂ and survival using multivariable logistic regression adjusting for potential confounders. Sensitivity analyses, including propensity score matching were also performed.

Measurements and Main Results—Six hundred subjects were included and 429 (72%) survived to hospital discharge. The median [interquartile (IQR)] PaCO₂ was 42 (34-53) mmHg for the entire cohort and 44 (35-57) and 39 (31-45) mmHg among survivors and non-survivors respectively ($p < 0.0001$ Wilcoxon rank-sum test). On multivariable analysis, a 1 mmHg rise in PaCO₂ was associated with a 3% increase in odds of survival [aOR 1.03, 95% confidence interval (CI) 1.01-1.04] after adjusting for tidal volume and other potential confounders. These results remained significant on all sensitivity analyses.

Conclusion—In this sample of mechanically ventilated sepsis patients we found an association between increasing levels of PaCO₂ and survival to hospital discharge. These findings justify future studies to determine the optimal target PaCO₂ range for mechanically ventilated sepsis patients.

Keywords

mechanical ventilation; partial pressure of arterial carbon dioxide; PaCO₂; sepsis

Introduction

Sepsis incidence is increasing, and it continues to have high mortality and costs of care. Sepsis-associated respiratory failure is common,(1) and often requires mechanical ventilation in the emergency department (ED) and the intensive care unit (ICU). The mortality for mechanically ventilated sepsis patients remains unacceptably high at over 40%. (1) Thus finding new interventions to improve outcomes in this patient population is of the utmost importance.

Prescribing low tidal volume and limiting inspiratory pressures to prevent ventilator-associated lung injury (VALI) is associated with improved outcomes in mechanically ventilated sepsis patients.(2) However, this strategy can result in elevated levels of partial pressure of arterial carbon dioxide (PaCO₂). (3, 4) The literature has conflicting assessments of PaCO₂ and its effects on clinical outcomes. Elevated PaCO₂ (i.e. hypercapnia) has been shown to impair alveolar epithelial and neutrophil function and could in theory suppress immune responses and resistance to bacterial infection.(5-8) In addition, the acidosis induced by hypercapnia can potentially decrease antibiotic efficacy.(9) A recent secondary analysis of three cohort studies found severe hypercapnia (PaCO₂ > 50 mmHg) to be associated with increased mortality among patients with acute respiratory distress syndrome (ARDS).(10) Alternatively, hypercapnia can modulate several biologically-important mechanisms, which could be beneficial in the setting of sepsis, including provision of anti-inflammatory modulators, mitigation of VALI, and modulation of gene expression, which could be important in sepsis survival.(11-15) In addition, elevated PaCO₂ may inhibit bacterial growth, thus decreasing the overall infectious insult.(16) In an analysis of a heterogeneous group of mechanically ventilated patients without ARDS, our group previously found hypercapnia (PaCO₂ > 45 mmHg) was associated with increased survival.

(17) Given these conflicting reports, the effects of PaCO₂ on clinical outcomes among sepsis patients remains unclear.

The objective of this study was to test the association between PaCO₂ early after the initiation of mechanical ventilation and survival to hospital discharge among patients diagnosed with sepsis-associated respiratory failure requiring mechanical ventilation in the ED.

Material and Methods

Setting

We analyzed an ED registry of patients with acute initiation of mechanical ventilation, at a tertiary academic center (September 2009 to March 2016).(18) This registry was compiled as part of the Lung-Protective Ventilation Initiated in the Emergency Department (LOV-ED) trial.(19) That investigation was a before-after study, which evaluated the effectiveness of an ED-based lung-protective mechanical ventilation protocol on reducing the incidence of pulmonary complications [ARDS and ventilator-associated conditions (VACs)]. This registry was previously used in a secondary analysis to evaluate the relationship between PaCO₂ and survival among a heterogeneous group of mechanically ventilated patients (i.e. not specifically patients with sepsis).(17)

Participants

We included patients enrolled in the LOV-ED trial with initiation of mechanical ventilation in the ED. Inclusion criteria were: 1) age ≥ 18 years; 2) mechanical ventilation via an endotracheal tube, 3) diagnosis of sepsis [i.e. presumed infection plus two systemic inflammatory response syndrome (SIRS) criteria].(20) Exclusion criteria were: 1) death or discontinuation of mechanical ventilation within 24 hours; 2) chronic mechanical ventilation; 3) presence of a tracheostomy; 4) transfer to another hospital; and 5) presence of acute respiratory distress syndrome (ARDS) during ED presentation.(21) This study was approved by the institutional review board under waiver of informed consent, and is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies.(22)

Procedures

Data on baseline demographics, comorbid conditions, illness severity [i.e. Acute Physiology and Chronic Health Evaluation II (APACHE)], and blood pressure were collected in the ED as part of the primary study. Pertinent treatment variables in the ED were also recorded. The results of cultures drawn for suspected sepsis along with the source of positive cultures were recorded. We recorded the initial arterial blood gas (ABG) analyses performed after the initiation of mechanical ventilation, as well as the initial mechanical ventilator variables. We also collected ICU ventilation settings twice daily for up to two weeks.

Static compliance (mL/ cm H₂O) of the respiratory system (C_{RS}) was calculated as: tidal volume/[plateau pressure – positive end expiratory pressure (PEEP)]. Driving pressure (cm H₂O) was calculated as: plateau pressure - PEEP. For purposes of these analyses the initial

measured plateau pressure, C_{RS} , and driving pressure were used. The corrected minute ventilation for a normal PaCO_2 (VE_{corr}) was used as a surrogate for dead space to account for changes in dead space as PaCO_2 increases. This correction factor has been similarly reported in previous studies.(10, 23) We calculated VE_{corr} as: initial minute ventilation $\times$ actual $\text{PaCO}_2/40$ mmHg.(10, 23) All data was exported into Stata/SE 14.1 for Mac, StataCorp LP (College Station, TX, USA) for analysis.

Statistical analysis

Categorical variables were compared using the chi-square test. Continuous variables were compared using student's t-test or Wilcoxon rank-sum test as appropriate based on the distribution of data. Spearman's correlation coefficient (r) was used to assess the relationship between PaCO_2 , and VE_{corr} and pH.

The primary outcome was survival to hospital discharge. To test the relationship between PaCO_2 after initiation of mechanical ventilation and survival to hospital discharge, a multivariable logistic regression model was constructed. PaCO_2 was entered into the model as a continuous variable. *A priori*, identification of candidate co-variables for inclusion in the model was performed in two steps. First, we included patient characteristics and illness severity that were statistically significant in univariate analysis at $p < 0.10$. All variables were entered into a model and backwards elimination with a criterion of $p < 0.05$ for retention in the model was used. We then added in ventilator variables with clinically relevant differences that were statistically significant in univariate analysis at $p < 0.10$. Again backwards elimination was used with a criterion of $p < 0.05$ for retention in the final model. Statistical interactions and collinearity were assessed. Goodness-of-fit of the final model was evaluated with the Hosmer-Lemeshow test. To test if our model was correctly specified we used the linktest command in Stata. We performed several additional subgroup analyses for the primary outcome using multivariable logistic regression modeling (Supplemental material).

To test if a threshold effect between PaCO_2 and survival existed, PaCO_2 was entered into a logistic regression model as a categorical variable using ascending ranges (i.e. < 35 , 35-45, 46-55, 56-65, > 65 mmHg), with 35-45 mmHg as the reference range. The model was adjusted for variables that were retained in the original model. Given PaCO_2 is the function of gas exchange and minute ventilation we also forced VE_{corr} and initial minute ventilation into this model. Odds ratios for ascending PaCO_2 ranges were graphed and this graph was visually inspected to assess if there was a threshold signal for survival over the PaCO_2 ranges. For all models, robust standard errors to reduce the risk of type I error was used.

Finally, we performed a sensitivity analysis calculating the average treatment effect for hypercapnia ($\text{PaCO}_2 > 45$ mmHg) compared to normocapnia (PaCO_2 35-45 mmHg) using propensity score matching. The propensity that a patient had hypercapnia (i.e. propensity score) was modeled using logistic regression as a function of the co-variables. We used co-variables, which were included in the original logistic regression model to determine the propensity score. We then performed, nearest neighbor matching [with 0.15 set as the largest absolute difference compatible with a valid match (i.e. caliper width)] on the basis of hypercapnia exposure (yes/no) and the propensity score to calculate the average treatment

effect for hypercapnia. We evaluated for covariate imbalance between the hypercapnia and matched normocapnia groups using Rubins' B (the absolute standardized difference of the means of the linear index of the propensity score in the hypercapnia and matched normocapnia groups) and Rubin's R (the ratio of the hypercapnia vs. matched normocapnia variances of the propensity score index). A Rubins' B <0.25 and a R between 0.5-2 is generally considered sufficiently balanced.(24)

Sample Size Calculation

For multivariable logistic modeling, it is common to assume an event per co-variable ratio of 10:1 is necessary to ensure adequate power.(25, 26) Our "event" in this study is non-survival to hospital discharge (i.e. the less frequent outcome). Based on the number of patients who did not survive to hospital discharge we were powered to evaluate 17 co-variables in a model.

Results

Six hundred patients met all inclusion and no exclusion criteria. Baseline characteristics of the entire cohort, as well as for survivors and non-survivors are shown in Table 1. The median (IQR) APACHE II score for the entire cohort was 17 (13-22). Non-survivors were more likely to have a malignancy compared to survivors. Non-survivors were also more likely to receive a vasopressor infusion, central venous catheter, or blood product transfusion.

Table 2 displays the post-intubation ventilator variables. The median (IQR) PaCO₂ for the entire cohort was 42 (34-53) mmHg. The median (IQR) was significantly higher among survivors compared to non-survivors [44 (35-57) vs. 39 (31-45) mmHg respectively, $p < 0.001$]. PaCO₂ was found to have a strong correlation with VECorr ($r = 0.81$, $p < 0.001$), but only a modest correlation with pH ($r = -0.48$, $p < 0.001$). Non-survivors and survivors had similar PaO₂ [148 (92-208) vs. 132 (88-204) respectively, $p = 0.128$].

Seventy-two percent (429/600) of subjects survived to hospital discharge. Table 3 displays the multivariable logistic regression model with PaCO₂ treated as a continuous variable and survival to hospital discharge as the dependent variable. After adjusting for all identified significant confounders, elevated PaCO₂ was an independent predictor of survival to hospital discharge [aOR 1.03, 95% confidence interval (CI) 1.01-1.04, $p = 0.001$]. Thus for every 1 mmHg rise in PaCO₂ the odds of survival to hospital discharge increased by 3%. Our final model was found to have good fit (Hosmer-Lemeshow test, $p = 0.73$), and to be correctly specified ($\hat{y}$, $p < 0.001$; $\hat{y}^2$, $p = 0.88$). These results remained consistent across multiple subgroup analyses (Supplemental material).

Figure 1 displays odds ratios for survival to hospital discharge across ascending ranges of PaCO₂. We found increased odds of survival to hospital discharge among all PaCO₂ ranges above 45 mmHg compared to the reference range of 35-45 mmHg, after adjusting for VECorr and initial minute ventilation.

Two hundred and thirty patients were found to have hypercapnia and 210 subjects had normocapnia. Survival to hospital discharge occurred in 83% vs. 68% of patients with hypercapnia vs normocapnia respectively ($p < 0.001$). Using propensity score matching, we were able to include 206 subjects in the normocapnia group and 221 in the hypercapnia group and found the average treatment effect for hypercapnia was 0.17 (95% CI 0.07-0.27, $p = 0.001$). This suggests that hypercapnia increased the probability of survival to hospital discharge by 17%. The Rubins B was 0.21 and Rubins R was 1.34.

Discussion

In this study we analyzed 600 mechanically ventilated sepsis patients and tested the association between PaCO_2 after initiation of mechanical ventilation and survival to hospital discharge. After adjusting for multiple potential confounders and performing propensity score matching we found higher PaCO_2 levels to be independently associated with survival to hospital discharge in this patient population. Given that elevated PaCO_2 can be a marker of minute ventilation, we adjusted our original model for initial tidal volume, and adjusted our sensitivity model for initial minute ventilation. When entered into the model with PaCO_2 , tidal volume was removed for non-significance, suggesting that the association between PaCO_2 and survival is independent of the tidal volume. Our findings remained consistent across several sensitivity and subgroup analyses, even when adjusted for other ventilator settings, severity of illness, and lactate acid production. These findings suggest hypercapnia during the initial mechanical ventilation period may be beneficial in patients with severe sepsis.

The effects of PaCO_2 among critically ill patients have been unclear. Several studies have suggested a beneficial effect of hypercapnia in the setting of sepsis. Hypercapnia has been demonstrated to attenuate key components of the over-amplified inflammatory pathways seen in sepsis, as well as to reduce the severity of lung injury. First, hypercapnia decreases tumor necrosis factor- α and interleukin (IL)-1 production, which contributes to tissue injury in septic patients.(27, 28) Second, hypercapnia attenuates neutrophil activity through lowered intracellular pH.(29, 30) Third, in pulmonary endothelial cells, hypercapnia decreases the DNA-binding activity of nuclear factor (NF)- κB , a regulator of pro-inflammatory pathways. This decreased binding attenuates IL-8 production, with a corresponding decrease in endothelial cell injury.(31) Fourth, hypercapnia has been demonstrated to reduce endogenous nitric oxide (NO).(15, 32, 33) Endogenous NO production resulting from high-pressure mechanical ventilation has been demonstrated to be harmful in models of endotoxemia.(34) In addition, hypercapnia suppression of endogenous NO production has been demonstrated to augment hypoxic pulmonary vasoconstriction, resulting in improved ventilation-perfusion matching.(33) Finally, hypercapnia can inhibit bacterial growth, thus decreasing the overall infectious insult.(16) In summary, our findings are biologically plausible and congruent with the pre-clinical data that demonstrates a potential beneficial role to manipulating PaCO_2 to improve outcome in septic patients.

Our results differ from previous observational studies of patients with community-acquired pneumonia, which found an association between hypercapnia and in-hospital mortality.(35, 36) However, it is possible that in these previous studies hypercapnia was a marker of

increased dead-space(37) (i.e. worse pneumonia) as opposed to the *cause* of poor outcomes. The strong correlation between PaCO₂ and V_Ecorr in our study, suggests elevated PaCO₂ could be a marker for dead-space. However, we entered V_Ecorr into our logistic regression model, as previously described,(10) and found when PaCO₂ and V_Ecorr were entered into the model together, V_Ecorr was not found to be significantly associated with survival (removed from the final model for non-significance). This suggests PaCO₂ was associated with survival independent of dead-space. A recent secondary analysis of three cohort studies found an association between severe hypercapnia (PaCO₂ > 50 mmHg) and mortality among patients with ARDS after adjusting for V_Ecorr.(10) Our study excluded patients with ARDS and it is likely that our cohort was less ill compared to those patients with ARDS upon presentation to the ED. The differences in the relationship between PaCO₂ and survival between these two studies may suggest PaCO₂ is associated with worse outcomes in patients who already have a high degree of lung injury and increased dead-space,(10, 35, 36) while conferring a beneficial effect on subjects at risk for severe lung injury.(14, 15, 38) In addition, patients with ARDS can have a higher degree of dead-space, which may not be completely corrected for by V_Ecorr.

This study has several limitations. First, this observational cohort study can only describe associations and cannot suggest causal inference. Although we used V_Ecorr as a marker for dead-space, there still remains the possibility that elevated PaCO₂ is a marker for dead-space and not independently associated with survival. However, given increased dead-space has been demonstrated to be associated with mortality in mechanically ventilated patients, the positive association between PaCO₂ and dead-space is unlikely to confound the association between PaCO₂ and survival in a positive direction. In addition, although we used multivariable logistic regression analyses to adjust for multiple potential confounders, there still exists the possibility that an unmeasured PaCO₂-associated confounder drove the observed association between hypercapnia and survival, thus our results must be interpreted with caution. Second, hypercapnia may also reflect a patient population that is less ill and therefore has a higher likelihood to survive. A higher APACHE II score in the hypercapnic group compared to the non-hypercapnic group [median (IQR) 19 (14-24) vs. 16 (12-21) respectively, $p < 0.001$] suggests that this was not the case. Third, we analyzed the initial PaCO₂ after mechanical ventilation as a surrogate for total post-intubation PaCO₂ exposure similar to methodologies used in previous studies of other disease processes.(39, 40) However, there was no standardization with respect to the time to analysis. While our study is representative of real-world care, it is possible that it does not accurately represent the true PaCO₂ exposure (i.e. measurement bias). Finally, although there was no association between initial pH and survival to hospital discharge, we did find a lower pH during ICU stay to be associated with increased in-hospital mortality. Given the interdependence of PaCO₂ and pH, any clinical intervention to intentionally maintain an elevation of PaCO₂ will lead to a lower pH, possibly negating some (if not all) of the potential benefit. However, we found only a moderate correlation between initial PaCO₂ and initial pH with an $r^2 = 0.23$, suggesting PaCO₂ is only responsible for 23% of the variation in pH. As such these findings should be considered hypothesis generating and further research is warranted to determine the clinical implications of targeting hypercapnia in this patient population.

Conclusion

In this cohort study of mechanically ventilated sepsis patients, we found increasing PaCO₂ levels are associated with increased survival to hospital discharge. These findings suggest that permissive hypercapnia is safe among patients diagnosed with sepsis in the ED and future clinical investigation into early manipulation of PaCO₂ in this patient population is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Adjusted odds ratios (circles) with 95% confidence intervals (horizontal lines) for survival to hospital discharge across ascending partial pressure of arterial carbon dioxide ranges.

*Odds ratios were calculated using multivariable logistic regression analysis (reference range 35-45 mmHg) adjusting for age, malignancy, initial total bilirubin, ED blood product administration, positive culture, intensive care unit (ICU) fraction of inspired oxygen, ICU pH, corrected minute ventilation for a normal PaCO₂ (VE_{corr}), and initial minute ventilation.

Table 1

Subject characteristics in the emergency department.

Variables	All Subjects n = 600	Survivors n = 429	Non-survivors n = 171	p - values
Age [mean (SD)]	61 (16)	60 (16)	65 (16)	<0.001
Female gender, n (%)	282 (47)	205 (48)	77 (45)	0.541
Race, n (%)				
Black	314 (52)	223 (52)	91 (53)	0.170
White	277 (46)	202 (47)	75 (44)	
Other	9 (2)	4 (1)	5 (3)	
Body mass index	27 (23-23)	27 (23-23)	25 (22-22)	0.020
Predicted body weight (kg)	65 (55-73)	66 (55-73)	64 (55-73)	0.929
Comorbidities, n (%)				
Chronic obstructive pulmonary disease	174 (29)	131 (31)	43(25)	0.189
Malignancy	131 (22)	76 (18)	55 (32)	<0.001
Congestive heart failure	168 (28)	124 (29)	44 (26)	0.435
Diabetes mellitus	229 (38)	170 (40)	59 (35)	0.243
End stage renal disease	53 (9)	33 (8)	20 (12)	0.119
Cirrhosis	46 (8)	28 (7)	18 (11)	0.096
APACHE II score	17 (13-13)	17 (13-13)	18 (14-14)	0.019
Mean arterial pressure (mmHg)	77 (63-97)	78 (63-97)	76 (63-98)	0.774
Hypotension (MAP < 65 mmHg), n (%)	169 (28)	117 (27)	52 (30)	0.441
ED Interventions				
IVF administration (L)	2 (1-1)	2 (1-1)	2 (1-1)	0.634
Vasopressor infusion, n (%)	215 (36)	143 (33)	72 (42)	0.043
Central line insertion, n (%)	267 (45)	178 (41)	89 (52)	0.019
Blood product administration, n(%)	78 (13)	37 (9)	41 (24)	<0.001
InitialLab values				
Creatinine (mg/dL)	1.36 (0.87-2.56)	1.35 (0.86-2.38)	1.45 (0.91-2.74)	0.167
Total bilirubin (mg/dL)	0.5 (0.3-0.9)	0.5 (0.3-0.9)	0.6 (0.4-1.0)	0.002
Platelets ($\times 10^3 / \mu\text{L}$)	207 (146-283)	217 (159-293)	175 (107-252)	<0.001
INR	1.3 (1.1-1.6)	1.2 (1.1-1.5)	1.4 (1.2-1.8)	<0.001
Albumin (g/dL)	3.1 (2.6-3.6)	3.2 (2.7-3.7)	2.8 (2.3-3.5)	<0.001
Culture positive, n (%)	470 (78)	328 (77)	142 (83)	0.085
Culture source, n (% of culture positive)				
Tracheal/BAL	268 (57)	198 (60)	70 (49)	0.026

Variables	All Subjects n = 600	Survivors n = 429	Non-survivors n = 171	p - values
Urine	104 (22)	79 (24)	25 (18)	0.120
Blood	142 (30)	84 (26)	58 (41)	0.001
CSF	8 (2)	6 (2)	2 (1)	0.746
Other	28 (6)	12 (4)	16 (11)	0.001

Continuous variables are reported as median (interquartile range) unless otherwise noted.

APACHE, acute physiology and chronic health evaluation; BAL, bronchoalveolar lavage; CSF, cerebral spinal fluid; ED, emergency department; INR, international normalized ratio; IVF, intravenous fluid; MAP, mean arterial pressure; SD, standard deviation.

Table 2
Post-intubation ventilator variables

Variables	All Subjects n = 600	Survivors n = 429	Non-survivors n = 171	p - values
Initial ventilator settings				
Tidal volume (mL/kg PBW)	7.3 (6.4-8.7)	7.3 (6.4-8.5)	7.6 (6.7-9.1)	0.063
Lung-protective tidal volume, ^a n (%)	378 (63)	274 (64)	104 (61)	0.485
Respiratory rate	16 (14-14)	16 (14-14)	15 (14-14)	0.182
Minute Ventilation (mL/kg PBW*min)	122 (105-141)	122 (104-144)	122 (105-140)	0.777
FiO ₂	100 (50-100)	100 (50-100)	100 (60-100)	0.010
PEEP	5 (5-5)	5 (5-5)	5 (5-5)	0.035
Initial arterial blood gas measurements				
pH	7.31 (7.22-7.40)	7.30 (7.21-7.39)	7.33 (7.24-7.42)	0.239
PaCO ₂ (mmHg)	42 (34-53)	44 (35-57)	39 (31-45)	<0.001
PaO ₂ (mmHg)	137 (89-204)	132 (88-204)	148 (92-208)	0.128
Hypoxia (PaO ₂ < 60 mmHg), n (%)	31 (5)	26 (6)	5 (3)	0.117
PaO ₂ / FiO ₂	211 (132-305)	212 (135-312)	206 (125-298)	0.371
Corrected minute ventilation (L/kg*min)	8.1 (6.2-10.8)	8.5 (6.5-11.3)	7.4 (5.9-9.2)	<0.001
Initial pulmonary Mechanics				
Plateau pressure (cm H ₂ O)	20 (17-17)	20 (17-17)	20 (17-17)	0.302
Plateau pressure >30 cm H ₂ O, n (%)	55 (9)	34 (8)	21 (12)	0.097
Static compliance (mL/ cm H ₂ O)	33 (26-46)	33 (26-46)	33 (25-46)	0.916
Driving pressure (cm H ₂ O)	15 (11-11)	15 (11-11)	15 (11-11)	0.558
Intensive care unit				
Tidal volume (mL/kg PBW)	8 (7-7)	8 (7-7)	8 (7-7)	0.329
Lung-protective tidal volume, ^a n (%)	396 (66)	284 (66)	112 (66)	0.870
FiO ₂	44 (40-51)	43 (40-49)	47 (41-59)	<0.001
PEEP	5 (5-5)	5 (5-5)	5 (5-5)	0.143
pH	7.39 (7.35-7.43)	7.39 (7.36-7.43)	7.37 (7.32-7.42)	0.002
Duration of mechanical ventilation (hours)	103 (52-197)	103 (52-197)	103 (52-194)	0.920

^a tidal volume of 8 mL/kg predicted body weight (PBW).

FiO₂, fraction of inspired oxygen; PaO₂, partial pressure of arterial oxygen; PaCO₂; partial pressure of arterial carbon dioxide; PEEP, positive end expiratory pressure;

Table 3

Final multivariable logistic regression model with partial pressure of arterial carbon dioxide (PaCO₂) entered as a continuous variable and survival to hospital discharge as the dependent variable.

Variables	Odds Ratio	95% CI	p-value
PaCO ₂	1.03	1.01 - 1.04	0.001
Age ^a	0.77	0.67 - 0.89	<0.001
Malignancy	0.41	0.26 - 0.65	<0.001
Initial total bilirubin	0.68	0.51 - 0.91	0.010
Blood product administered	0.47	0.26 - 0.86	0.013
Positive culture	0.56	0.34 - 0.93	0.025
ICU FiO ₂	0.96	0.94 - 0.98	<0.001
ICU pH	1.63	1.25 - 2.11	<0.001

^aCalibrated for a rise of 10 years. CI, confidence interval; ED, emergency department; FiO₂, fraction of inspired oxygen; ICU, intensive care unit

Removed for non-significance: ED Acute Physiology and Chronic Health Evaluation (APACHE) II score (p = 0.701); vasopressor infusion (p = 0.648); initial international normalized ratio (INR) (p = 0.566); body mass index (p = 0.528); liver cirrhosis (p = 0.494); central venous catheter insertion (p = 0.328); initial albumin (p = 0.074); corrected minute ventilation for a normal PaCO₂ (VEcorr) (p = 0.713); initial tidal volume (p = 0.618); initial positive end expiratory pressure (p = 0.169); initial FiO₂ (p = 0.357); initial platelets (p = 0.077); initial plateau pressure (p = 0.216).