The Association between Arterial Oxygen Tension, Hemoglobin Concentration, and Mortality in Mechanically Ventilated Critically Ill Patients

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Abstract

Background: Hypoxemia and anemia are common findings in critically ill patients admitted to Intensive Care Units. Both are independently associated with significant morbidity and mortality. However, the interaction between oxygenation and anemia and their impact on mortality in critically ill patients has not been clearly defined. We undertook this study to determine whether hemoglobin (Hb) level would modify the association between hypoxemia and mortality in mechanically ventilated critically ill patients. **Methods:** We performed a retrospective cohort study of all mechanically ventilated adult patients (aged >16 years) in the Australian and New Zealand Intensive Care Society Adult Patient Database (APD) admitted over a 10-year period. Multivariate hierarchical logistic regression was used to assess the relationship between hypoxemia and hospital mortality stratified by Hb. **Results:** Of 1,196,089 patients in the APD, 219,723 satisfied our inclusion and exclusion criteria. There was a linear negative relationship between hypoxemia and hospital mortality which was significantly modified when stratified by Hb. Hb independently increased the risk of mortality in patients with arterial oxygen tension <102. **Conclusions:** Hb is an effect modifier on the association between oxygenation and mortality.

Keywords: Anemia, blood gas analysis, critical illness, hypoxia, Intensive Care Units

INTRODUCTION AND OBJECTIVES

Delivery of oxygen to the tissues (DO₂) is a necessary condition for cellular respiration. DO₂ is determined by the product of cardiac output and arterial oxygen content (CaO₂). CaO₂ is determined by hemoglobin concentration (Hb, g/L), arterial oxygen tension (PaO₂, mmHg), and arterial oxygen saturation (SaO₂) as per the equation: $\text{CaO}_2 (\text{ml/L}) = (\text{SaO}_2 \times \text{Hb} [\text{g/L}] \times 1.37) + (\text{PaO}_2 [\text{mmHg}] \times 0.003)$. Hypoxemia^[1,2] and anemia^[3,4] are common among critically ill patients admitted to Intensive Care Units (ICUs). They are both associated with increased mortality.^[5,6] Hypoxemia is frequently treated with supplemental oxygen delivery and mechanical ventilation in ICUs.^[7] However, high fractional inspired oxygen^[8-10] (FiO₂) and possibly hyperoxemia^[1,2,11] have also been associated with increased mortality and morbidity. Anemia can be treated with red cell transfusion, but liberal transfusion strategies have also been associated with higher mortality and morbidity in ICU and non-ICU patients.^[12-15] Nonetheless, both supplemental oxygen and

red cell transfusion are frequently administered therapies for critically ill patients. A better understanding of the association between CaO₂ and mortality may help us better elucidate triggers and targets for these therapies and guide future trials of these therapies in critically ill patients. We undertook this study to investigate the interaction between hypoxemia, as characterized by PaO₂ and PaO₂/FiO₂ ratio (PFR), and Hb levels, and their association with hospital mortality in mechanically ventilated critically ill patients. Our hypothesis was that patients' Hb level would modify the relationship between oxygenation and mortality, specifically that the presence of lower Hb levels would increase the independent risk of death with increasing hypoxemia.

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METHODS

Study design

We performed a retrospective cohort study of all mechanically ventilated adult patients (aged >16 years) in the Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD) admitted between January 1, 2006 and December 31, 2015. The APD is one of four clinical quality registries run by the ANZICS Centre for Outcome and Resource Evaluation (CORE). The APD contained data submitted by 162 sites (ICUs) during the study. Cardiac surgical patients were excluded in accordance with previous studies that examined the relationship between hyperoxemia and mortality.^[1,2] Patients with repeat ICU admission for the same hospital admission and missing data for PaO₂, FiO₂, hospital mortality, and Hb were also excluded.

The FiO₂ and PaO₂ from the arterial blood gas analysis which produces the highest score from the Acute Physiology and Chronic Health Evaluation (APACHE III) Score are recorded in the APD. These are the FiO₂ and PaO₂ values used in our study. The PFR was calculated from these values. The PFR was included in this study as it may be a better marker of lung pathology causing hypoxemia than PaO₂ alone. The highest and lowest Hb (Hbhi and Hblo) in the first 24 h of ICU admission are recorded in the APD. We constructed separate models with Hbhi and Hblo in our study.

Data extraction

The following variables were extracted from the APD: demographic information, year of admission, admission status (elective or nonelective), admission source (operating theater, emergency department, ward, other hospital, other ICU), APACHE III diagnostic categories and chronic comorbidities, Glasgow coma score, vital status at ICU and hospital discharge and laboratory and physiological variables used in calculating APACHE III score, and Australian and New Zealand Risk of Death (ANZROD).

As we were interested in studying the effect of arterial oxygenation on mortality, we removed the oxygenation component of the APACHE III score and created an adjusted APACHE III score as described in a previous study.^[1]

Data access for the purposes of this study was approved by the ANZICS CORE Directorate. Ethics approval was obtained from the Prince Charles Hospital Human Research Ethics Committee (Approval number HREC/17/QPCH/193).

Statistical analysis

Analyses were performed using Stata 13.0 (StatsCorp LP, College Station, TX, USA) and Python in Anaconda (Continuum Analytics, Austin, TX, USA).

Continuous data were summarized as means (standard deviation [SD]) and medians (interquartile range [IQR]) for approximately normally distributed and skewed data, respectively. Categorical data were summarized as proportions. PaO₂ and PFR were divided into deciles and

Hb (both Hbhi and Hblo) was dichotomized by performing a median split. The PaO₂ 88–102 mmHg and PFR >477 deciles and the higher Hb group were defined as the reference groups for calculation of mortality.

The primary outcome measure was odds ratio (OR) with 95% confidence intervals of hospital mortality. A stringent $P = 0.001$ was used as the threshold of significance in the regression analysis to reduce false positive associations due to the large size of the dataset. Multivariate hierarchical logistic regression analysis was performed with patients nested within sites and sites treated as random effects. In the multivariate model, we adjusted for year of ICU admission,^[16] elective admission, adjusted APACHE III score, APACHE III diagnostic category, and FiO₂. Year of admission was initially fitted as a categorical variable, with a plan to fit it as a continuous variable if linearity was confirmed. We also adjusted for gender as the Hb distribution was expected to be different between the genders. Separate models were created to assess the effect of PaO₂ and PFR, entered as categorical variables using deciles, on mortality. In the PFR analysis, FiO₂ was removed from the multivariate model. To these two models, Hbhi and Hblo were added as continuous covariates to assess their effects on mortality. Interaction terms were created for admission year and PaO₂/PFR and for Hb (both Hbhi and Hblo) and PaO₂/PFR to check for effect modification. We planned to perform appropriate stratifications if we detected evidence of effect modification ($P < 0.001$ for the interaction term).

The C-statistic for area under receiver operating characteristic (AUROC) curve was calculated to assess model discrimination for each of the multivariate models.^[17] The Hosmer–Lemeshow goodness of fit test to assess model calibration was not used as our large sample size was likely to guarantee statistical significance.^[18]

RESULTS

Of 1,196,089 patients in the APD in our selected timeframe, 902,061 were excluded [Figure 1] as they were not mechanically ventilated (734,435, 61.4%), were readmissions to ICU (20,646, 1.7%), or were cardiac surgical admissions (146,980, 12.3%). 74,305 (16.1%) records were excluded due to missing data. This left a total of 219,723 (62%) patients who were included in this study.

The overall rate of hospital mortality [Table 1] was 21% (45,348/219,723) and ICU mortality was 15% (33,395/219,723). The average age was 58.6 years (SD: 19), with nonsurvivors being older (mean: 66.1 years, SD: 16) than survivors (mean: 56.6 years, SD: 19). The number of males was 128,443 (58%). The predicted median mortality from the ANZROD model was 0.087 (IQR: 0.024–0.29) with survivors having a significantly ($P < 0.001$) lower risk (median: 0.055, IQR: 0.017–0.16) than nonsurvivors (median: 0.47, IQR: 0.23–0.72). The median APACHE III score was 69 (IQR: 50–93) with survivors having a median of

63 (IQR: 46–82) and nonsurvivors 102 (IQR: 80–125). Mean PaO₂ was 159 mmHg (SD: 113) overall, 163 (SD: 114) for survivors and 146 (SD: 109) for nonsurvivors. Median PFR was 250 (IQR: 155–372) overall, 263 (IQR: 168–384) for survivors and 194 (IQR: 115–314) for nonsurvivors. Mean Hb was 108 g/L (SD: 23) overall, 109 (SD: 22) for survivors and 106 (SD: 26) for nonsurvivors.

Univariate logistic regression analysis revealed a U-shaped relationship between PaO₂ and OR of hospital mortality [Supplementary Appendix]. Mortality was highest with low PaO₂, but was also increased with PaO₂ >225 mmHg. Univariate analysis of PFR and hospital mortality showed increasing mortality with decreasing PFR, with a steep increase in mortality with PFR <174 [Supplementary Appendix].

In the multivariate models for PaO₂ [Figure 2] and PFR [Figure 3], there was a negative linear association between oxygenation and mortality. The U-shaped relationship observed for the association between PaO₂ and mortality did not persist in the multivariate model. Hb (either hbhi or Hblo), when added as a continuous model into the PaO₂ and PFR

models, was strongly associated with mortality ($P < 0.001$ in all four models). When the four models were fitted with the corresponding Hb-oxygenation interaction terms, there was strong evidence of effect modification with $P < 0.001$ in all four models. There was no evidence of effect modification when interaction terms for admission year and PaO₂ ($P = 0.02$) and admission year and PFR ($P = 0.03$) were added.

As effect modification was demonstrated when Hb interaction terms were introduced, the four models were stratified by Hb (entered as a dichotomous variable) to yield four final models [Figures 4-7]. All four models yielded very similar curves. In the highest six deciles (at PaO₂ >102 and PFR >210), there was an extensive overlap of the 95% CIs for OR of mortality between the Hb strata (in both the Hbhi and Hblo analyses). However, in the lowest four deciles (or at PaO₂ ≤102 and PFR ≤210), there was a clear separation between the two Hb strata with higher mortality with increasing hypoxemia in the lower Hb group.

The c-statistic for the two PaO₂ models was 0.8341 and for the PFR models was 0.8338, indicating good discrimination (for full regression model) [Supplementary Appendix].

Figure 1: Flowchart of patient selection

Figure 3: Odds ratio of mortality by arterial oxygen tension/fractional inspired oxygen ratio deciles with 95% confidence intervals

Figure 2: Odds ratio of mortality by arterial oxygen tension deciles with 95% confidence intervals

Figure 4: Odds ratio of mortality by arterial oxygen tension deciles stratified by hemoglobin (low) with 95% confidence intervals

Table 1: Patient characteristics

Patient characteristics	Total	Died	Survived
Number of patients	219,723		
ICU mortality (%)	219,467	33,395 (15)	186,072 (85)
Hospital mortality (%)	219,723	45,348 (21)	174,375 (79)
Age, mean (SD)	58.6 (19)	66.1 (16)	56.6 (19)
Males (%)	128,443 (58)	27,111 (21)	101,332 (79)
ANZROD risk of death, median (IQR)	0.087 (0.024-0.29)	0.47 (0.23-0.72)	0.055 (0.017-0.16)
APACHE 3 Score, median (IQR)	69 (50-93)	102 (80-125)	63 (46-82)
PaO ₂ (mmHg), mean (SD)	159 (113)	146 (109)	163 (114)
FiO ₂ , median (IQR)	0.5 (0.4-0.9)	0.6 (0.5-1)	0.5 (0.4-0.8)
PaO ₂ /FiO ₂ , median (IQR)	250 (155-372)	194 (115-314)	263 (168-384)
Hb (g/L), mean (SD)	10.8 (2.30)	10.6 (2.55)	10.9 (2.23)
Elective admission			
Yes	35,930	2767 (8)	33,163 (92)
No	182,726	42,490 (23)	140,236 (77)
ICU admission diagnostic group (%)			
Cardiovascular	28,080	12,138 (43)	15,942 (57)
Respiratory	36,075	7674 (21)	28,401 (79)
Neurological	7658	2359 (31)	5299 (69)
Gastrointestinal	20,944	5952 (28)	14,992 (72)
Hematology	641	311 (49)	330 (51)
Renal	1708	328 (19)	1380 (81)
Medical-other	46,935	7515 (16)	39,420 (84)
Surgical-respiratory	12,395	894 (7)	11,501 (93)
Surgical-gastrointestinal	36,799	4688 (13)	32,111 (87)
Surgical-neurological	9448	1795 (19)	7653 (81)
Surgical-other	18,323	1597 (9)	16,726 (91)
ICU admission source (%)			
OT	73,751	8493 (12)	65,258 (88)
ED	81,112	18,776 (23)	62,336 (77)
Ward	33,439	11,482 (34)	21,957 (66)
Other ICU, same hospital	569	174 (31)	395 (69)
Other hospital	27,600	5681 (21)	21,919 (79)
Other hospital ICU	3102	710 (23)	2392 (77)
Chronic comorbidity (%)			
Resp	20,217	5264 (26)	14,953 (74)
CVS	19,263	5899 (31)	13,364 (69)
Renal	6969	2403 (34)	4566 (66)
GIT	6227	2100 (34)	4127 (66)
GCS <15 (%)	119,772	32,971 (28)	86,801 (72)

ICU: Intensive Care Unit; ANZROD: Australian and New Zealand Risk of Death; IQR: Interquartile range; APACHE: Acute Physiology and Chronic Health Evaluation; SD: Standard deviation; OT: Operating theatre; ET: Emergency department; CVS: Cardiovascular system; GCS: Glasgow Coma Scale; Hb: Hemoglobin; Resp: Respiratory; CVS: Cardiovascular; Renal: Renal; GIT: Gastrointestinal Tract

DISCUSSION

Summary of findings

In our retrospective, multicenter study of critically ill mechanically ventilated patients admitted to Australian and New Zealand ICUs, we found that Hb significantly modified the association between hypoxemia, regardless of whether PaO₂ or PFR was studied, and hospital mortality. Specifically, lower Hb was an independent predictor of mortality in patients with PaO₂ ≤102 or PFR ≤210, but not in patients with PaO₂ >102 or PFR >210.

Comparisons with other literature

Hypoxemia is a common finding in critically ill patients,^[19]

known to be deleterious,^[20] and supplemental oxygen is frequently administered both for treatment and prophylaxis.^[21,22] The use of oxygen in a variety of critical illness and other acute conditions is recommended in various guidelines.^[22,23] Relative hypoxemia is however beneficial under some circumstances.^[24,25] Hyperoxemia is also associated with significant morbidity^[8,9,26] and possibly mortality^[27] though there are conflicting findings from large observational studies.^[1,2] Several recent randomized trials^[25,28,29] have also demonstrated increased mortality with liberal oxygen administration. Anemia is likewise commonly observed in critically ill patients^[3,4,30] and

Figure 5: Odds ratio of mortality by arterial oxygen tension deciles stratified by hemoglobin (high) with 95% confidence intervals

Figure 6: Odds ratio of mortality by arterial oxygen tension/fractional inspired oxygen ratio deciles stratified by hemoglobin (low) with 95% confidence intervals

Figure 7: Odds ratio of mortality by arterial oxygen tension/fractional inspired oxygen ratio deciles stratified by hemoglobin (high) with 95% confidence intervals

associated with increased morbidity, in the form of failure to liberate from mechanical ventilation,^[31] type 2 myocardial infarction,^[32] reintubation, overestimation of serum glucose resulting in hypoglycemia,^[33] and mortality.^[34,34] Red cell transfusion to treat anemia has been associated with a number of complications,^[35] including transfusion reactions, nosocomial infectious complications, transfusion-associated circulatory overload, transfusion-related lung injury, and

transfusion-related immunomodulation. Transfused blood may also cause sludging in capillaries, vasoconstriction due to free Hb, and reduced tissue oxygen delivery due to high oxygen affinity of the transfused blood.^[35] Most importantly, transfusion^[3,4] and liberal transfusion strategies^[12,13,36] have also been associated with increased mortality. However, both treatments are extensively administered to critically ill patients^[3,4,37,38] and the ideal triggers and targets are unknown. An understanding of the interaction between PaO₂ and Hb, a surrogate for CaO₂, may assist in determining which patients would most benefit from oxygen therapy and transfusions. To our knowledge, ours is the first investigation of this interaction between PaO₂ and Hb, a surrogate for CaO₂, and their association with mortality among critically ill mechanically ventilated patients.

Significance

We have shown that Hb acts as an effect modifier on the association between hypoxemia and mortality. This indicates that the effect of hypoxemia on mortality should be studied in Hb strata for patients with PFR ≤ 210 or PaO₂ ≤ 102 . Due to the limitations of our study as explained below, these findings are not practice changing and should be considered hypothesis generating.

Strengths and limitations

This was a large retrospective cohort study of 219,723 critically ill mechanically ventilated patients from Australian and New Zealand ICUs over a 10-year period. It is highly likely to be representative of the patient group we intended to study. The data were sourced from a well-established binational high-quality database that has been extensively interrogated for quality assurance and research purposes. This is the first study of its kind to investigate the association between PaO₂, Hb, and mortality in critically ill patients.

However, we were limited by the nature of the data that was available. This was a retrospective, observational study and we were only able to demonstrate association rather than causation. SaO₂, which is necessary to calculate CaO₂, was not available. We only had the Hbhi and Hblo and oxygenation from the blood gas that was used for the APACHE III scoring algorithm within the first 24 h of ICU admission. It remains possible that changes in PaO₂ and Hb over the course of an ICU admission may affect mortality. We did not study patients with missing data for PaO₂, Hb, and mortality. There may be systematic differences between these patients and those we included, possibly introducing bias. Treatment data, such as transfusions, mode and targets of oxygen therapy, and modes of ventilation and other therapeutic data were not available and hence may introduce another layer of bias.

Future research

We suggest that future research on the use of oxygen and red cell transfusions in critically ill patients should use our findings for the purpose of prognostic enrichment,^[39] i.e., to better target the patient groups who would most benefit from liberal and restrictive uses of these commonly administered therapies.

As we lacked SaO₂ data, we could not calculate the actual CaO₂. We also did not have data beyond the first 24 h of ICU admission. Therefore, prospective observational studies of CaO₂ over the course of entire ICU admissions would be valuable to shed further light on this topic.

CONCLUSIONS

In this retrospective cohort study of 219,723 mechanically ventilated critically ill patients, we report that Hb was an effect modifier on the relationship between hypoxemia and mortality. The effect of hypoxemia on mortality should be studied and reported in Hb strata. Future studies should focus on the association between CaO₂ and mortality and on tailoring triggers and targets for oxygen and transfusion therapy to the higher-risk group we have identified.

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Conflicts of interest

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Figure 1: Unadjusted odds ratio of mortality by arterial oxygen tension

Model 1: Unadjusted model of PaO ₂ on mortality				
PaO ₂	n	OR	Lower 95% CI	Upper 95% CI
<65	21,352	1.43	1.37	1.49
65-75	21,188	1.09	1.04	1.13
76-87	22,720	1.03	0.99	1.07
88-102	22,335	1	1	1
103-120	21,764	0.87	0.83	0.91
121-143	21,755	0.76	0.73	0.8
144-176	22,221	0.69	0.66	0.72
177-225	22,434	0.66	0.63	0.69
226-323	21,872	0.72	0.68	0.75
>324	22,082	0.77	0.74	0.81

CI: Confidence interval; OR: Odds ratio

Model 2: Unadjusted model of PaO ₂ /FiO ₂ ratio on mortality				
PFR	n	OR	Lower 95% CI	Upper 95% CI
<99	21,741	4.48	4.27	4.7
99-137	22,179	2.88	2.77	2.99
138-173	21,931	2.17	2.08	2.26
174-210	21,788	1.84	1.77	1.93
211-250	22,095	1.67	1.6	1.75
251-294	22,050	1.49	1.42	1.56
295-344	22,019	1.39	1.33	1.46
345-402	21,956	1.31	1.25	1.37
403-476	21,856	1.17	1.12	1.23
>477	22,108	1	1	1

CI: Confidence interval; OR: Odds ratio; PFR: PaO₂/FiO₂ ratio

Figure 2: Unadjusted odds ratio of mortality by arterial oxygen tension/fractional inspired oxygen ratio

Model 3: Multivariate mixed-effects logistic regression of PaO₂ on mortality adjusted for admission year, gender, elective admission, diagnostic group, Acute Physiology and Chronic Health Evaluation III score without oxygenation score and FiO₂

Covariate	n	OR	Lower 95% CI	Upper 95% CI
PaO ₂				
<65	21,352	1.49	1.41	1.57
65-75	21,188	1.22	1.16	1.29
76-87	22,720	1.08	1.02	1.13
88-102	22,335	1		
103-120	21,764	0.94	0.89	0.99
121-143	21,755	0.86	0.82	0.91
144-176	22,221	0.81	0.76	0.85
177-225	22,434	0.78	0.74	0.82
226-323	21,872	0.73	0.69	0.77
>324	22,082	0.65	0.62	0.69
Admission year (OR change per year)		0.98	0.97	0.98
Male gender		1.03	1	1.05
Elective admission		0.71	0.68	0.75
Diagnostic group				
Cardiovascular	28,080	1		
Respiratory	36,075	0.85	0.81	0.88
Neurological	7658	0.85	0.79	0.9
Gastrointestinal	20,944	1.3	1.24	1.36
Hematology	641	1.5	1.25	1.8
Renal	1708	0.39	0.34	0.45
Medical-other	46,935	0.49	0.47	0.51
Surgical-respiratory	12,395	0.5	0.46	0.55
Surgical-gastrointestinal	36,799	0.61	0.58	0.63
Surgical-neurological	9448	1.37	1.28	1.46
Surgical-other	18,323	0.45	0.42	0.48
APACHE III Score (without oxygenation score; OR change per 1 point change in score)		1.04	1.04	1.04
FiO ₂ (OR change per 0.1 increase in FiO ₂)		1.08	1.08	1.09
AUROC	c=0.8331			

APACHE: Acute Physiology and Chronic Health Evaluation; AUROC: Area under receiver operating characteristic; CI: Confidence interval; OR: Odds ratio

Model 4: Multivariate mixed-effects logistic regression of PaO₂/FiO₂ ratio on mortality adjusted for admission year, gender, elective admission, diagnostic group and Acute Physiology and Chronic Health Evaluation III score without oxygenation score

Covariate	n	OR	Lower 95% CI	Upper 95% CI
PaO ₂ /FiO ₂ ratio				
<99	21,741	2.29	2.15	2.43
99-137	22,179	1.88	1.8	1.98
138-173	21,931	1.64	1.56	1.73
174-210	21,788	1.52	1.44	1.6
211-250	22,095	1.41	1.34	1.49
251-294	22,050	1.33	1.26	1.4
295-344	22,019	1.28	1.21	1.36
345-402	21,956	1.22	1.15	1.29
403-476	21,856	1.15	1.08	1.22
>477	22,108	1		
Admission year (OR change per year)		0.98	0.97	0.98
Male gender		1.02	1	1.05
Elective admission		0.72	0.6	0.75
Diagnostic group				
Cardiovascular		1		
Respiratory		0.86	0.83	0.9
Neurological		0.85	0.79	0.9

Contd...

Model 4: Contd...				
Covariate	<i>n</i>	OR	Lower 95% CI	Upper 95% CI
Gastrointestinal		1.31	1.25	1.37
Hematology		1.51	1.26	1.81
Renal		0.39	0.34	0.45
Medical-other		0.49	0.47	0.51
Surgical-respiratory		0.51	0.47	0.55
Surgical-gastrointestinal		0.6	0.57	0.63
Surgical-neurological		1.36	1.28	1.46
Surgical-other		0.45	0.42	0.48
APACHE III Score (without oxygenation score; OR change per 1 point change in score)		1.04	1.04	1.04
AUROC	c=0.8329			
APACHE: Acute Physiology and Chronic Health Evaluation; AUROC: Area under receiver operating characteristic; CI: Confidence interval; OR: Odds ratio				

Model 5: Multivariate mixed-effects logistic regression of PaO₂ on mortality stratified by hemoglobin lowest and adjusted for admission year, gender, elective admission, diagnostic group, Acute Physiology and Chronic Health Evaluation III score without oxygenation score and FiO₂

Covariate	Mean Hb	<i>n</i>	OR	Lower 95% CI	Upper 95% CI
PaO ₂					
<65	89.3	10,025	1.81	1.68	1.94
65-75	89.3	9733	1.49	1.38	1.6
76-87	89.3	10,520	1.33	1.24	1.43
88-102	89.3	10,548	1.16	1.08	1.25
103-120	89.3	10,454	1.1	1.02	1.19
121-143	89.3	10,690	0.99	0.91	1.06
144-176	89.3	11,157	0.94	0.88	1.02
177-225	89.3	11,629	0.92	0.86	0.99
226-323	89.3	11,546	0.84	0.78	0.91
>324	89.3	12,087	0.74	0.68	0.79
<65	126.4	11,327	1.42	1.32	1.52
65-75	126.4	11,455	1.17	1.08	1.25
76-87	126.4	12,200	1.01	0.94	1.09
88-102	126.4	11,787	1		
103-120	126.4	11,310	0.93	0.87	1.01
121-143	126.4	11,065	0.87	0.81	0.94
144-176	126.4	11,064	0.8	0.74	0.86
177-225	126.4	10,805	0.75	0.69	0.81
226-323	126.4	10,326	0.74	0.68	0.8
>324	126.4	9995	0.67	0.62	0.73
Admission year (OR change per year)			0.98	0.97	0.98
Male gender			1.05	1.02	1.08
Elective admission			0.71	0.67	0.75
Diagnostic group					
Cardiovascular			1		
Respiratory			0.83	0.79	0.86
Neurological			0.79	0.74	0.85
Gastrointestinal			1.31	1.25	1.37
Hematology			1.36	1.13	1.64
Renal			0.36	0.31	0.41
Medical-other			0.47	0.45	0.49
Surgical-respiratory			0.48	0.4	0.52
Surgical-gastrointestinal			0.57	0.54	0.6
Surgical-neurological			1.33	1.24	1.42
Surgical-other			0.42	0.39	0.45
APACHE III Score (without oxygenation score; OR change per 1 point change in score)			1.04	1.04	1.04

Contd...

Model 5: Contd...					
Covariate	Mean Hb	n	OR	Lower 95% CI	Upper 95% CI
FiO ₂ (OR change per 0.1 increase in FiO ₂)			1.09	1.08	1.09
AUROC		c=0.8341			

APACHE: Acute Physiology and Chronic Health Evaluation; AUROC: Area under receiver operating characteristic; CI: Confidence interval; OR: Odds ratio; Hb: Hemoglobin

Model 6: Multivariate mixed-effects logistic regression of PaO ₂ on mortality stratified by hemoglobin highest and adjusted for admission year, gender, elective admission, diagnostic group, Acute Physiology and Chronic Health Evaluation III score without oxygenation score and FiO ₂					
Covariate	Mean Hb	n	OR	Lower 95% CI	Upper 95% CI
PaO ₂					
<65	101.3	10,147	1.87	1.74	2.01
65-75	101.3	9872	1.54	1.43	1.65
76-87	101.3	10,647	1.38	1.28	1.48
88-102	101.3	10,528	1.22	1.14	1.31
103-120	101.3	10,473	1.12	1.04	1.21
121-143	101.3	10,837	1.03	0.95	1.11
144-176	101.3	11,326	0.95	0.88	1.02
177-225	101.3	11,643	0.95	0.88	1.02
226-323	101.3	11,498	0.85	0.79	0.92
>324	101.3	11,952	0.74	0.68	0.8
<65	137.7	11,205	1.43	1.34	1.54
65-75	137.7	11,316	1.18	1.1	1.27
76-87	137.7	12,073	1.02	0.95	1.1
88-102	137.7	11,807	1		
103-120	137.7	11,291	0.96	0.89	1.03
121-143	137.7	10,918	0.87	0.81	0.94
144-176	137.7	10,895	0.83	0.77	0.9
177-225	137.7	10,791	0.76	0.71	0.83
226-323	137.7	10,374	0.76	0.7	0.82
>324	137.7	10,130	0.7	0.64	0.76
Admission year (OR change per year)			0.98	0.97	0.98
Male gender			1.05	1.02	1.08
Elective admission			0.71	0.67	0.75
Diagnostic group					
Cardiovascular			1		
Respiratory			0.83	0.79	0.86
Neurological			0.79	0.74	0.85
Gastrointestinal			1.31	1.25	1.37
Hematology			1.36	1.13	1.64
Renal			0.36	0.31	0.41
Medical-other			0.47	0.45	0.49
Surgical-respiratory			0.48	0.4	0.52
Surgical-gastrointestinal			0.57	0.54	0.6
Surgical-neurological			1.33	1.24	1.42
Surgical-other			0.42	0.39	0.45
APACHE III Score (without oxygenation score; OR change per 1 point change in score)			1.04	1.04	1.04
FiO ₂ (OR change per 0.1 increase in FiO ₂)			1.09	1.08	1.09
AUROC		c=0.8341			

APACHE: Acute Physiology and Chronic Health Evaluation; AUROC: Area under receiver operating characteristic; CI: Confidence interval; OR: Odds ratio; Hb: Hemoglobin

Model 7: Multivariate mixed-effects logistic regression of PaO₂/FiO₂ ratio on mortality stratified by hemoglobin lowest and adjusted for admission year, gender, elective admission, diagnostic group and Acute Physiology and Chronic Health Evaluation III score without oxygenation score

Covariate	Mean Hb	n	OR	Lower 95% CI	Upper 95% CI
PaO ₂ /FiO ₂ ratio					
<99	89.3	10,607	2.83	2.61	3.07
99-137	89.3	10,583	2.22	2.08	2.37
138-173	89.3	10,430	1.92	1.79	2.05
174-210	89.3	10,278	1.77	1.65	1.9
211-250	89.3	10,581	1.55	1.44	1.67
251-294	89.3	10,903	1.51	1.4	1.62
295-344	89.3	11,192	1.45	1.35	1.56
345-402	89.3	11,395	1.35	1.26	1.46
403-476	89.3	11,454	1.27	1.18	1.37
>477	89.3	10,966	1.07	0.99	1.16
<99	126.4	11,134	2.31	2.17	2.47
99-137	126.4	11,596	1.83	1.71	1.96
138-173	126.4	11,501	1.53	1.43	1.64
174-210	126.4	11,510	1.38	1.28	1.48
211-250	126.4	11,514	1.34	1.25	1.44
251-294	126.4	11,147	1.22	1.13	1.31
295-344	126.4	10,827	1.18	1.1	1.28
345-402	126.4	10,561	1.17	1.08	1.26
403-476	126.4	10,402	1.12	1.03	1.21
>477	126.4	11,142	1		
Admission year (OR change per year)			0.98	0.97	0.98
Male gender			1.05	1.02	1.08
Elective admission			0.71	0.67	0.75
Diagnostic group					
Cardiovascular			1		
Respiratory			0.83	0.8	0.87
Neurological			0.79	0.74	0.84
Gastrointestinal			1.3	1.24	1.36
Hematology			1.36	1.13	1.63
Renal			0.36	0.31	0.41
Medical-other			0.47	0.45	0.49
Surgical-respiratory			0.47	0.44	0.51
Surgical-gastrointestinal			0.56	0.54	0.59
Surgical-neurological			1.32	1.23	1.41
Surgical-other			0.42	0.39	0.45
APACHE III Score (without oxygenation score; OR change per 1 point change in score)			1.04	1.04	1.04
AUROC		c=0.8338			

APACHE: Acute Physiology and Chronic Health Evaluation; AUROC: Area under receiver operating characteristic; CI: Confidence interval; OR: Odds ratio; Hb: Hemoglobin

Model 8: Multivariate mixed-effects logistic regression of PaO₂/FiO₂ ratio on mortality stratified by hemoglobin highest and adjusted for admission year, gender, elective admission, diagnostic group and Acute Physiology and Chronic Health Evaluation III score without oxygenation score

Covariate	Mean Hb	<i>n</i>	OR	Lower 95% CI	Upper 95% CI
PaO ₂ /FiO ₂ ratio					
<99	101.3	10,130	2.81	2.59	3.05
99-137	101.3	10,438	2.25	2.1	2.4
138-173	101.3	10,444	1.91	1.78	2.05
174-210	101.3	10,402	1.74	1.62	1.87
211-250	101.3	10,764	1.54	1.44	1.66
251-294	101.3	11,100	1.41	1.31	1.52
295-344	101.3	11,401	1.41	1.31	1.51
345-402	101.3	11,566	1.28	1.19	1.38
403-476	101.3	11,656	1.23	1.14	1.33
>477	101.3	11,022	1.01	0.93	1.1
<99	137.7	11,611	2.23	2.09	2.38
99-137	137.7	11,741	1.73	1.61	1.85
138-173	137.7	11,487	1.46	1.36	1.57
174-210	137.7	11,386	1.33	1.24	1.43
211-250	137.7	11,331	1.27	1.18	1.37
251-294	137.7	10,950	1.24	1.15	1.33
295-344	137.7	10,618	1.15	1.07	1.25
345-402	137.7	10,390	1.17	1.08	1.27
403-476	137.7	10,200	1.09	1.01	1.18
>477	137.7	11,086	1		
Admission year (OR change per year)			0.98	0.97	0.98
Male gender			1.05	1.02	1.08
Elective admission			0.71	0.67	0.75
Diagnostic group					
Cardiovascular			1		
Respiratory			0.83	0.8	0.87
Neurological			0.79	0.74	0.84
Gastrointestinal			1.3	1.24	1.36
Hematology			1.36	1.13	1.63
Renal			0.36	0.31	0.41
Medical-other			0.47	0.45	0.49
Surgical-respiratory			0.47	0.44	0.51
Surgical-gastrointestinal			0.56	0.54	0.59
Surgical-neurological			1.32	1.23	1.41
Surgical-other			0.42	0.39	0.45
APACHE III Score (without oxygenation score; OR change per 1 point change in score)			1.04	1.04	1.04
AUROC		c=0.8338			

APACHE: Acute Physiology and Chronic Health Evaluation; AUROC: Area under receiver operating characteristic; CI: Confidence interval; OR: Odds ratio; Hb: Hemoglobin