Research Article

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: CaO2 (ml/L) = (SaO2 × Hb [g/L] × 1.37) + (PaO2 [mmHg] × 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].

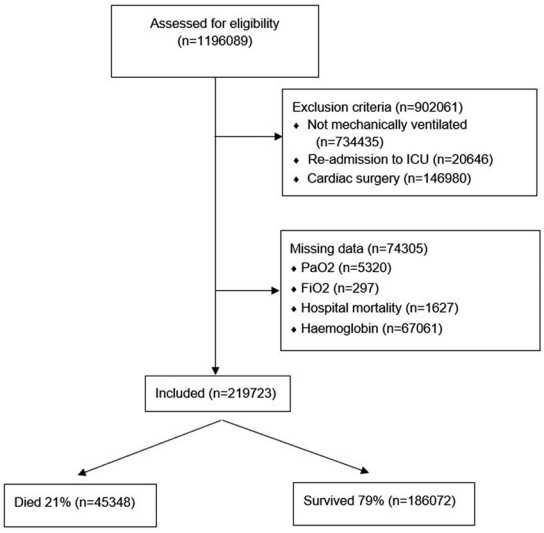

Figure 1: Flowchart of patient selection

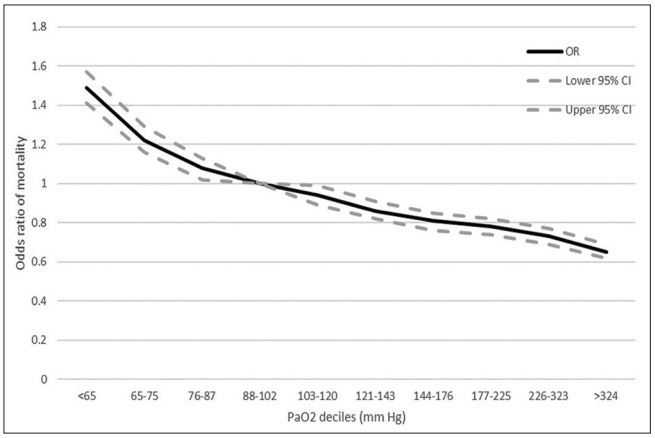

Figure 2: Odds ratio of mortality by arterial oxygen tension deciles with 95% confidence intervals

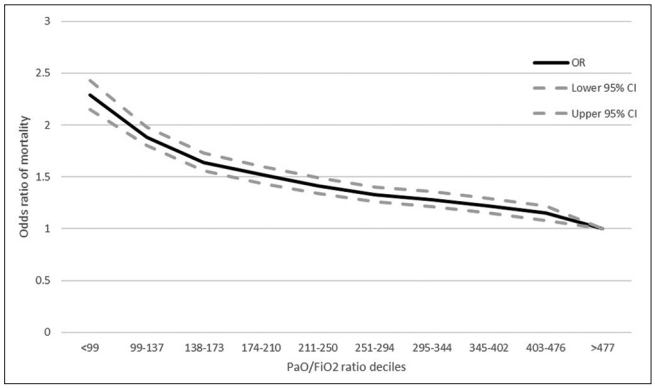

Figure 3: Odds ratio of mortality by arterial oxygen tension/fractional inspired oxygen ratio deciles with 95% confidence intervals

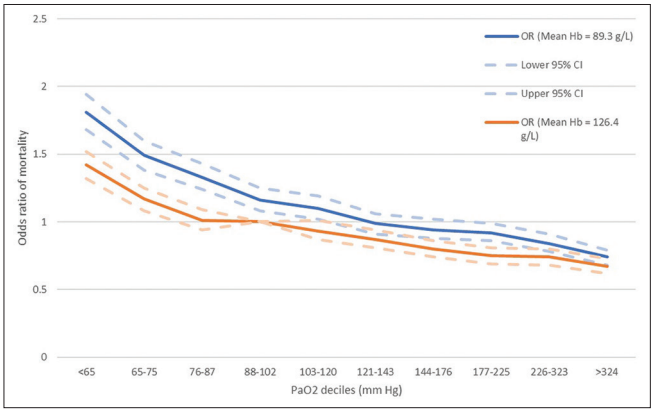

Figure 4: Odds ratio of mortality by arterial oxygen tension deciles stratified by hemoglobin (low) with 95% confidence intervals

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: Gastrotintestinal 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

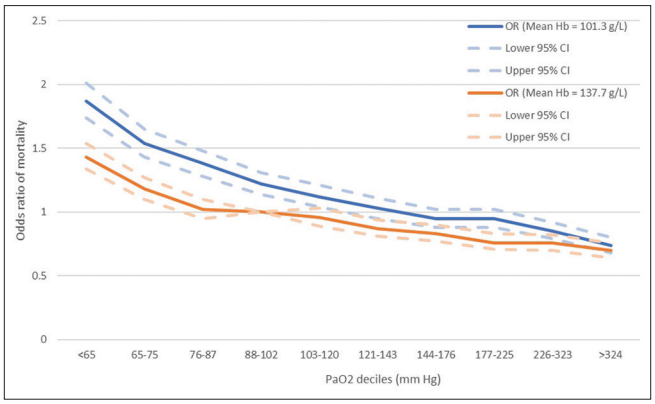

Figure 5: Odds ratio of mortality by arterial oxygen tension deciles stratified by hemoglobin (high) with 95% confidence intervals

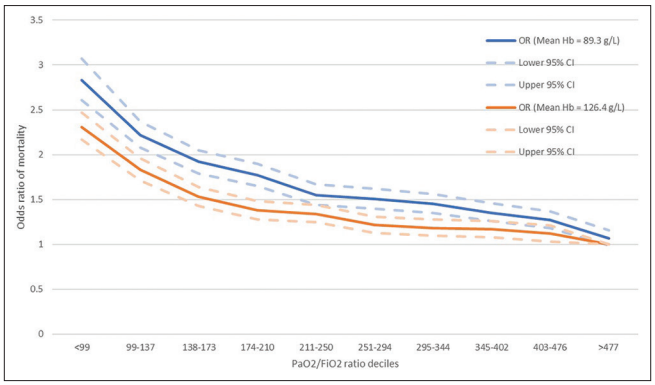

Figure 6: Odds ratio of mortality by arterial oxygen tension/fractional inspired oxygen ratio deciles stratified by hemoglobin (low) with 95% confidence intervals

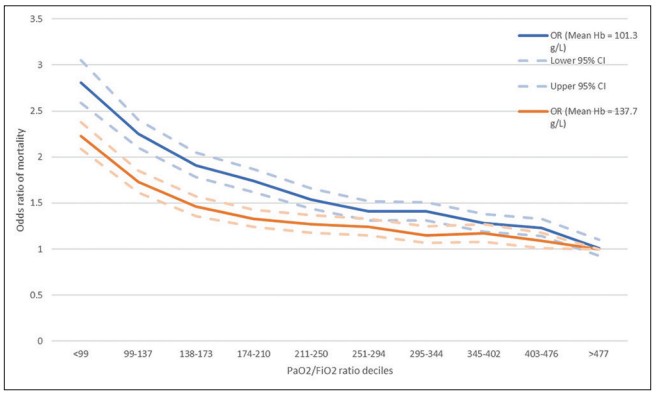

Figure 7: Odds ratio of mortality by arterial oxygen tension/fractional inspired oxygen ratio deciles stratified by hemoglobin (high) with 95% confidence intervals

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.[3,4,34] 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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Hospital (Adelaide) ICU, Campbelltown Hospital ICU, Canberra Hospital ICU, Central Gippsland Health Service ICU, Christchurch Hospital ICU, Coffs Harbour Health Campus ICU, Concord Hospital (Sydney) ICU, Dandenong Hospital ICU, Dubbo Base Hospital ICU, Dunedin Hospital ICU, Epworth Eastern Private Hospital ICU, Epworth Freemasons Hospital ICU, Epworth Hospital (Richmond) ICU, Figtree Private Hospital ICU, Flinders Medical Centre ICU, Flinders Private Hospital ICU, Footscray Hospital ICU, Frankston Hospital ICU, Fremantle Hospital ICU, Gold Coast University Hospital ICU, Gosford Hospital ICU, Gosford Private Hospital ICU, Goulburn Base Hospital ICU, Goulburn Valley Health ICU, Grafton Base Hospital ICU, Greenslopes Private Hospital ICU, Griffith Base Hospital ICU, Hawkes Bay Hospital ICU, Hervey Bay Hospital ICU, Hollywood Private Hospital ICU, Holy Spirit Northside Hospital ICU, Hornsby Ku-ring-gai Hospital ICU, Hutt Hospital ICU, Ipswich Hospital ICU, John Fawkner Hospital ICU, John Flynn Private Hospital ICU, John Hunter Hospital ICU, Joondalup Health Campus ICU, Knox Private Hospital ICU, Latrobe Regional Hospital ICU, Launceston General Hospital ICU, Lismore Base Hospital ICU, Liverpool Hospital ICU, Logan Hospital ICU, Lyell McEwin Hospital ICU, Mackay Base Hospital ICU, Macquarie University Private Hospital ICU, Manly Hospital and Community Health ICU, Manning Rural Referral Hospital ICU, Maroondah Hospital ICU, Mater Adults Hospital (Brisbane) ICU, Mater Health Services North Queensland ICU, Mater Private Hospital (Brisbane) ICU, Mater Private Hospital (Sydney) ICU, Melbourne Private Hospital ICU, Mersey Community Hospital ICU, Middlemore Hospital ICU, Mildura Base Hospital ICU, Modbury Public Hospital ICU, Monash Medical Centre-Clayton Campus ICU, Mount Hospital ICU, Mount Isa Hospital ICU, Nambour General Hospital ICU, Nambour Selangor Private Hospital ICU, National Capital Private Hospital ICU, Nelson Hospital ICU, Nepean Hospital ICU, Newcastle Private Hospital ICU, Noosa Hospital ICU, North Shore Hospital ICU, North Shore Private Hospital ICU, North West Regional Hospital (Burnie) ICU, Northeast Health Wangaratta ICU, Norwest Private Hospital ICU, Orange Base Hospital ICU, Peninsula Private Hospital ICU, Peter MacCallum Cancer Institute ICU, Pindara Private Hospital ICU, Port Macquarie Base Hospital ICU, Prince of Wales Hospital (Sydney) ICU, Prince of Wales Private Hospital (Sydney) ICU, Princess Alexandra Hospital ICU, Queen Elizabeth II Jubilee Hospital ICU, Redcliffe Hospital ICU, Repatriation General Hospital (Adelaide) ICU, Robina Hospital ICU, Rockhampton Hospital ICU, Rockingham General Hospital ICU, Rotorua Hospital ICU, Royal Adelaide Hospital ICU, Royal Brisbane and Women's Hospital ICU, Royal Darwin Hospital ICU, Royal Hobart Hospital ICU, Royal Melbourne Hospital ICU, Royal North Shore Hospital ICU, Royal Perth Hospital ICU, Royal Prince Alfred Hospital ICU, Shoalhaven Hospital ICU, Sir Charles Gairdner Hospital ICU, 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Hospital ICU, Taranaki Health ICU, Tauranga Hospital ICU, The Memorial Hospital (Adelaide) ICU, The Northern Hospital ICU, The Prince Charles Hospital ICU, The Queen Elizabeth (Adelaide) ICU, The Sunshine Coast Private Hospital ICU, The Townsville Hospital ICU, The Valley Private Hospital ICU, The Wesley Hospital ICU, Timaru Hospital ICU, Toowoomba Hospital ICU, Tweed Heads District Hospital ICU, University Hospital

Geelong ICU, Wagga Wagga Base Hospital and District Health ICU, Waikato Hospital ICU, Warringal Private Hospital ICU, Wellington Hospital ICU, Western District Health Service (Hamilton) ICU, Westmead Hospital ICU, Westmead Private Hospital ICU, Whangarei Area Hospital, Northland Health Ltd ICU, Wimmera Health Care Group (Horsham) ICU, Wollongong Hospital ICU, Wyong Hospital ICU.

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Conflicts of interest

There are no conflicts of interest.

References

1. Eastwood G, Bellomo R, Bailey M, Taori G, Pilcher D, Young P, *et al.* Arterial oxygen tension and mortality in mechanically ventilated patients. Intensive Care Med 2012;38:91-8.
2. de Jonge E, Peelen L, Keijzers PJ, Joore H, de Lange D, van der Voort PH, *et al.* Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated Intensive Care Unit patients. Crit Care 2008;12:R156.
3. Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Abraham E, *et al.* The CRIT study: Anemia and blood transfusion in the critically ill – Current clinical practice in the United States. Crit Care Med 2004;32:39-52.
4. Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, *et al.* Anemia and blood transfusion in critically ill patients. JAMA 2002;288:1499-507.
5. Hébert PC, Wells G, Tweeddale M, Martin C, Marshall J, Pham B, *et al.* Does transfusion practice affect mortality in critically ill patients? Transfusion requirements in critical care (TRICC) investigators and the Canadian critical care trials group. Am J Respir Crit Care Med 1997;155:1618-23.
6. Carson JL, Duff A, Poses RM, Berlin JA, Spence RK, Trout R, *et al.* Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. Lancet 1996;348:1055-60.
7. Esteban A, Anzueto A, Alía I, Gordo F, Apezteguía C, Pálizas F, *et al*. How is mechanical ventilation employed in the Intensive Care Unit? An international utilization review. Am J Respir Crit Care Med 2000;161:1450-8.
8. Crapo JD, Hayatdavoudi G, Knapp MJ, Fracica PJ, Wolfe WG, Piantadosi CA, *et al.* Progressive alveolar septal injury in primates exposed to 60% oxygen for 14 days. Am J Physiol 1994;267:L797-806.
9. Fracica PJ, Knapp MJ, Piantadosi CA, Takeda K, Fulkerson WJ, Coleman RE, *et al.* Responses of baboons to prolonged hyperoxia: Physiology and qualitative pathology. J Appl Physiol (1985) 1991;71:2352-62.
10. Altemeier WA, Sinclair SE. Hyperoxia in the Intensive Care Unit: Why more is not always better. Curr Opin Crit Care 2007;13:73-8.
11. Damiani E, Adrario E, Girardis M, Romano R, Pelaia P, Singer M, *et al.* Arterial hyperoxia and mortality in critically ill patients: A systematic review and meta-analysis. Crit Care 2014;18:711.
12. Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, *et al.* A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion requirements in critical care investigators, Canadian critical care trials group. N Engl J Med 1999;340:409-17.
13. Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S, *et al.* Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med 2014;371:1381-91.
14. Chatterjee S, Wetterslev J, Sharma A, Lichstein E, Mukherjee D. Association of blood transfusion with increased mortality in myocardial infarction: A meta-analysis and diversity-adjusted study sequential analysis. JAMA Intern Med 2013;173:132-9.
15. Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: A systematic review of the literature. Crit Care Med 2008;36:2667-74.
16. ANZICS Management Committee. ANZICS Centre for Outcome and Resource Evaluation Adult Patient Database (APD) Activity Report 2015-2016; 2016.
17. Pencina MJ, D'Agostino RB Sr. Evaluating discrimination of risk prediction models: The C statistic. JAMA 2015;314:1063-4.
18. Meurer WJ, Tolles J. Logistic regression diagnostics: Understanding how well a model predicts outcomes. JAMA 2017;317:1068-9.
19. Ridler N, Plumb J, Grocott M. Oxygen therapy in critical illness: Friend or foe? A review of oxygen therapy in selected acute illnesses. J Intensive Care Soc 2014;15:190-8.
20. Hopkins RO, Weaver LK, Pope D, Orme JF, Bigler ED, Larson-Lohr V, *et al.* Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. Am J Respir Crit Care Med 1999;160:50-6.
21. Eastwood GM, Reade MC, Peck L, Jones D, Bellomo R. Intensivists' opinion and self-reported practice of oxygen therapy. Anaesth Intensive Care 2011;39:122-6.
22. O'Driscoll BR, Howard LS, Davison AG; British Thoracic Society. BTS guideline for emergency oxygen use in adult patients. Thorax 2008;63 Suppl 6:vi1-68.
23. Beasley R, Chien J, Douglas J, Eastlake L, Farah C, King G, *et al.* Thoracic society of Australia and New Zealand oxygen guidelines for acute oxygen use in adults: 'Swimming between the flags'. Respirology 2015;20:1182-91.
24. Austin MA, Wills KE, Blizzard L, Walters EH, Wood-Baker R. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: Randomised controlled trial. BMJ 2010;341:c5462.
25. Stub D, Smith K, Bernard S, Nehme Z, Stephenson M, Bray JE, *et al.* Air versus oxygen in ST-segment-elevation myocardial infarction. Circulation 2015;131:2143-50.
26. Zwemer CF, Whitesall SE, D'Alecy LG. Hypoxic cardiopulmonary-cerebral resuscitation fails to improve neurological outcome following cardiac arrest in dogs. Resuscitation 1995;29:225-36.
27. Kilgannon JH, Jones AE, Shapiro NI, Angelos MG, Milcarek B, Hunter K, *et al.* Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA 2010;303:2165-71.
28. Girardis M, Busani S, Damiani E, Donati A, Rinaldi L, Marudi A, *et al.* Effect of conservative vs conventional oxygen therapy on mortality among patients in an Intensive Care Unit: The oxygen-ICU randomized clinical trial. JAMA 2016;316:1583-9.
29. Meyhoff CS, Wetterslev J, Jorgensen LN, Henneberg SW, Høgdall C, Lundvall L, *et al*. Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery: The PROXI randomized clinical trial. JAMA 2009;302:1543-50.
30. Thomas J, Jensen L, Nahirniak S, Gibney RT. Anemia and blood transfusion practices in the critically ill: A prospective cohort review. Heart Lung 2010;39:217-25.
31. Khamiees M, Raju P, DeGirolamo A, Amoateng-Adjepong Y, Manthous CA. Predictors of extubation outcome in patients who have successfully completed a spontaneous breathing trial. Chest 2001;120:1262-70.
32. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. Eur Heart J 2007;28:2525-38.
33. Karon BS, Griesmann L, Scott R, Bryant SC, Dubois JA, Shirey TL, *et al.* Evaluation of the impact of hematocrit and other interference on the accuracy of hospital-based glucose meters. Diabetes Technol Ther 2008;10:111-20.
34. Rasmussen L, Christensen S, Lenler-Petersen P, Johnsen SP. Anemia and 90-day mortality in COPD patients requiring invasive mechanical ventilation. Clin Epidemiol 2010;3:1-5.
35. Hayden SJ, Albert TJ, Watkins TR, Swenson ER. Anemia in critical illness: Insights into etiology, consequences, and management. Am J Respir Crit Care Med 2012;185:1049-57.
36. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, *et al.* Transfusion strategies for acute upper gastrointestinal

bleeding. N Engl J Med 2013;368:11-21.
37. Vincent JL, Sakr Y, Sprung C, Harboe S, Damas P; Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators, *et al*. Are blood transfusions associated with greater mortality rates? Results of the Sepsis Occurrence in Acutely Ill Patients study. Anesthesiology 2008;108:31-9.
38. O'Driscoll BR, Howard LS, Bucknall C, Welham SA, Davison AG; British Thoracic Society, *et al.* British Thoracic Society emergency oxygen audits. Thorax 2011;66:734-5.
39. Bhatt DL, Mehta C. Adaptive designs for clinical trials. N Engl J Med 2016;375:65-74.