# Differences in mortality based on worsening ratio of partial pressure of oxygen to fraction of inspired oxygen corrected for immune system status and respiratory support

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## ABSTRACT

**Objective:** To define the relationship between worsening oxygenation status (worst $PaO_2/FiO_2$ ratio in the first 24 hours after intensive care unit admission) and mortality in immunosuppressed and immunocompetent ICU patients in the presence and absence of mechanical ventilation.

**Design:** Retrospective cohort study.

**Setting:** Data were extracted from the Australian and New Zealand Intensive Care Society Adult Patient Database.

**Participants:** Adult patients admitted to 129 ICUs in Australasia, 2000–2010.

**Main outcome measures:** Inhospital and ICU mortality; relationship between mortality and declining $PaO_2/FiO_2$ ratio by ventilation status and immune status.

**Results:** 457 750 patient records were analysed. Worsening oxygenation status was associated with increasing mortality in all groups. Higher mortality was seen in immunosuppressed patients than immunocompetent patients. After multivariate analysis, in mechanically ventilated patients, declining $PaO_2/FiO_2$ ratio in the first 24 hours of ICU admission was associated with a more rapidly rising mortality rate in immunosuppressed patients than non-immunosuppressed patients. Immunosuppression did not affect the relationship between oxygenation status and mortality in non-ventilated patients.

**Conclusion:** Immunosuppression increases the risk of mortality with progressively worsening oxygenation status, but only in the presence of mechanical ventilation. Further research into the impact of mechanical ventilation in immunosuppressed patients is required.


Crit Care Resusc 2012; 14: 25–32

Respiratory failure in immunosuppressed patients carries a high mortality, particularly if mechanical ventilation is required.[1-8] One study found a mortality rate in the order of 85%–90% in this population.[3] Mechanical ventilation for longer than 4 days has been noted to be a particularly strong negative prognostic marker.[8] It is unknown whether this is due to the severity of the underlying condition leading to immunosuppression, to the severity of overall acute physiological disturbance, directly to hypoxia, or to an adverse effect of ventilation itself. The use of non-invasive ventilation may be associated with improved outcomes.[9,10] However, the impact of oxygenation status itself (independent from overall severity of illness) on mortality has been less well described in these patients.

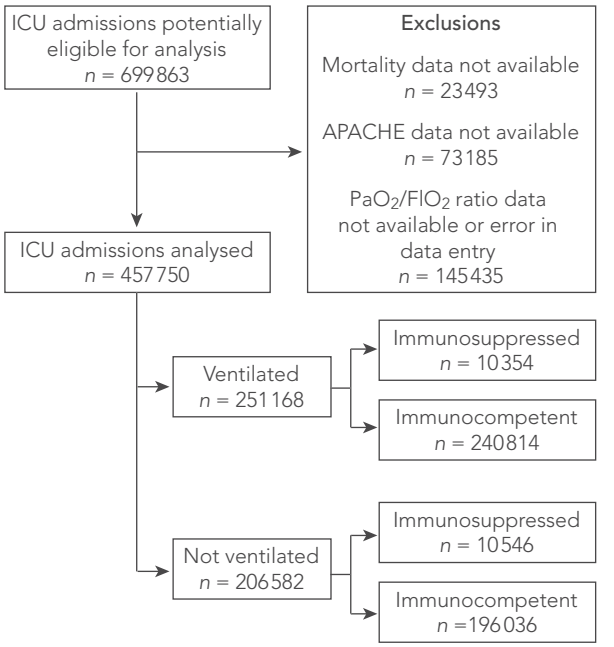
Originally described in 1974 by Horovitz and colleagues,[11] the $PaO_2/FiO_2$ ratio is used in the estimation of shunt fraction,[12-15] stratification of acute lung injury and acute respiratory distress syndrome,[16,17] and classification of primary graft dysfunction in lung transplantation,[18] and is a commonly used respiratory index to describe oxygenation status in the intensive care unit. Despite its widespread use, the relationship between $PaO_2/FiO_2$ ratio and mortality has not been consistently demonstrated across several studies,[19-22] and the influence of immunosuppression on the nature of this relationship has not been previously defined. However, two recent large studies designed to specifically examine hyperoxia demonstrated increasing mortality at lower $PaO_2/FiO_2$ ratios.[23,24]

Our objective was to describe the association between worsening oxygenation status, using the $PaO_2/FiO_2$ ratio, and mortality in immunosuppressed patients admitted to ICU, and to assess the impact of mechanical ventilation on this relationship using data from the Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD). The ANZICS APD records demographic, severity of illness and outcome data from adult ICU admissions at submitting hospitals in Australia, New Zealand and Hong Kong. It records the immune status of the patient, required for calculation of the chronic health components of the Acute Physiology and Chronic Health Evaluation (APACHE) II and III-j illness severity scoring systems. APACHE III-j is the 10th iteration of APACHE III, released into the public domain in 2002. Also recorded is information from arterial blood gases taken in the first 24 hours of the ICU stay.

We had three hypotheses:

- After correction for severity of illness and changes over time, worsening oxygenation status (defined by the $PaO_2/FiO_2$ ratio in the first 24 hours of ICU) will correlate with increasing mortality.

**Figure 1. Flow diagram of study population and subgroup division**




APACHE = Acute Physiology and Chronic Health Evaluation.
ICU = intensive care unit.

- Worsening oxygenation status will have a relatively greater effect on mortality risk in immunosuppressed patients.
- The relationship between worsening oxygenation status and mortality will be independent of the requirement for mechanical ventilation.

## Methods

Ethics approval was granted by the Alfred Hospital Ethics Committee (approval no. 234/11). Data were extracted from the ANZICS APD. All patients admitted to ICU between 2000 and 2010 were considered.

### Data included

Patients were identified as immunosuppressed if they had been classified by any one of the following codes: "Immunosuppressed by Disease", "Immunosuppressed by Therapy", or "AIDS". Clinicians at the submitting sites in Australia, New Zealand and Hong Kong allocate patients to these codes as defined by the ANZICS APD data dictionary[25] before submission of data.

Sites record all arterial blood gas measurements during the first 24 hours of ICU admission in a standard data collection system. In accordance with the APACHE III scoring system, the most abnormal set of arterial blood gas measurements by analysis of simultaneous recordings of the $FiO_2$ and $PaO_2$ are entered in the database. If the $FiO_2$ is $\geq 0.5$, the $PaO_2$ associated with the highest alveolar–arterial (A–a) gradient is selected, and if the $FiO_2$ is $< 0.5$, the measurement with the lowest $PaO_2$ is selected. If arterial blood gas measurements are taken on both an $FiO_2$ $< 0.5$ and an $FiO_2 \geq 0.5$ during the first 24 hours, the $PaO_2$ derived from measurements taken on $\geq 0.5$ is used in preference to those taken on $< 0.5$.

In our study, this $PaO_2$ value was defined as the "worst" $PaO_2$ and the $PaO_2/FiO_2$ ratio was calculated from the accompanying $FiO_2$ value. If the patient is receiving invasive mechanical ventilation when arterial blood gases are taken, this is also noted. This allows definition of a population of patients who received mechanical ventilation during the first 24 hours of ICU admission.

Readmission episodes to ICU, patients ineligible for scoring by APACHE III-j (age < 16 years and ICU length of stay < 4 hours), and patients whose eventual outcome was unknown due to transfer to another ICU (standard practice for ANZICS), were not eligible for inclusion in the study cohort. Patients with no chronic health variables (and therefore immune status) listed, no recorded outcome, missing APACHE III-j scores, missing ventilation status, missing $PaO_2$ or $FiO_2$ variables, or in whom the $PaO_2/FiO_2$ ratio was greater than 650 (assumed to be erroneous) were excluded from the analysis.

About 85% of all ICU admissions in Australia are included in the APD. Data are collected under the quality assurance legislation of Part VC of the *Health Insurance Act 1973* (Cwlth). Such data are collected with government support and funding and are submitted on behalf of each ICU director. Each hospital allows subsequent use as appropriate under the ANZICS Centre for Outcome and Resource Evaluation (CORE) standing procedures and in compliance with the ANZICS CORE terms of reference.

### Statistical analysis

The primary outcomes for analysis were hospital and ICU mortality. Following initial patient selection, eligible participants were divided into cohorts ("ventilated" or "not ventilated") based on whether or not they received mechanical ventilation in the first 24 hours of ICU admission. All analyses were performed using SAS, version 9.2 (SAS Institute Inc, Cary, NC, USA). Continuous data were compared using Wilcoxon rank-sum tests and are presented as median (interquartile range [IQR]). Categorical data were compared using $\chi^2$ tests for equal proportion and are reported as number (%).

The relationship between mortality and $PaO_2/FiO_2$ ratio was determined using logistic regression with $PaO_2/FiO_2$

**Table 1. Characteristics of immunosuppressed and immunocompetent patients who did and did not receive ventilation in the first 24 hours of intensive care***

| | Not ventilated | | Ventilated | |
|---|---|---|---|---|
| | Immunosuppressed | Immunocompetent | Immunosuppressed | Immunocompetent |
| Demographic data | | | | |
| Total no. | 10 546 | 196 036 | 10 354 | 240 814 |
| Median age in years (IQR) | 64 (53–73.5) | 66.4 (52.1–76.8) | 63 (51–73) | 64 (48.4–74.9) |
| Male, no. (%) | 5578 (52%) | 110 702 (56%) | 5557 (53%) | 151 558 (62%) |
| Elective surgery, no. (%) | 3521 (33%) | 93 378 (47%) | 2294 (22%) | 89 141 (37%) |
| Haematological malignancy (leukaemia, lymphoma), no. (%) | 2122 (19%) | 2407 (0.01%) | 2018 (19%) | 1853 (1%) |
| AIDS, no. (%) | 95 (< 1%) | 0 | 134 (1%) | 0 |
| No. requiring immunosuppressive therapy (%) | 6312 (69%) | 0 | 7192 (69%) | 436 (0.2%) |
| Clinical parameters, median (IQR) | | | | |
| $FiO_2$ | 0.40 (0.30–0.50) | 0.40 (0.28–0.50) | 0.60 (0.5–1.0) | 0.59 (0.4–1.0) |
| $PaO_2$, mmHg | 93 (73–127) | 98 (77–133) | 106 (77–172) | 119 (84–195) |
| $PaO_2/FiO_2$ ratio | 260 (165–397) | 287 (195–388) | 207 (122–318) | 243 (157–352) |
| $PaCO_2$, mmHg | 38 (33–45) | 41 (36–46) | 41 (35–49) | 41 (36–47) |
| pH | 7.38 (7.31–7.43) | 7.36 (7.3–7.40) | 7.31 (7.21–7.39) | 7.33 (7.26–7.4) |
| Haematocrit, % | 0.3 (0.27–0.36) | 0.34 (0.29–0.39) | 0.29 (0.26–035) | 0.32 (0.27–0.38) |
| Platelet count, $\times 10^9$/L | 170 (88–248) | 196 (146–254) | 156 (81–237) | 171 (122–229) |
| White cell count, $\times 10^9$/L | 8.9 (5.0–13.1) | 9.9 (7.4–13.0) | 9.4 (5.3–14) | 9.9 (7.3–3.1) |
| Outcome data | | | | |
| Intensive care unit mortality, no. (%) | 1043 (10%) | 8247 (4%) | 2696 (26%) | 31 734 (13%) |
| Inhospital mortality, no. (%) | 2140 (20%) | 16405 (8%) | 3778 (36%) | 43 847 (18%) |
| Median APACHE III-j predicted risk of death (IQR) | 0.12 (0.03–0.35) | 0.03 (0.01–0.12) | 0.29 (0.08–0.65) | 0.07 (0.01–0.31) |
| Median adjusted APACHE III-j predicted risk of death (IQR) | 0.10 (0.03–0.29) | 0.03 (0.01–0.10) | 0.19 (0.05–0.52) | 0.05 (0.01–0.24) |

APACHE = Acute Physiology and Chronic Health Evaluation. *$P < 0.001$ for all values.

ratio divided into increments of 50 (< 50, 50–99, 100–149, etc, to 600) and results reported as odds ratios (95% CI). The reference category for the presentation of odds ratios was the highest $PaO_2/FiO_2$ ratio (550–600). To determine whether the relationship between mortality and $PaO_2/FiO_2$ ratio differed significantly between immunosuppressed and immunocompetent patients, an interaction term was fitted between $PaO_2/FiO_2$ ratio and immunosuppression.

To establish that any observed effects were not due to either patient severity or changes over time, multivariate models were created adjusting for patient severity and year of admission. To facilitate a measure of severity that was independent of both arterial oxygenation and immune status, an adjusted APACHE III-j risk of death score was calculated whereby the components relating to oxygen and immune system status were removed. A two-sided $P < 0.05$ was considered to be statistically significant.

## Results

Between the years 2000 and 2010, 699 863 patient records were submitted to the ANZICS APD. Of these, 242 133 patients were deemed ineligible, either due to missing data or presumed incorrect data entry. Of the remaining 457 750 patients, 20 900 were immunosuppressed (Figure 1).

Basic characteristics of the non-ventilated and ventilated groups comparing immunocompetent to immunosuppressed patients are shown in Table 1. The immunosuppressed patients in both non-ventilated and ventilated cohorts were younger, less likely to have been admitted after elective surgery, and had higher predicted

**Table 2. Raw mortality and adjusted odds ratios for inhospital mortality by $PaO_2/FiO_2$ ratio category in patients who did not receive mechanical ventilation in the first 24 hours after intensive care unit admission**

| | Immunosuppressed | | Immunocompetent | |
|---|---|---|---|---|
| $PaO_2/FiO_2$ ratio | No. (%) | Adjusted odds ratio (95% CI) | No. (%) | Adjusted odds ratio (95% CI) |
| < 50 | 47 (51.65%) | 3.59 (1.81–7.15) | 293 (27.10%) | 4.04 (3.17–5.15) |
| 50–99 | 418 (44.61%) | 3.61 (2.18–5.96) | 2407 (23.96%) | 3.73 (3.14–4.45) |
| 100–149 | 436 (32.66%) | 2.15 (1.31–3.54) | 2950 (11.29%) | 2.61 (2.21–3.10) |
| 150–199 | 345 (23.08%) | 1.47 (0.89–2.43) | 2593 (8.82%) | 2.11 (1.78–2.51) |
| 200–249 | 311 (20.56%) | 1.36 (0.83–2.43) | 1942 (6.42%) | 1.72 (1.45–2.04) |
| 250–299 | 223 (15.31%) | 0.99 (0.59–1.64) | 1591 (5.60%) | 1.34 (1.13–1.60) |
| 300–349 | 176 (12.89%) | 0.93 (0.55–1.54) | 1223 (5.35%) | 1.23 (1.03–1.47) |
| 350–399 | 133 (12.24%) | 0.93 (0.55–1.56) | 853 (4.49%) | 1.19 (1.00–1.42) |
| 400–449 | 99 (11.57%) | 0.85 (0.50–1.45) | 540 (4.20%) | 1.03 (0.86–1.23) |
| 450–499 | 52 (9.14%) | 0.72 (0.40–1.27) | 319 (3.92%) | 1.01 (0.84–1.22) |
| 500–549 | 44 (12.50%) | 0.99 (0.55–1.81) | 199 (4.01%) | 0.98 (0.80–1.20) |
| 550–600 | 16 (7.62%) | 0.64 (0.31–1.33) | 225 (3.85%) | 1.02 (0.81–1.28) |

**Table 3. Raw mortality and adjusted odds ratios for intensive care unit mortality by $PaO_2/FiO_2$ ratio category in patients who did not receive mechanical ventilation in the first 24 hours after ICU admission**

| | Immunosuppressed | | Immunocompetent | |
|---|---|---|---|---|
| $PaO_2/FiO_2$ ratio | No. (%) | Adjusted odds ratio (95% CI) | No. (%) | Adjusted odds ratio (95% CI) |
| < 50 | 29 (31.18%) | 5.60 (2.05–15.30) | 210 (19.16%) | 7.19 (5.13–10.07) |
| 50–99 | 273 (29.20%) | 7.02 (2.95–16.69) | 1608 (16.09%) | 6.36 (4.82–8.40) |
| 100–149 | 244 (18.28%) | 3.73 (1.59–8.86) | 1825 (9.45%) | 4.01 (3.04–5.29) |
| 150–199 | 190 (12.68%) | 2.86 (1.20–6.81) | 1565 (6.02%) | 3.03 (2.30–4.00) |
| 200–249 | 142 (9.45%) | 1.95 (0.82–4.69) | 1187 (4.05%) | 2.07 (1.57–2.73) |
| 250–299 | 81 (5.53%) | 1.19 (0.49–2.89) | 854 (2.82%) | 1.62 (1.21–2.13) |
| 300–349 | 66 (4.84%) | 1.20 (0.48–4.94) | 665 (2.34%) | 1.39 (1.05–1.85) |
| 350–399 | 48 (4.41%) | 1.21 (0.49–3.00) | 487 (2.13%) | 1.29 (0.96–1.72) |
| 400–449 | 30 (3.50%) | 1.05 (0.41–2.66) | 340 (1.79%) | 1.17 (0.87–1.57) |
| 450–499 | 19 (3.50%) | 1.08 (0.41–2.87) | 198 (1.54%) | 1.02 (0.75–1.37) |
| 500–549 | 16 (4.56%) | 1.52 (0.55–4.15) | 134 (1.64%) | 1.16 (0.83–1.62) |
| 550–600 | 7 (3.30%) | 1.16 (0.36–3.69) | 74 (1.33%) | 1.04 (0.71–1.52) |

and observed mortality than their immunocompetent counterparts. They had lower white cell counts and lower platelet counts.

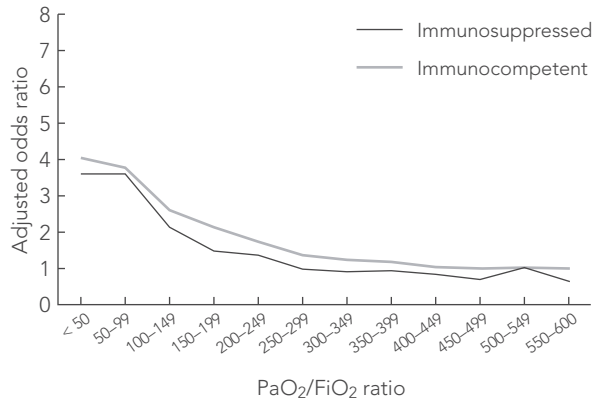
### Univariate analysis: mortality at different levels of $PaO_2/FiO_2$ ratio

Table 2 and Table 3 show observed mortality by $PaO_2/FiO_2$ ratio category. Increasing mortality was seen with decreasing $PaO_2/FiO_2$ ratios. Mortality in immunosuppressed patients was higher than in immunocompetent patients at all levels of $PaO_2/FiO_2$ ratio.

### Multivariate analysis

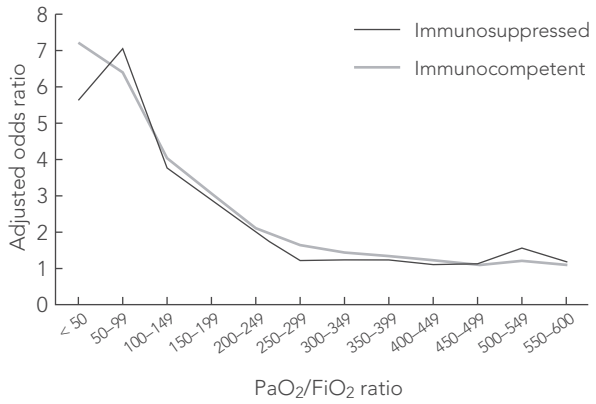
After adjustment for severity of illness, among patients not receiving mechanical ventilation, there was no evidence to suggest that the relationship between mortality and $PaO_2/FiO_2$ ratio differed between immunosuppressed and immunocompetent patients. This was determined by non-significant interaction between $PaO_2/FiO_2$ ratio and immunosuppression for inhospital mortality ($P = 0.13$) and ICU mortality ($P = 0.24$), and can be observed in Figure 2 and Figure 3 where immunosuppressed and immunocompetent patients can be seen to behave similarly across the range of $PaO_2/FiO_2$ ratios for hospital and ICU mortality.

**Figure 2. Inhospital mortality for non-ventilated patients**



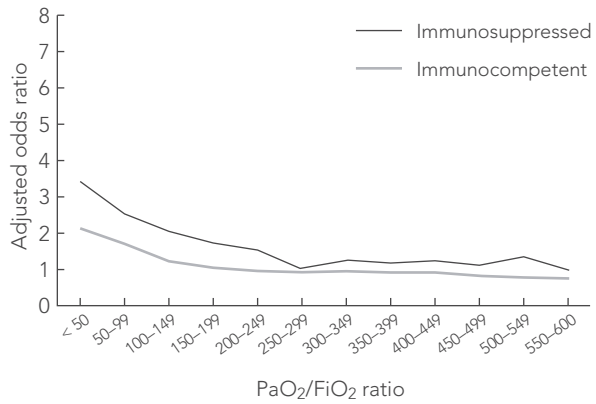

*Note the similar relationship with decreasing $PaO_2/FiO_2$ ratio between immunosuppressed and immunocompetent patients.*

**Figure 3. Intensive care unit mortality for non-ventilated patients**



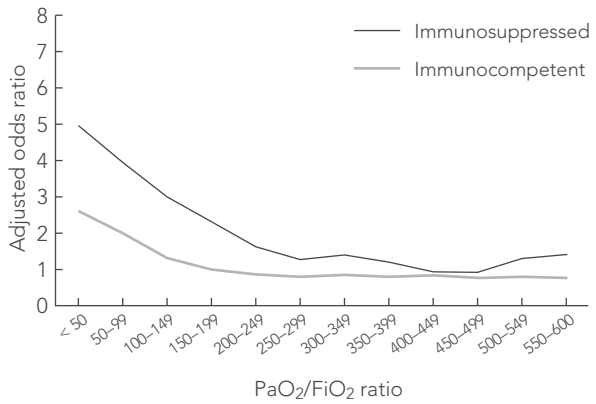

*The similar relationship with decreasing $PaO_2/FiO_2$ ratio continues between immunosuppressed and immunocompetent patients.*

**Figure 4. Inhospital mortality for ventilated patients**




*As $PaO_2/FiO_2$ ratio decreases, immunosuppressed patients have a worse prognosis than immunocompetent patients.*

**Figure 5. Intensive care unit mortality for ventilated patients**




*$PaO_2/FiO_2$ ratio decreases, immunosuppressed patients have a worse prognosis than immunocompetent patients.*

In ventilated patients, the nature of the relationship between mortality and $PaO_2/FiO_2$ ratio differed with immunosuppression status. This was reflected by a significant interaction between $PaO_2/FiO_2$ ratio and immunosuppression for inhospital mortality ($P=0.01$) and ICU mortality ($P<0.001$) and can be observed in Figure 4 and Figure 5, where immunosuppressed and immunocompetent patients' mortality rates can be seen to behave differently. This difference is most apparent for $PaO_2/FiO_2$ ratios below 250. As the $PaO_2/FiO_2$ ratio dropped, the adjusted risk of death increased, with this increase being more notable among patients who are immunosuppressed. However, in both groups, the $PaO_2/FiO_2$ ratio was independently associated with an increased risk of mortality only when the ratio was below 150.

Table 2 and Table 3 (non-ventilated) and Table 4 and Table 5 (ventilated) show the adjusted odds ratios with 95% confidence intervals for each $PaO_2/FiO_2$ ratio category for immunosuppressed and immunocompetent patients, as well as raw mortality.

## Discussion

We found that worsening oxygenation status is associated with increased mortality. Among patients who do not receive mechanical ventilation in the first 24 hours of ICU admission, this relationship is not significantly different between immunosuppressed and immunocompetent patients. Among patients who received mechanical ventila-

**Table 4. Raw mortality and adjusted odds ratios for inhospital mortality by $PaO_2/FiO_2$ ratio category in patients who received mechanical ventilation in the first 24 hours after intensive care unit admission**

| | Immunosuppressed | | Immunocompetent | |
|---|---|---|---|---|
| $PaO_2/FiO_2$ ratio | No. (%) | Adjusted odds ratio (95% CI) | No. (%) | Adjusted odds ratio (95% CI) |
| < 50 | 162 (65.32%) | 3.40 (1.60–7.21) | 1508 (42.45%) | 2.12 (1.76–2.56) |
| 50–99 | 978 (55.01%) | 2.53 (1.27–5.05) | 8901 (34.59%) | 1.70 (1.42–2.01) |
| 100–149 | 864 (43.61%) | 2.05 (1.03–4.09) | 8271 (20.65%) | 1.22 (1.04–1.44) |
| 150–199 | 580 (34.83%) | 1.72 (0.86–3.44) | 7408 (15.47%) | 1.03 (0.88–1.22) |
| 200–249 | 478 (30.66%) | 1.53 (0.77–3.05) | 6057 (13.69%) | 0.95 (0.81–1.12) |
| 250–299 | 302 (24.26%) | 1.02 (0.51–2.06) | 4847 (12.79%) | 0.91 (0.77–1.07) |
| 300–349 | 288 (26.52%) | 1.22 (0.60–2.46) | 3982 (12.38%) | 0.94 (0.80–1.12) |
| 350–399 | 187 (23.94%) | 1.18 (0.58–2.39) | 3174 (12.31%) | 0.91 (0.77–1.07) |
| 400–449 | 159 (24.92%) | 1.23 (0.60–2.52) | 2469 (12.41%) | 0.91 (0.77–1.08) |
| 450–499 | 95 (22.14%) | 1.10 (0.53–2.29) | 1644 (11.77%) | 0.82 (0.69–0.98) |
| 500–549 | 77 (28.21% | 1.33 (0.63–2.84) | 952 (11.68%) | 0.77 (0.64–0.93) |
| 550–600 | 20 (25.64%) | 1.00 (0.43–2.34) | 470 (12.45%) | 0.76 (0.62–0.93) |

**Table 5. Raw mortality and adjusted odds ratios for intensive care unit mortality by $PaO_2/FiO_2$ ratio category in patients who received mechanical ventilation in the first 24 hours after ICU admission**

| | Immunosuppressed | | Immunocompetent | |
|---|---|---|---|---|
| $PaO_2/FiO_2$ ratio | No. (%) | Adjusted odds ratio (95% CI) | No. (%) | Adjusted odds ratio (95% CI) |
| < 50 | 138 (56.33%) | 4.94 (1.97–12.40) | 1320 (37.62%) | 2.62 (2.13–3.22) |
| 50–99 | 818 (46.64%) | 3.70 (1.66–9.48) | 7509 (29.63%) | 1.99 (1.65–2.99) |
| 100–149 | 675 (34.32%) | 2.98 (1.25–7.14) | 6344 (16.07%) | 1.30 (1.07–1.56) |
| 150–199 | 419 (25.32%) | 2.31 (0.96–5.53) | 5271 (11.12%) | 1.01 (0.83–1.21) |
| 200–249 | 295 (19.02%) | 1.62 (0.67–3.89) | 4101 (9.36%) | 0.87 (0.72–1.05) |
| 250–299 | 198 (15.70%) | 1.25 (0.52–3.03) | 3160 (8.41%) | 0.79 (0.66–0.96) |
| 300–349 | 177 (16.40%) | 1.37 (0.57–3.33) | 2607 (8.17%) | 0.84 (0.69–1.02) |
| 350–399 | 110 (14.21%) | 1.17 (0.48–2.88) | 2046 (8.00%) | 0.78 (0.65–0.95) |
| 400–449 | 80 (14.21%) | 0.92 (0.37–2.30) | 1616 (8.19%) | 0.82 (0.67–0.99) |
| 450–499 | 45 (10.49%) | 0.91 (0.36–2.31) | 1090 (7.88%) | 0.75 (0.61–0.91) |
| 500–549 | 43 (16.17%) | 1.28 (0.49–3.31) | 667 (8.27%) | 0.77 (0.62–0.95) |
| 550–600 | 21 (17.65%) | 1.40 (0.49–3.92) | 320 (8.59%) | 0.74 (0.58–0.93) |

tion, the immunosuppressed population demonstrated a greater increase in mortality for any given drop in $PaO_2/FiO_2$ ratio than the immunocompetent population. Below a $PaO_2/FiO_2$ ratio of 250, the relationship between $PaO_2/FiO_2$ and mortality appeared to differ between immunosuppressed and immunocompetent patients who received mechanical ventilation. It was only at a $PaO_2/FiO_2$ ratio less than 150 that worsening oxygenation status itself appeared to be independently associated with mortality in both immunocompetent and immunosuppressed patients.

The effects of worsening hypoxia in the setting of immunosuppression have previously been noted to be associated with increasing mortality, although some more recent studies have not noted it to be an independent predictor after multivariate analysis.[7] Studies considering oxygenation and need for mechanical ventilation have shown that invasive respiratory support in the immunosuppressed population (notably in those receiving haematopoietic stem cell transplant) has also been associated with an extremely high mortality,[3] with ventilation for more than 4 days having been independently linked to worse outcomes.[8] It is worth highlighting the disparities in mortality between our study and previous work. This is likely because of the broad population our study examined — all forms of

immunosuppression were considered (regardless of perceived severity), as were elective admissions. Patients admitted to ICU as part of our study had a mean APACHE II score of 16 (SD, 7.9). This may be contrasted with a study by Benoit and colleagues, which reported a mean APACHE II score of 26 (SD, 7.7), and only considered patients admitted to the ICU with a haematological malignancy and life-threatening complication (ie, respiratory failure, sepsis or neurological impairment).[7]

Our finding that the relationship between oxygenation status and mortality is the same in non-ventilated patients with and without immunosuppressive disease, but different in the presence of mechanical ventilation, suggests that there may be another mechanism influencing the chances of survival in this latter group. Possible theories include:

- physician bias leading to premature withdrawal of active therapy in ventilated immunosuppressed patients, or reluctance to institute invasive ventilation unless disease is particularly severe;
- additive infective risks to the patients in the presence of invasive ventilation and immunosuppression (above the independent risks of each alone);
- additional risks associated with immunosuppressive disease, such as bleeding due to thrombocytopenia and coagulopathy, which manifests as increased mortality at the time of or after intubation;
- increased metabolic burden in the immunosuppressed population leading to difficulty weaning from mechanical ventilation;
- direct effect of immunosuppressive disease, leading to hypoxia which impairs V/Q matching only in the presence of positive pressure ventilation; or
- an unknown effect of non-invasive ventilation protecting immunosuppressed patients from the need for invasive ventilation; or
- some combination of these.

It is not possible to know from this study which of the above options are correct, or whether an unconsidered factor is responsible.

Our study had some shortcomings. Firstly, a retrospective review of existing data was performed. Regardless of the quality of the data, it is not as strong as a prospective review. Secondly, the researchers cannot determine the effect of potential confounding factors not collected. The $PaO_2/FiO_2$ ratio used is the worst such value recorded in the first 24 hours of ICU admission. It is unknown which (if any) additional therapies were received by patients (eg, inhaled nitric oxide, prone positioning, exogenous surfactant). Furthermore, it is only known whether each patient required mechanical ventilation within the first 24 hours of ICU admission. The specific ventilatory strategy employed, including positive end-expiratory pressure, airway pressures and tidal volume and, indeed, whether the patients who were initially not ventilated received mechanical ventilation later in their ICU admission, is not known. It is not certain whether the degree of oxygenation impairment represented in the patient population is due to primary disease or was a consequence of a deliberate low tidal volume ventilation strategy to minimise lung injury.[26] There was no information about the other non-ventilatory therapies or processes of care which patients received. Finally, due to the nature of the database, only patients admitted to the ICU can be analysed and these results cannot be extrapolated to patients outside the ICU.

Despite these drawbacks, use of the ANZICS APD confers some important benefits. The large size of the database confers statistical power to the study, allowing even small differences between patient populations to be detected. The multicentre contribution to the database from 129 centres across Australia, New Zealand and Hong Kong allows the results to be generalised to adult ICU practice. Because of the large number of physiological variables entered for each patient encounter, a comprehensive multivariate analysis could be performed, correcting for disease severity.

Our results serve to generate new hypotheses for future prospective work examining the effects of differing ventilation strategies on the immunosuppressed and immunocompetent patients and how these may have different effects in patients whose $PaO_2/FiO_2$ ratios are less than 250. Our results highlight the fact that ventilatory therapies that affect oxygenation may have greatest impact on mortality at $PaO_2/FiO_2$ ratios less than 150 in all patients with and without immunosuppression (since oxygenation status is only significantly associated with mortality at $PaO_2/FiO_2$ ratios less than 150). They raise the possibility that there may be a minimum $PaO_2/FiO_2$ threshold where therapies designed to improve oxygenation should be targeted or alternatively whether protective lung ventilation strategies should be introduced. Such studies would need to take into account the ventilation duration and strategy employed as well as the severity of hypoxia and immunosuppression before analysis.

If such a study can be performed, the critical care community may be closer to understanding specific effects of positive pressure ventilation on the immunosuppressed population and whether ventilation strategies might improve survival to the level currently seen in the immunocompetent population for a given degree of hypoxia.

## Conclusion

In this large, retrospective multicentre study, we confirmed that worsening $PaO_2/FiO_2$ ratio is associated with increased mortality. On further analysis, we found no difference in

outcome between non-ventilated immunosuppressed and immunocompetent patients as oxygenation status worsened. However, when mechanical ventilation was introduced in the first 24 hours after admission, immunosuppressed patients demonstrated increased mortality relative to the immunocompetent patients for a given drop in $PaO_2/FiO_2$ ratio. The reason for this observation is uncertain. Further research into these findings is required.

## Acknowledgements

Funding for this project was generously provided by a small grant from the Alfred Research Trusts.

## Competing interests

None declared.

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