Maximum Pao$_2$ in the First 72 Hours of Intensive Care Is Associated With Risk-Adjusted Mortality in Pediatric Patients Undergoing Mechanical Ventilation

**Abstract**: A relationship between Pao$_2$ and mortality has previously been observed in single-center studies. We performed a retrospective cohort study of the Pediatric Health Information System plus database including patients less than or equal to 21 years old admitted to a medical or cardiac ICU who received invasive ventilation within 72 hours of admission. We trained and validated a multivariable logistic regression mortality prediction model with very good discrimination (C-statistic, 0.86; 95% CI, 0.79–0.92; area under the precision-recall curve, 0.39) and acceptable calibration (standardized mortality ratio, 0.96; 95% CI, 0.75–1.23; calibration belt $p = 0.07$). Maximum Pao$_2$ measurements demonstrated a parabolic (“U-shaped”) relationship with PICU mortality (Box-Tidwell $p < 0.01$). Maximum Pao$_2$ was a statistically significant predictor of risk-adjusted mortality (standardized odds ratio, 1.27; 95% CI, 1.23–1.32; $p < 0.001$). This analysis is the first multicenter pediatric study to identify a relationship between the extremes in Pao$_2$ values and PICU mortality. Clinicians should remain judicious in the use of oxygen when caring for children.

**Key Words**: child; critical care; death; hyperoxia; oxygen; ventilators, mechanical

Recently, there has been increasing interest in hyperoxemia. Several randomized controlled trials and meta-analyses of oxygen management strategies in adults have come to differing conclusions regarding the importance of hyperoxemia (1–3). While fewer data exist for children, there is a growing body of literature identifying a relationship between the Pao$_2$ values and mortality in PICU settings (4–7). Limitations of these previous studies include data from single centers, variable definitions of hyperoxemia, and absent or uncalibrated risk-adjustment strategies. Our objective was to examine the relationship between the Pao$_2$ values and mortality among critically ill children in a large multicenter cohort, adjusting with a well-calibrated mortality risk model. We hypothesized that both hypoxemia and hyperoxemia would demonstrate an association with risk-adjusted mortality.

**MATERIALS AND METHODS**

We performed a retrospective cohort study of the Pediatric Health Information System plus (PHIS+) database, a collection of federated electronic health record data containing laboratory results and quality-controlled administrative data from six large pediatric hospitals between 2010 and 2012 (8). We included patients with 21 years old or younger that were admitted to a pediatric general or cardiac ICU with a hospital discharge date between January 1, 2010, and December 31, 2012, who received invasive mechanical ventilation within 72 hours of admission and who had at least one Pao$_2$ value obtained. We excluded patients who were admitted to a neonatal ICU or who received extracorporeal membrane oxygenation. The primary outcome was in-hospital mortality. The study was approved by the University of Pittsburgh Institutional Review Board.

Because prior work has suggested a parabolic (“U-shaped”) relationship between Pao$_2$ and mortality (5, 6), we performed a Box-Tidwell test. We developed a multivariable logistic regression model of predicted mortality, with a random effect for hospital, and plotted the expected and actual mortalities of patients grouped by differing maximum Pao$_2$ values using bin widths of 100 mm Hg. The variables used in the mortality prediction model are listed in Table 1. We divided the cohort into 80% training and 20% testing subsets. Backward stepwise selection was performed, taking variables with $p$ value of less than 0.05 as statistically significant. Discrimination was assessed using C-statistics with DeLong 95% CIs and area under the precision-recall curve (AUPRC). Calibration was assessed with standardized mortality ratios (SMRs) with Hosmer 95% CI and calibration belts, with $p$ value of greater than or equal to 0.05 deemed acceptable (9). Because the relationship between Pao$_2$ and mortality was nonlinear, we performed polynomial (parabolic) regression. This approach is similar to standard logistic regression, but allows the demonstration of the “U-shaped” relationship between the patients’ maximum Pao$_2$ value and risk-adjusted mortality (with all other variables in the model taken into account), and calculation of where the lowest risk-adjusted mortality occurred.

We conducted five sensitivity analyses. First, we excluded patients with a cardiovascular complex chronic condition flag (10). Second, we excluded patients with burns, carbon monoxide poisoning, or traumatic brain injury. Third, we excluded patients with cardiac arrest prior to admission. Fourth, because prior work has suggested a time-dependent effect of hyperoxemia (4–7), we restricted the cohort to patients with invasive mechanical ventilation and Pao$_2$ measurements within 24 hours of admission. Fifth, we broadened the cohort to include patients who underwent invasive mechanical ventilation and Pao$_2$ measurements at any time during admission. All analyses were performed in R (Versions 3.5.1 and 4.0.0; R Foundation for Statistical Computing, Vienna, Austria).
### Results

Cohort demographics are listed in Table 1. The mortality prediction model had very good discrimination (C-statistic, 0.86; 95% CI, 0.79–0.92; AUPRC, 0.39) and acceptable calibration (SMR, 0.96; 95% CI, 0.75–1.23; calibration belt p = 0.07). The Box-Tidwell test indicated that the relationship between PaO\(_2\) and mortality was nonlinear (p < 0.01). The relationship between maximum PaO\(_2\) and mortality is shown in Figure 1. Predicted and actual mortalities are shown on the left axis, and the effect plot of maximum PaO\(_2\) measurement with 95% CI is shown on the right axis. Maximum PaO\(_2\) had a statistically significant effect on risk-adjusted mortality. We observed a parabolic ("U-shaped") relationship between maximum PaO\(_2\) and unadjusted mortality. Both absolute and risk-adjusted mortalities fell until a maximum PaO\(_2\) value of 384 mm Hg

### Table 1. Cohort Demographics, Mortality Prediction Models, and Effect of Maximum PaO\(_2\)

| Characteristics                          | Within 72 hr of Admission | Excluding Cardiovascular CCC | Excluding Burns, Carbon Monoxide Poisoning, and Traumatic Brain Injury | Excluding Cardiac Arrest | Within 24 hr of Admission | Any Time During Admission |
|------------------------------------------|---------------------------|------------------------------|------------------------------------------------------------------------|--------------------------|---------------------------|---------------------------|
| Cohort demographics                      |                           |                              |                                                                        |                          |                           |                           |
| Cohort size, n (%)                       | 4,469 (100)               | 2,072 (100)                  | 4,390 (100)                                                           | 4,416 (100)              | 2,396 (100)               | 5,994 (100)               |
| Median age (IQR), yr                     | 1.8 (0.4–8.4)             | 3.7 (0.9–11.3)               | 1.7 (0.4–8.3)                                                         | 1.8 (0.4–8.4)            | 1.9 (0.5–9.1)             | 1.3 (0.2–7.5)             |
| Male, n (%)                              | 2,480 (55.5)              | 1,144 (55.2)                 | 2,426 (55.3)                                                         | 2,447 (55.4)             | 1,347 (56.2)              | 3,307 (55.2)              |
| White, n (%)                             | 3,151 (70.5)              | 1,469 (70.9)                 | 3,086 (70.3)                                                         | 3,119 (70.6)             | 1,681 (70.2)              | 4,192 (69.9)              |
| Commercial insurance, n (%)             | 2,058 (46.1)              | 883 (42.6)                   | 2,015 (45.9)                                                         | 2,034 (46.1)             | 1,086 (45.3)              | 2,704 (45.1)              |
| Any CCC, n (%)                           | 3,924 (87.8)              | 1,527 (73.7)                 | 3,872 (88.2)                                                         | 3,873 (87.7)             | 2,081 (86.9)              | 5,393 (90)                |
| Median ICU length of stay (IQR)          | 6 (3–11)                  | 6 (3–11)                     | 6 (3–11)                                                              | 5 (2–10)                 | 7 (3–15)                  |                           |
| Received vasopressors, n (%)             | 3,364 (75.3)              | 1,296 (62.5)                 | 3,314 (75.5)                                                         | 3,322 (75.2)             | 1,630 (68)                | 2,758 (46)                |
| Survived to discharge, n (%)             | 4,235 (94.8)              | 1,927 (93)                   | 4,169 (95)                                                           | 4,209 (95.3)             | 2,271 (94.8)              | 5,594 (93.3)              |
| Median number of PaO\(_2\) values (IQR)  | 9 (4–16)                  | 8 (3–16)                     | 9 (4–16)                                                             | 9 (4–16)                 | 5 (2–8)                   | 13 (6–29)                 |

**Mortality prediction model characteristics**

| C-statistic (DeLong 95% CI)              | 0.86 (0.79–0.92)          | 0.87 (0.79–0.96)             | 0.89 (0.84–0.95)                                                     | 0.87 (0.81–0.94)         | 0.92 (0.87–0.97)          | 0.9 (0.86–0.94)           |
|-----------------------------------------|---------------------------|------------------------------|----------------------------------------------------------------------|--------------------------|--------------------------|---------------------------|
| Area under the precision-recall curve   | 0.39                      | 0.58                         | 0.46                                                                 | 0.35                     | 0.47                     | 0.55                      |
| Italian Group for the Evaluation of the Interventions in ICUs Calibration belt p | 0.07                      | 0.49                         | 0.49                                                                 | 0.56                     | 0.67                     | < 0.01                    |
| Standardized mortality ratio (Hosmer 95% CI) | 0.96 (0.75–1.23)        | 0.87 (0.64–1.19)             | 0.9 (0.69–1.17)                                                      | 1.03 (0.8–1.33)          | 0.87 (0.62–1.23)         | 1.01 (0.86–1.19)          |

**Effect of maximum PaO\(_2\) on mortality**

| Standardized odds ratio (95% CI) | 1.27 (1.23–1.32)        | 1.18 (1.13–1.24)             | 1.24 (1.20–1.29)                                                     | 1.20 (1.16–1.24)         | 1.22 (1.10–1.36)         | 1.15 (1.13–1.17)          |
|----------------------------------|-------------------------|------------------------------|----------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|
| Lowest risk-adjusted mortality (mm Hg) | 384                     | 341                          | 398                                                                 | 348                     | 466                     | 391                      |

CCC = complex chronic condition, IQR = interquartile range.

*Mortality prediction models were developed from the following list of terms: admission priority, cardiovascular CCC, gastrointestinal CCC, hematologic or immunologic CCC, malignancy CCC, metabolic CCC, neurologic and neuromuscular CCC, congenital or genetic defect CCC, renal or urologic CCC, respiratory CCC, premature and neonatal CCC, technology dependence, transplant recipient, mental health disorder CCC (primary or secondary), dobutamine use, dopamine use, epinephrine use, norepinephrine use, vasopressin use, maximum PaCO\(_2\), maximum lactate, maximum and minimum WBC count, maximum and minimum platelet count, maximum international normalized ratio, and minimum pH.

*Odds ratio is standardized to one sd of the model term.

*p < 0.001.
of lowest risk-adjusted mortality was between 341 and 466 mm Hg.

A parabolic Pao2 term was a significant predictor of mortality in all sensitivity analyses. The point
bribration (calibration belt
p < 0.01). A parabolic Pao2 term was a sig-
ificant predictor of mortality in both analyses were present for patients with maximum Pao2 values
values and mortality. In polynomial regression, odds of mortality increased with a maximum Pao2 value
value less than 250 mm Hg or
values either less than 100 or greater than or equal to 400 mm Hg.
A comparable effect was evident in multiple sensitivity analyses. A parabolic Pao2 term was a sig-
ificant predictor of mortality in both analyses were present for patients with maximum Pao2 values
either less than 100 or greater than or equal to 400 mm Hg.
A comparable effect was evident in multiple sensitivity analyses.

DISCUSSION

This is the first multicenter study of critically ill pediatric patients to identify a nonlinear (“U-shaped”) relationship between the Pao2 values and mortality. In polynomial regression, odds of mortality increased with a maximum Pao2 value less than 250 mm Hg or greater than 450 mm Hg. However, in the binned analysis, patients with Pao2 values between 100 and 400 mm Hg had variable risk-adjusted mortality. Clear trends of worsened risk-adjusted mortality in both analyses were present for patients with maximum Pao2 values either less than 100 or greater than or equal to 400 mm Hg. A comparable effect was evident in multiple sensitivity analyses.

Previous studies have observed Pao2 threshold values between 300 and 550 mm Hg to be associated with increased mortality admission, the findings of our sensitivity analysis, combined with prior studies of the impact of early hyperoxemia, would suggest this is less likely (6, 7).

Many administrative databases contain limited clinical data, precluding risk-adjustment according to previously validated severity of illness scores. The PHIS+ data include federated laboratory results, allowing for improved risk-adjustment compared with administrative data alone. Our risk model incorporated important laboratory measures of organ dysfunction, including Pco2, lactate, WBC count, platelet count, international normalized ratio, and pH. However, in the absence of granular clinical data, the findings from the database review such that the present study should be considered hypothesis-generating.

This work has several limitations, including the retrospective observational design. Additionally, because the maximum Pao2 value for each patient in the first 72 hours was examined, this study does not address what Pao2 should be targeted for a sustained period of time. Because PHIS+ does not include provider notes, it is possible that children with hyperoxemia or hypoxemia were managed according to specific therapeutic targets. We attempted to control for such scenarios by excluding patients with burns, carbon monoxide poisoning, or traumatic brain injury; however, we cannot fully exclude confounding by indication. Similarly, we cannot exclude that these children were moribund for other reasons.
that are not captured by the variables listed in Table 1. Finally, bin widths of 100 mm Hg were chosen to ensure adequate sample size in each bin (e.g., using a bin width of 50 mm Hg would have resulted in zero patients with a maximum Pao2 between 450 and 499 mm Hg). Exploratory analyses did not suggest that smaller bin widths would have altered the analysis findings (e.g., patients with maximum Pao2 values of < 50 and 50–99 mm Hg had mortalities of 8.2% and 8.0%, respectively). However, the precision of the binned analysis is limited by sample size.

The present work is the first multicenter pediatric study to confirm a parabolic relationship between the Pao2 values and risk-adjusted PICU mortality. Maximum Pao2 values less than 100 or greater than or equal to 400 mm Hg were associated with increased mortality among invasively ventilated patients. While a prospective study is necessary to determine whether a causal relationship exists, the present results suggest clinicians should be judicious in the use of high Fio2 therapy in the absence of a specific indication.

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