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).

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)	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[a]						
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)[b]	1.27 (1.23–1.32)[c]	1.18 (1.13–1.24)[c]	1.24 (1.20–1.29)[c]	1.20 (1.16–1.24)[c]	1.22 (1.10–1.36)[c]	1.15 (1.13–1.17)[c]
Lowest risk-adjusted mortality (mm Hg)	384	341	398	348	466	391

CCC = complex chronic condition, IQR = interquartile range.

[a]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 Pco_2, maximum lactate, maximum and minimum WBC count, maximum and minimum platelet count, maximum international normalized ratio, and minimum pH.

[b]Odds ratio is standardized to one SD of the model term.

[c]$p < 0.001$.

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
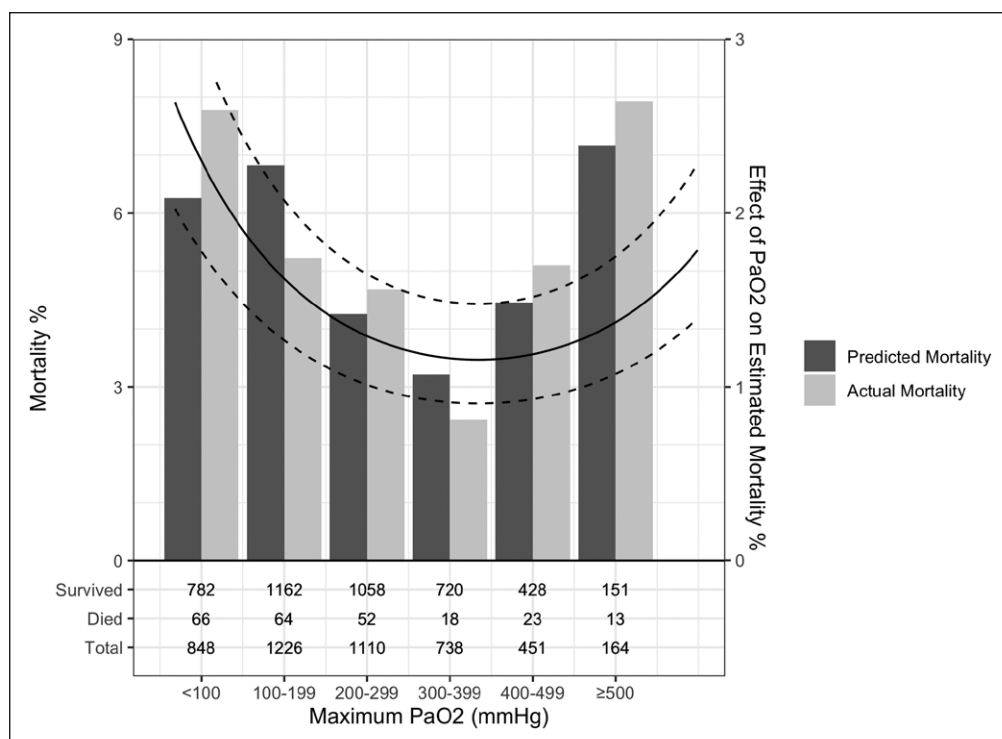
Figure 1. Maximum Pao_2 value versus mortality for patients intubated and mechanically ventilated within 72 hr of admission. The *x*-axis shows the maximum Pao_2 value obtained within 72 hr of admission. The *bars* on the *left y*-axis divide patients into bins based on their maximum Pao_2 value (using a bin width of 100 mm Hg) and show the actual (*light gray*) and predicted (*dark gray*) percent mortalities for each of the bins, using a multivariable model that does not include a Pao_2 term. The numbers below the *bars* show the number of patients in each bin. The *solid* and *dashed lines* on the *right y*-axis show an effect plot of a parabolic Pao_2 term on a multivariable mortality prediction model. This represents the effect of maximum Pao_2 value on mortality when all other variables in the model are held constant. The *solid line* represents the line of best fit, and the *dashed lines* represent the 95% CI.

Hg and then rose again. The relationship between maximum Pao_2 and risk-adjusted mortality was relatively flat between the values of 250–450 mm Hg.

Model performance was similar between the main analysis and the sensitivity analyses (Table 1), except that a model including Pao_2 values from any time during admission displayed poor calibration (calibration belt $p < 0.01$). A parabolic Pao_2 term was a significant predictor of mortality in all sensitivity analyses. The point of lowest risk-adjusted mortality was between 341 and 466 mm Hg for all analyses.

DISCUSSION

This is the first multicenter study of critically ill pediatric patients to identify a nonlinear ("U-shaped") relationship between the Pao_2 values and mortality. In polynomial regression, odds of mortality increased with a maximum Pao_2 value less than 250 mm Hg or greater than 450 mm Hg. However, in the binned analysis, patients with Pao_2 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 Pao_2 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 Pao_2 threshold values between 300 and 550 mm Hg to be associated with increased mortality

(4–7). Together, these results suggest that both hypoxemia and extreme hyperoxemia are associated with risk-adjusted mortality; however, the precise thresholds associated with clinical harm remain uncertain and likely vary by clinical condition (4–7). A recent randomized controlled trial among adults demonstrated no difference between conservative and liberal oxygen management strategies (3). However, the highest Pao_2 measurements in the liberal oxygen therapy group from that study were less than 150 mm Hg. In contrast, the present study and several prior pediatric studies (4–7) have demonstrated a significant association only with either extreme hyperoxemia and death. In the present study, the optimal maximum Pao_2 value in the first 72 hours of mechanical ventilation appears to be between 100 and 400 mm Hg.

Expert opinion has suggested that extreme hyperoxemia may be an indirect measurement of patients undergoing brain death testing or being assessed for organ donation eligibility (4). However, as relatively few PICU patients undergo brain death testing within 24 hours of 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 Pco_2, 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 Pao_2 value for each patient in the first 72 hours was examined, this study does not address what Pao_2 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 Pao_2 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 Pao_2 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 Pao_2 values and risk-adjusted PICU mortality. Maximum Pao_2 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 Fio_2 therapy in the absence of a specific indication.

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