HHS Public Access

Author manuscript

Pediatr Crit Care Med. Author manuscript; available in PMC 2017 October 01.

Published in final edited form as:

Pediatr Crit Care Med. 2016 October ; 17(10): 907–916. doi:10.1097/PCC.0000000000000865.

A Simple and Robust Bedside Model for Mortality Risk in Pediatric Patients with ARDS

Aaron C Spicer, MD, MAS[1], **Carolyn S Calfee, MD, MAS**[2], **Matthew S Zinter, MD**[3,8], **Robinder G Khemani, MD, MsCI**[4], **Victoria P Lo, BS**[5], **Mustafa F Alkhouli, BA**[3], **Benjamin E Orwoll, MD**[3,8], **Ana L Graciano, MD**[6], **Juan P Boriosi, MD**[7], **James P Howard, MD, PhD**[8], **Heidi R Flori, MD**[8], **Michael A Matthay, MD**[2], and **Anil Sapru, MD, MAS**[3]

[1]Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, MA

[2]Departments of Anesthesia and Medicine, University of California, San Francisco, San Francisco, CA

[3]Department of Pediatrics, Division of Critical Care, University of California, San Francisco Benioff Children's Hospital-San Francisco, San Francisco, CA

[4]Departments of Anesthesiology and Critical Care Medicine, Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA

[5]Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD

[6]Department of Pediatrics, Children's Hospital of Central California, Fresno, CA

[7]Department of Pediatrics, University of Wisconsin-Madison, Madison, WI

[8]Division of Pediatric Critical Care, University of California, San Francisco Benioff Children's Hospital-Oakland, Oakland, CA

Abstract

Objective—Despite declining mortality, ARDS is still involved in up to one third of pediatric intensive care deaths. The recently convened Pediatric Acute Lung Injury Consensus Conference has outlined research priorities for the field, which include the need for accurate bedside risk-stratification of patients. We aimed to develop a simple yet robust model of mortality risk among pediatric patients with ARDS to facilitate the targeted application of high-risk investigational therapies and stratification for enrollment in clinical trials.

Design—Prospective, multi-center cohort.

Setting—Five academic pediatric intensive care units.

Patients—308 children ages >1 month and ≤ 18 years, admitted to the intensive care unit, with bilateral infiltrates on chest x-ray and P/F ratio <300 in the clinical absence of left atrial hypertension.

Corresponding author: Anil Sapru MD MAS, 550 16th St, University of California, San Francisco, San Francisco, CA, 94143. anil.sapru@ucsf.edu, Telephone: (415) 476-0963, Fax: (415) 502-4186.

Copyright form disclosures: The remaining authors have disclosed that they do not have any potential conflicts of interest.

Interventions—None.

Measurements and Main Results—Twenty clinical variables were recorded in the following 6 categories: demographics, medical history, oxygenation, ventilation, radiographic imaging, and multi-organ dysfunction. Data were measured 0–24 and 48–72 hours after ARDS onset (Day 1 and Day 3) and examined for associations with hospital mortality. Among 308 enrolled patients, mortality was 17%. Children with a history of cancer and/or hematopoietic stem cell transplant (HSCT) had higher mortality (47% vs. 11%, $p<0.001$). Oxygenation index (OI), the P/F ratio, extrapulmonary organ dysfunction, PRISM-3, and positive cumulative fluid balance were each associated with mortality. Using two statistical approaches, we found that a parsimonious model of mortality risk using only OI and cancer/HSCT history performed as well as other more complex models that required additional variables.

Conclusions—In the pediatric intensive care unit, OI and cancer/HSCT history can be used on ARDS Day 1 or Day 3 to predict hospital mortality without the need for more complex models. These findings may simplify risk assessment for clinical trials, counseling families, and high-risk interventions such as extracorporeal life support.

Keywords

Acute Lung Injury; Respiratory Distress Syndrome; Acute; Prognosis; Hospital Mortality; Intensive Care Units; Pediatric

Introduction

In the past 20 years, mortality for children with acute respiratory distress syndrome (ARDS) has decreased from 62% to 18%, likely due in part to the application of ventilator and fluid management strategies proven beneficial in adults (1–3). Despite this fall in mortality, pediatric ARDS still contributes to 30% of pediatric intensive care mortalities (4). The Pediatric Acute Lung Injury Consensus Conference (PALICC) recently published guidelines outlining research priorities for the field, which include a crucial need for accurate bedside risk-stratification of patients (5–7). Identification of patients at the highest risk of death might enable the targeted application of higher-risk therapies, such as prone positioning, neuromuscular blockade, renal replacement therapy, and extracorporeal life support, and may facilitate stratification for enrollment in clinical trials (8–12).

Currently, several clinical parameters are known to relate to pediatric ARDS mortality. Among markers of oxygenation failure, both the P/F ratio and the oxygenation index (OI) have been correlated with mortality (13–15). Radiographic findings such as the Lung Injury Score show association with mortality, as do markers of global illness severity such as the Pediatric Risk of Mortality (PRISM) and Pediatric Logistic Organ Dysfunction (PELOD) scores (16–19). Elevated cumulative fluid balance has been associated with mortality as well (20, 21). Studies of pediatric ARDS completed after the ARDSNet trial of lower tidal volumes (1) have demonstrated that the P/F ratio and OI remain associated with mortality in the current era, and have further shown that the P/F ratio and OI measured between 24 hours to 3 days after ARDS onset are more robustly associated with mortality than values obtained at onset of ARDS (3, 4, 14, 16–19, 22). A recent publication has reported the utility of OI

and underlying disease in predicting mortality among children undergoing high frequency oscillatory ventilation (15). However, the combined independent prognostic utility of these variables using multivariate models has not been assessed in an all-inclusive cohort of children with ARDS in recent era of widespread use of low tidal volume ventilation. While a variety of biomarkers have been measured and correlated with mortality (6, 23), they are not yet available in clinical settings, which precludes their use and underscores the importance of engaging clinical variables if possible.

We therefore undertook a comprehensive evaluation of 20 clinically relevant variables, available on the first and third days after ARDS onset from a multi-center cohort of children enrolled after the wide-spread adoption of lung-protective ventilation, in order to identify clinical variables independently associated with mortality. We then derived the simplest best-fit model of mortality risk for bedside application, which may be useful for selection of high-risk patients for investigational therapies and stratification for clinical trials enrollment.

Materials and Methods

Design, Setting, and Patients

Data were derived from an ongoing prospective cohort of children with ARDS enrolled from September 2008 – September 2014 in five academic pediatric intensive care units. The study was approved by Institutional Review Boards at all participating centers. Children were screened for eligibility if they received high flow nasal cannula (with flow above 5L/min), CPAP, BiPAP, or invasive positive pressure ventilation. Guardians were approached for informed consent if the child met the American-European Consensus Conference definition of Acute Lung Injury/Acute Respiratory Distress Syndrome (24), with chest x-ray interpretation performed by site investigators. Patients were excluded for a documented limitation of care at the time of screening, age <1 month or >18 years, corrected gestational age <36 weeks, or prior enrollment in the cohort. Saturation/FiO2 ratios were accepted for enrollment if arterial blood gas data were not collected (25). All participating sites did not keep complete logs, but available screening records indicate that 90% of patients meeting enrollment criteria were approached, and 85% of those approached were enrolled, for an overall enrollment of 76% of eligible subjects.

Data Collection and Management

Twenty variables were collected in the following six areas: demographics, including age, sex, race, and ethnicity; medical history, including pre-existing medical conditions and lung injury etiology; oxygenation metrics, including FiO_2, P/F ratio, mean airway pressure, and OI; ventilation metrics, including peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), respiratory rate, and dynamic compliance; imaging metrics, including number of chest x-ray quadrants involved and Lung Injury Score (LIS); and multi-organ dysfunction metrics, including use of vasoactive infusion, cumulative fluid balance, initial PRISM-3, daily PELOD, and daily extrapulmonary PELOD score. Demographics and medical history were chosen for face validity and due to prior association with outcomes in ARDS; clinical data were chosen after a comprehensive literature review, for prior association with outcomes. Daily data from as close as possible to 8:00 AM were recorded

through PICU discharge, in order to standardize data collection. Tidal volume and dynamic compliance of the respiratory system were evaluated only in intubated, conventionally mechanically ventilated subjects. Oxygenation index was evaluated only in intubated patients. Details of calculated variables, with a selection of references detailing prior associations with outcomes, are available in the eMethods (see online Supplement). The primary outcome was mortality prior to hospital discharge. Data forms were collected from participating sites and entered into REDCap (26) at UCSF Benioff Children's Hospital San Francisco.

Statistical Analysis

Associations between mortality and categorical variables, normally distributed continuous data, and non-parametric continuous data were analyzed by the χ^2 test, t-test, and Wilcoxon rank-sum, respectively. Spearman rank correlation tested correlation between nonparametric continuous variables. Sensitivity analyses included comparison of mortality between subjects with and without data recorded for each clinical variable. Discrimination was evaluated by receiver operator characteristics (ROC) and quantified by the area under the curve/C-statistic.

Logistic models were used to quantify the independent prognostic value of identified risk factors and included the following *a priori* selected variables: age, sex, race, ethnicity, and direct (vs. indirect) etiology of lung injury; ARDS etiology was classified as direct lung injury if reported as pneumonia, aspiration, or pulmonary hemorrhage. Risk factors associated with mortality on univariate analysis were added to the initial logistic models.

Model selection was performed by two techniques. The first was stepwise backwards elimination with likelihood ratio testing in order to generate the most parsimonious model without losing significant discrimination. Calibration was evaluated by the Hosmer-Lemeshow test by decile of fitted risk values. The second technique was 10-fold cross-validation with 20 repetitions (27), which minimizes overfitting by deriving the model in 90% of randomly-selected subjects and validating the model in the remaining 10%, minimizing variability by repeating the process and averaging the results. Cross-validation estimates unbiased associations without compromising sample size by withholding a validation sample.

Data from within 24 hours of ARDS onset ("Day 1") and 48–72 hours after ARDS onset ("Day 3") were analyzed separately. Day 1 was chosen to evaluate prognostic data as early as possible in the course of ARDS, minimizing the effects of therapies. Day 3 was used to explore potential changes in prognostic utility over the initial days of illness (21, 28, 29). Subjects were excluded from individual analyses if data required for those analyses were incomplete. All analyses were performed using STATA statistical software, version 13.1 (StataCorp, College Station, Texas). P-values below 0.05 were considered significant.

Results

Cohort Characteristics

A total of 308 subjects were enrolled. Baseline characteristics, stratified by mortality, are shown in Table 1. The cohort had a 64% prevalence of pre-existing chronic medical conditions, most commonly cancer or hematopoietic stem cell transplantation (HSCT, 15%), neurologic (15%), respiratory (15%), gastrointestinal/nutritional (11%), or genetic (10%). Timing of ARDS onset ranged from the day prior to PICU admission to 84 days later, with a median of 1 day after PICU admission. Pneumonia (59%) and sepsis (21%) were the most common etiologies of ARDS. Direct lung injury caused 63% of ARDS cases. Most subjects (77%) were receiving conventional mechanical ventilation at enrollment, with high-flow nasal cannula (15%) being the next most common respiratory support. Approximately half of the patients receiving noninvasive ventilation at ARDS onset eventually required intubation (32/60). A total of 51 children (17%) died during hospitalization, with 45 deaths during the PICU stay, for a PICU mortality of 15%. The first death occurred 3 days after ARDS onset, and the last occurred 265 days after ARDS onset.

Baseline Characteristics Associated With Mortality

Age, sex, race, and ethnicity were not significantly associated with mortality (Table 1). The mortality of children with cancer/HSCT was 47%, versus 11% for children without cancer/HSCT ($p<0.001$); no other pre-existing medical history was associated with mortality (see Supplemental Table 2). Site of enrollment was not significantly associated with mortality ($p=0.4$; see Supplemental Table 1). Initial mode of respiratory support was also not associated with mortality. PRISM-3 scores were associated with mortality ($p<0.001$).

Day 1 Clinical Variables Associated With Mortality

We examined the association between mortality and clinical variables within 24 hours of ARDS onset in the categories of ventilation, oxygenation, imaging findings, fluid and hemodynamics, and quantification of organ dysfunction (Table 2, which includes the number of subjects with available data). Elevated ventilator pressures (PIP, PEEP, mean airway pressure), worsening oxygenation (P/F ratio, OI), and severity of multi-organ dysfunction (Day 1 PELOD score and Day 1 extrapulmonary PELOD) were all associated with mortality. There was no significant difference in mortality between subjects with available vs. unavailable OI ($p=0.76$). P/F and OI were imputed from pulse oximetry in 13 and 8 children, respectively, without arterial blood gas measurements. OI discriminated mortality better than the P/F ratio (C-statistic 0.67, 95% CI 0.57–0.76 vs. 0.62, 0.53–0.71; $p=0.01$). There was no statistically significant difference between daily PELOD (C-statistic 0.61, 95% CI 0.52–0.69) and daily extrapulmonary PELOD (0.61, 95% CI 0.53–0.69) in mortality discrimination ($p=0.64$).

Day 1 Multivariate Analysis

The initial logistic model for mortality included age, sex, race, ethnicity, direct vs. indirect lung injury, cancer/HSCT, PRISM-3, OI, and daily extrapulmonary PELOD (Table 3; n=206). Only cancer/HSCT and OI remained significantly associated with mortality

independent of the other variables. This initial model discriminated mortality with a C-statistic of 0.77 (95% CI 0.68–0.86). The 10-fold cross-validated C-statistic was 0.66 (95% CI 0.55–0.77). Elimination of the daily extrapulmonary PELOD, PRISM-3 score, or both did not significantly change the association of the model with mortality (p=0.25, p=0.77, p=0.51, respectively). OI and Day 1 extrapulmonary PELOD were correlated (Spearman's rho 0.23, p<0.001).

A final simplified model, incorporating OI and cancer/HSCT, adjusted for the *a priori* variables, was not inferior to the initial model (C-statistic 0.75, 95% CI 0.66–0.85; p=0.51). The cross-validated C-statistic was 0.67 (95% CI 0.57–0.78). This simplified model was well calibrated (Hosmer-Lemeshow p=0.18). Figure 1 illustrates the predicted increase in mortality with increasing Day 1 OI, stratified by cancer and/or HSCT and controlled for patient age, sex, race, ethnicity, and direct vs. indirect lung injury.

Day 3 Clinical Variables Associated With Mortality

The associations between Day 3 clinical variables and mortality are presented in Table 2, which includes the number of subjects with available data. P/F and OI were imputed from pulse oximetry in 17 and 0 children, respectively, without arterial blood gas measurements. In addition to those variables associated with mortality on Day 1, FiO_2, modified lung injury score (LIS), and cumulative fluid balance on Day 3 were associated with mortality. In contrast with Day 1, PEEP was not significantly associated with mortality. There was no significant difference in mortality between subjects with available vs. unavailable OI (p=0.29). On analysis of receiver-operator curves, there was no significant difference between the performance of OI (C-statistic 0.68, 95% CI 0.59–0.77) and P/F (0.69, 0.61–0.78; p=0.68). As on Day 1, daily PELOD and daily extrapulmonary PELOD were similarly discriminative of mortality (C-statistic 0.64, 95% CI 0.56–0.72 vs. 0.63, 95% CI 0.55–0.71, p=0.54).

Day 3 Multivariate Analysis

The initial logistic model incorporated age, sex, race, ethnicity, direct vs indirect lung injury, cancer/HSCT, PRISM-3 score, OI, cumulative fluid balance, and daily extrapulmonary PELOD (Table 4; n=194). As on Day 1, OI and cancer/HSCT history were the only variables independently associated with mortality in this model. Backwards elimination again indicated that the model was not significantly weakened by removal of any of the other variables. As with Day 1, Day 3 OI and non-pulmonary PELOD were correlated (Spearman's rho 0.25; p<0.001). The cross-validated C-statistic for the simplified model incorporating OI, cancer/HSCT history, and *a priori* variables was 0.73 (95% CI 0.63–0.82). This simplified model was well-calibrated (Hosmer-Lemeshow p=0.96). Figure 2 illustrates the association between predicted mortality and Day 3 OI, stratified by cancer/HSCT history.

Discussion

In this large, prospective cohort of children with ARDS, we have developed a simple yet robust tool for mortality prediction. In deriving this model, we confirmed that markers of

oxygenation (P/F ratio and OI), initial severity of illness, accumulation of organ dysfunction, fluid overload, and history of cancer/HSCT continue to be associated with mortality. Most importantly we found that OI on either Day 1 or Day 3, along with a history of cancer/HSCT, provides prognostic information that is not improved by the addition of other variables. This parsimonious model lends itself to bedside application by clinicians in real-time and is equally as robust as more complex multivariable models involving additional clinical parameters. This study is timely and consistent with recommendations of the PALICC definition group to update risk-stratification models for clinical and research utility (5, 6).

A number of the 20 clinical variables assessed for the Day 1 model demonstrated univariate significance worthy of discussion. Of the oxygenation and ventilation variables, PIP, PEEP, P/F ratio, MAP, and OI were all associated with mortality. We found that OI discriminated mortality better than the P/F ratio on day 1, which affirms the prognostic utility of incorporating MAP into bedside risk-stratification on ARDS Day 1. In children, both P/F ratio and OI have been associated with mortality (14, 15, 18, 19, 28), but to our knowledge, this is the first study to find that OI is more closely associated with mortality than is the P/F ratio on Day 1. This finding is consistent with the PALICC recommendation of OI as an important marker of ARDS severity (5). Our findings are also consistent with a recently published study of children with ARDS undergoing high frequency oscillatory (HFO) ventilation, which reported that OI obtained immediately preceding HFO and underlying diagnosis are significant predictors of mortality. (15). However, the OI had been measured anywhere between 0 to 125 hours after initiation of mechanical ventilation (15).

We also found that markers of global organ dysfunction including PRISM-3, PELOD, and extrapulmonary PELOD were each associated with mortality, but these associations did not hold after controlling for demographics, OI, and cancer/HSCT. Interestingly, elevated OI was strongly correlated with elevated extrapulmonary PELOD, supporting decades of work demonstrating that ARDS pathophysiology involves systemic inflammation both within and outside of the lung (29, 30). Thus, the severity of extrapulmonary organ dysfunction may be associated with the severity of lung injury, rather than having an independent association with mortality. It is possible that both pulmonary and extrapulmonary organ dysfunction may result from and reflect one underlying insult, such as systemic inflammation, rather than being pathophysiologically distinct processes. The most convenient indicator of this underlying pathophysiology would be most prognostically useful; our data suggest that OI may be a useful indicator of risk for both extrapulmonary organ dysfunction and hospital mortality.

In the final multivariable model using Day 1 variables, only OI and history of cancer/HSCT were independently associated with mortality and this model was equally as robust as more complicated models. Addition of PRISM-3 to this model did not improve the model fit, likely due to strong collinearity between PRISM-3 and OI.

Because risk-prediction on Day 1 of ARDS may seem premature to many families and clinicians, our Day 3 model is equally as important and takes into account the clinical evolution of the patient. Of the 21 clinical variables assessed for inclusion in this model, we

again found that oxygenation and ventilation variables such as PIP, FiO2, P/F ratio, MAP, and OI were all associated with mortality. As on Day 1, markers of multi-organ dysfunction, including PRISM-3, cumulative fluid balance, PELOD, and extrapulmonary PELOD were associated with mortality, but these associations did not hold after controlling for demographics, OI, and cancer/HSCT.

Interestingly, number of chest x-ray quadrants involved was not associated with mortality on either Day 1 or Day 3. Lung Injury Score, which was not associated with mortality on ARDS day 1, was associated with mortality on ARDS Day 3. However, this score incorporates radiographic findings as well as PEEP, P/F ratio, and lung compliance, and therefore the contribution of radiographic findings cannot be teased apart from the rest of the score components. Radiographic findings are known to have high inter-observer variability (34) and inconsistent association with outcomes, (19, 27) and our work suggests that they may have limited utility in mortality risk-stratification. We again identified the previously reported association between positive cumulative fluid balance on Day 3 and mortality, which may relate to the intensity of initial fluid resuscitation, the degree of capillary leak, or the amount of renal dysfunction. The significance of fluid conservative therapy has been proposed in multiple recent publications and there is growing evidence that limiting excess fluid administration after the initial resuscitation may improve outcomes for some patients (2, 20, 21, 28).

The significance of stratifying ARDS mortality risk by patient history of cancer or HSCT is also paramount. Cancer and HSCT have been associated with mortality since the first descriptions of ARDS in children (13, 30), and our recent work has shown that this continues to be true (31). The precise mechanisms responsible are multifactorial and may relate to pulmonary toxicity of chemotherapy, radiation therapy, opportunistic infections, and in the case of stem cell transplantation, alloreactivity in the setting of immune reconstitution (32). Of note, in the graphical representation of these models (Figure 1 and Figure 2), even cancer/HSCT patients with relatively low OI on Day 1 or Day 3 are at elevated risk for mortality, which may allude to intrinsic differences in their ARDS pathobiology, such as the slower progressive nature of lung disease in the setting of occult infection or pulmonary graft versus host disease. Alternatively, mortality may have been less directly related to ARDS than to other factors associated with their underlying disease. For both cancer/HSCT patients and non-cancer/HSCT patients, the association between OI and mortality is largely linear, with approximately 10–15% increase in mortality for every 20 point increase in OI. This mortality prediction may be useful for families and for clinicians considering additional invasive therapies such as renal replacement therapy and extracorporeal life support.

Consistent with prior work (28), we found that the same OI is associated with higher mortality on Day 3 vs. Day 1. For example, for a child without history of cancer/HSCT, an OI of 40 on Day 1 was associated with approximately 25% mortality, vs. 45% mortality for an OI of 40 on Day 3. This finding speaks to the importance of the first 3 days of ARDS management and also implies the poor prognosis of patients whose OI remains elevated on Day 3. In addition to the analyses reported, we did explore change in OI between days 1 and

3 for associations with mortality. However, that change did not add prognostic value after accounting for the daily OI value, and is therefore less likely to be useful at the bedside.

As the use of respiratory ECLS becomes more prevalent and data are published regarding ECLS outcomes and complications, the ARDS mortality curves presented may be used by clinicians to weigh the risks of using ECLS to the predicted mortality of the patient (33). Unfortunately, the relationship between OI and predicted mortality did not lend itself to clinical cut-offs. Thus, application of OI to patient management will require both consideration of duration of illness and individual patient-dependent risk/benefit analysis.

Our study has several strengths. First, we used a large pediatric ARDS cohort with broad enrollment criteria and the participation of multiple centers. Second, our cohort was contemporary and had mean tidal volume of just over 7 mL/kg, reflecting post-ARDSNet ventilator management strategies. Our focus on risk factors early in the course of ARDS will inform clinically useful mortality prediction, given that rescue therapy is more useful early in the course of disease (34). Finally, we have developed a simple framework for risk stratification, using easily calculable data already in clinical use.

Our study does have limitations. Specifically, we did not have the sample size to divide our cohort into derivation and validation sets. We ameliorated this limitation by using cross-validation to minimize overfitting. However, our novel findings should be validated externally in a large, multicenter study. Another limitation is varying data availability due to the observational nature of this study. For example, OI was unavailable for patients undergoing noninvasive ventilation. Missing data, if their absence was unrelated to outcome, would bias results towards the null. Reassuringly, there were no mortality differences between subjects with missing and non-missing values; to continue the OI example, there was no mortality difference between patients with vs. without recorded OI, but those with OI had increasing mortality with increasing OI. In addition, the underlying study population was identical on the two study days, as no patients had died or been transferred from intensive care by Day 3.

Conclusions

We have identified a simple framework for bedside prediction of mortality among children with ARDS that can be applied to patients on Day 1 or Day 3 of disease. We explored 21 clinical variables and using two statistical techniques, developed a robust best-fit model of mortality that employs only OI and history of cancer/HSCT only. Additional respiratory variables and complex scores quantifying severity of initial illness and accumulation of extrapulmonary organ dysfunction, while associated with mortality, did not add independent prognostic value. The predictive value of OI and cancer/HSCT history early in the course of pediatric ARDS may be helpful in the clinical risk stratification required for application of high-risk therapies, counseling families, and enrollment in clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: NIH 5T32HD049303-08 (ACS), HL110969 (CSC), NHLBI K23 HL085526 (AS), NHLBI HL114484 (R01) (AS).

Dr. Sapru received support for article research from the National Institutes of Health (NIH). His institution received funding from the NIH. Dr. Spicer received support for article research from the NIH. His institution received funding from the NIH. Dr. Calfee disclosed other support (Member of Board of Directors of American Thoracic Society) and received funding from Boehringer Ingelheim. Her institution received funding from Glaxo Smith Kline. Dr. Zinter received support for article research from the NIH. Dr. Khemani's institution received funding from the NIH. Dr. Alkhouli received support for article research from the NIH. His institution received funding from the NIH. Dr. Boriosi received support for article research from the NIH. His institution received funding from the NIH. Dr. Flori disclosed other support (She received Department of Defense funding for clinical decision support systems and received honoraria from hospitals for giving educational lectures. None of these activities are related to the research involved in this publication) and received support for article research from the NIH. Dr. Matthay received support for article research from the NIH; received funding from RocheGenentec (Chair of DSMB for a clinical trial of asthma); and disclosed other support from GlaxoSmithKline (part of a DSMB for trial in critically ill patients), Cerus Inc (consulting services), Biogen (consulting services), and Quark Pharmaceutical (consulting service). His institution received funding from GlaxoSmithKline (grant to study biomarkers of sepsis) and Amgen (grant to study lung injury in mice).

References

1. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. the acute respiratory distress syndrome network. N Engl J Med. 2000; 342:1301–1308. [PubMed: 10793162]
2. Wiedemann HP, Wheeler AP, et al. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006; 354:2564–2575. [PubMed: 16714767]
3. Albuali WH, Singh RN, Fraser DD, et al. Have changes in ventilation practice improved outcome in children with acute lung injury? Pediatr Crit Care Med. 2007; 8:324–330. [PubMed: 17545937]
4. Erickson S, Schibler A, Numa A, et al. Acute lung injury in pediatric intensive care in Australia and New Zealand: A prospective, multicenter, observational study. Pediatr Crit Care Med. 2007; 8:317–323. [PubMed: 17545931]
5. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: Consensus recommendations from the pediatric acute lung injury consensus conference. Pediatr Crit Care Med. 2015; 16:428–439. [PubMed: 25647235]
6. Sapru A, Flori H, Quasney MW, et al. Pathobiology of acute respiratory distress syndrome. Pediatr Crit Care Med. 2015; 16:S6–S22. [PubMed: 26035365]
7. Tamburro RF, Kneyber MC. Pediatric Acute Lung Injury Consensus Conference Group. Pulmonary specific ancillary treatment for pediatric acute respiratory distress syndrome: Proceedings from the pediatric acute lung injury consensus conference. Pediatr Crit Care Med. 2015; 16:S61–S72. [PubMed: 26035366]
8. Curley MA, Hibberd PL, Fineman LD, et al. Effect of prone positioning on clinical outcomes in children with acute lung injury: A randomized controlled trial. JAMA. 2005; 294:229–237. [PubMed: 16014597]
9. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013; 368:2159–2168. [PubMed: 23688302]
10. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med. 2010; 363:1107–1116. [PubMed: 20843245]
11. Elbahlawan L, Morrison RR. Continuous renal replacement therapy in children post-hematopoietic stem cell transplantation: The present and the future. Curr Stem Cell Res Ther. 2012; 7:381–387. [PubMed: 22834995]
12. Rehder KJ, Turner DA, Cheifetz IM. Extracorporeal membrane oxygenation for neonatal and pediatric respiratory failure: An evidence-based review of the past decade (2002–2012). Pediatr Crit Care Med. 2013; 14:851–861. [PubMed: 24108118]

13. Yehya N, Servaes S, Thomas NJ. Characterizing degree of lung injury in pediatric acute respiratory distress syndrome. Crit Care Med. 2015; 43:937–946. [PubMed: 25746744]
14. Flori HR, Glidden DV, Rutherford GW, et al. Pediatric acute lung injury: Prospective evaluation of risk factors associated with mortality. Am J Respir Crit Care Med. 2005; 171:995–1001. [PubMed: 15618461]
15. Rettig JS, Smallwood CD, Walsh BK, et al. High-Frequency Oscillatory Ventilation in Pediatric Acute Lung Injury: A Multicenter International Experience. Crit Care Med. 2015; 43(12):2660–2667. [PubMed: 26317570]
16. Hu X, Qian S, Xu F, et al. Incidence, management and mortality of acute hypoxemic respiratory failure and acute respiratory distress syndrome from a prospective study of Chinese paediatric intensive care network. Acta Paediatr. 2010; 99:715–721. [PubMed: 20096024]
17. Santschi M, Jouvet P, Leclerc F, et al. Acute lung injury in children: Therapeutic practice and feasibility of international clinical trials. Pediatr Crit Care Med. 2010; 11:681–689. [PubMed: 20228688]
18. Lopez-Fernandez Y, Azagra AM, de la Oliva P, et al. Pediatric acute lung injury epidemiology and natural history study: Incidence and outcome of the acute respiratory distress syndrome in children. Crit Care Med. 2012; 40:3238–3245. [PubMed: 22990455]
19. Zhu YF, Xu F, Lu XL, et al. Mortality and morbidity of acute hypoxemic respiratory failure and acute respiratory distress syndrome in infants and young children. Chin Med J (Engl). 2012; 125:2265–2271. [PubMed: 22882846]
20. Valentine SL, Sapru A, Higgerson RA, et al. Fluid balance in critically ill children with acute lung injury. Crit Care Med. 2012; 40:2883–2889. [PubMed: 22824936]
21. Willson DF, Thomas NJ, Tamburro R, et al. The relationship of fluid administration to outcome in the pediatric calfactant in acute respiratory distress syndrome trial. Pediatr Crit Care Med. 2013; 14:666–672. [PubMed: 23925143]
22. Zimmerman JJ, Akhtar SR, Caldwell E, et al. Incidence and outcomes of pediatric acute lung injury. Pediatrics. 2009; 124:87–95. [PubMed: 19564287]
23. Sapru A, Curley MA, Brady S, et al. Elevated PAI-1 is associated with poor clinical outcomes in pediatric patients with acute lung injury. Intensive Care Med. 2010; 36:157–163. [PubMed: 19855955]
24. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, Mechanisms, Relevant Outcomes, and Clinical Trial Coordination. Am J Respir Crit Care Med. 1994; 149:818–824. [PubMed: 7509706]
25. Khemani RG, Patel NR, Bart RD 3rd, Newth CJ. Comparison of the pulse oximetric saturation/fraction of inspired oxygen ratio and the PaO2/fraction of inspired oxygen ratio in children. Chest. 2009; 135(3):662–668. [PubMed: 19029434]
26. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009; 42:377–381. [PubMed: 18929686]
27. Vittinghoff, E. Regression methods in biostatistics: Linear, logistic, survival, and repeated measures models. 2nd. New York: Springer; 2012. p. 399-400.
28. Khemani RG, Conti D, Alonzo TA, et al. Effect of tidal volume in children with acute hypoxemic respiratory failure. Intensive Care Med. 2009; 35:1428–1437. [PubMed: 19533092]
29. Flori HR, Church G, Liu KD, et al. Positive fluid balance is associated with higher mortality and prolonged mechanical ventilation in pediatric patients with acute lung injury. Crit Care Res Pract. 2011; 2011:854142. [PubMed: 21687578]
30. Timmons OD, Dean JM, Vernon DD. Mortality rates and prognostic variables in children with adult respiratory distress syndrome. J Pediatr. 1991; 119:896–899. [PubMed: 1960603]
31. Zinter MS, DuBois SG, Spicer A, et al. Pediatric cancer type predicts infection rate, need for critical care intervention, and mortality in the pediatric intensive care unit. Intensive Care Med. 2014; 40:1536–1544. [PubMed: 25023526]
32. Zinter MS, Dvorak CC, Spicer A, et al. New insights into multicenter PICU mortality among pediatric hematopoietic stem cell transplant patients. Crit Care Med. 2015; 43:1986–1994. [PubMed: 26035280]

33. Dalton HJ, Macrae DJ. Pediatric Acute Lung Injury Consensus Conference Group. Extracorporeal support in children with pediatric acute respiratory distress syndrome: Proceedings from the pediatric acute lung injury consensus conference. Pediatr Crit Care Med. 2015; 16:S111–S117. [PubMed: 26035361]

34. Zabrocki LA, Brogan TV, Statler KD, et al. Extracorporeal membrane oxygenation for pediatric respiratory failure: Survival and predictors of mortality. Crit Care Med. 2011; 39:364–370. [PubMed: 20959787]

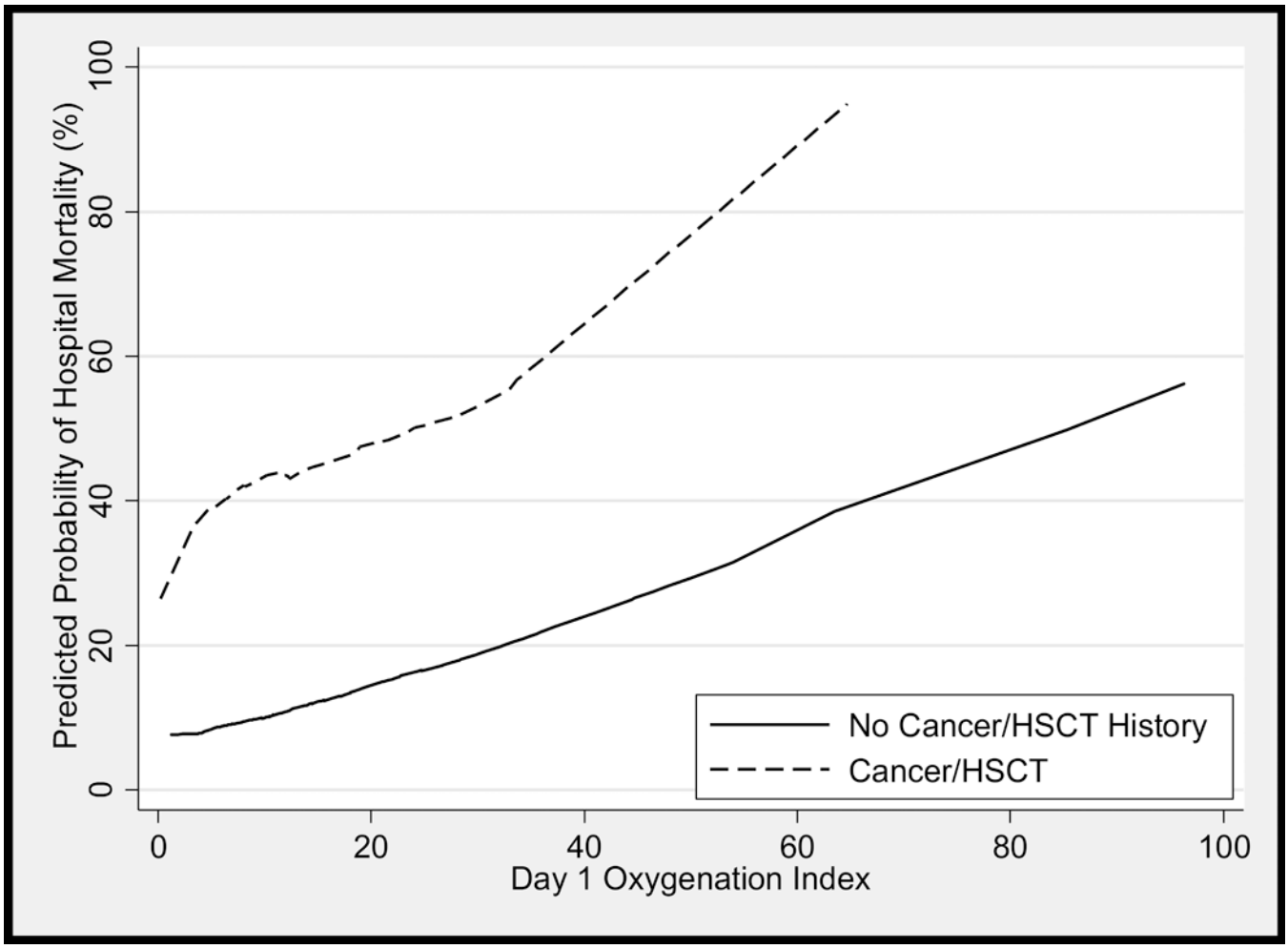

Figure 1. Predicted Probability of Hospital Mortality vs. Day 1 Oxygenation Index

Predicted probability of hospital mortality vs. oxygenation index on the first day after ARDS onset, stratified by history of cancer and/or hematopoietic stem cell transplant (HSCT) and adjusted for age, sex, race, ethnicity, and direct vs. indirect lung injury (n=206).

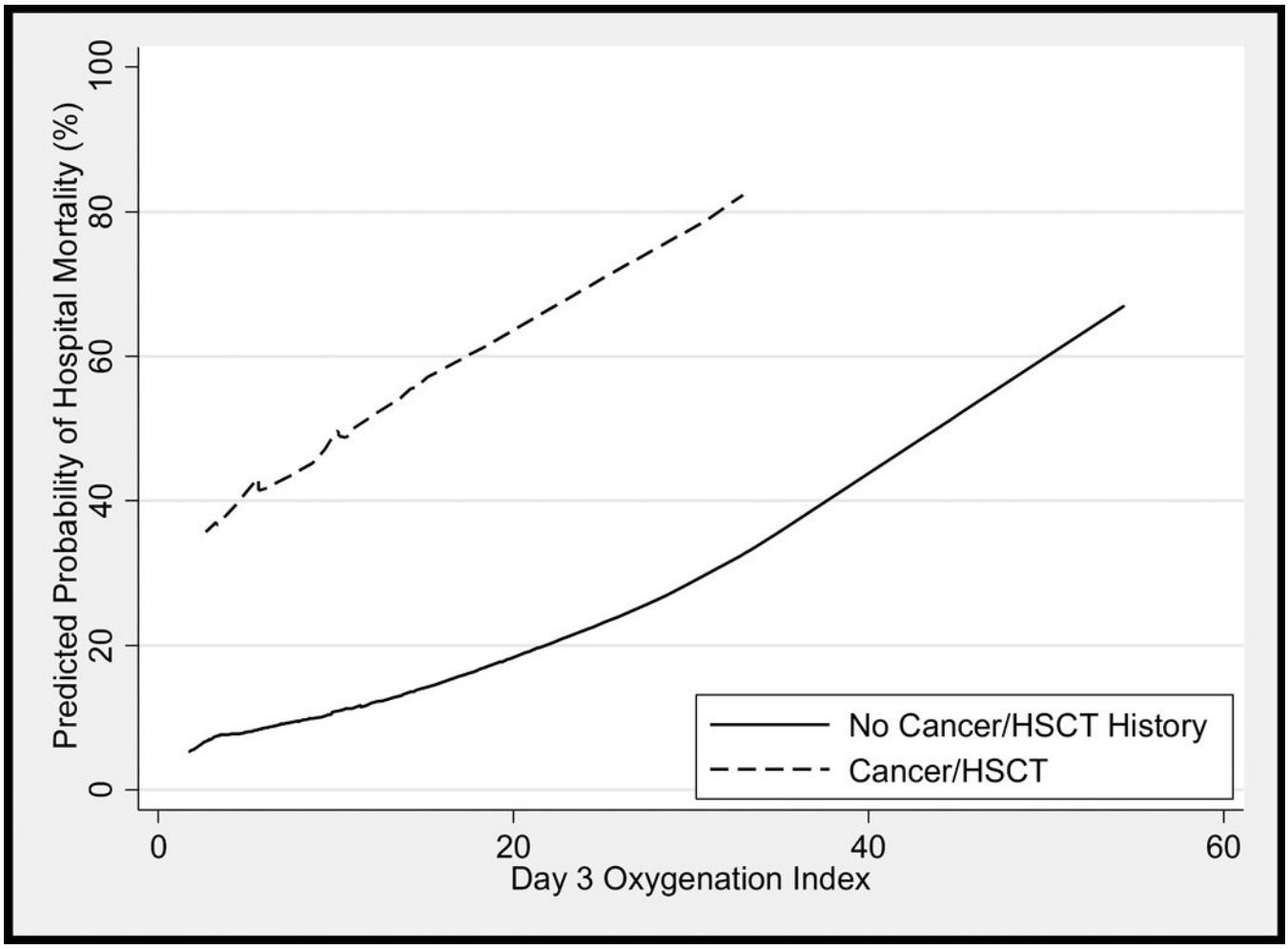

Figure 2. Predicted Probability of Hospital Mortality vs. Day 3 Oxygenation Index

Predicted probability of hospital mortality vs. oxygenation index on the third day after ARDS onset, stratified by history of cancer and/or hematopoietic stem cell transplant (HSCT) and adjusted for age, sex, race, ethnicity, and direct vs. indirect lung injury (n=194).

Table 1

Characteristics of ARDS Patients at Enrollment

Characteristic	All Subjects	Survivors	Non-Survivors	p-value
Number of Patients (%)	308 (100)	257 (83.4)	51 (16.6)	
Median Age, Years (IQR)	5.1 (1.2, 12.7)	4.9 (1.1, 12.7)	7.2 (2.4, 12.6)	0.31
Male (%)	56	53	67	0.08
Race				0.94
Asian/Pacific Islander (%)	6.8	6.6	7.8	
Black or African-American (%)	7.5	7.4	7.8	
White (%)	62.7	63.4	58.8	
Other/Unknown (%)	23	22.6	25.5	
Ethnicity				
Latino/Hispanic (%)	37.7	37.3	39.2	0.89
Past Medical History				
Cancer (%)	11.4	7.4	31.4	<0.001
HSCT (%)	8.8	4.3	31.4	<0.001
Cancer and/or HSCT (%)	15.3	9.7	43.1	<0.001
Other (%)	55.2	54.5	58.8	0.57
ARDS Etiology				
Pneumonia (%)	58.4	59.1	54.9	0.57
Aspiration (%)	3.3	3.1	3.9	0.77
Sepsis (%)	21.1	20.2	25.5	0.4
Trauma (%)	5.2	5.5	3.9	0.65
Transfusion-Related (%)	2.3	2	3.9	0.39
Other (%)	9.7	10.1	7.8	0.62
Initial Respiratory Support				
Conventional Mechanical Ventilation (%)	76.6	75.8	80.4	0.45
High Frequency Oscillator (%)	4.2	3.9	5.9	0.52
CPAP/BiPAP (%)	4.6	4.7	3.9	0.82
High Flow Nasal Cannula (%)	14.7	15.6	9.8	0.29

Characteristic	All Subjects	Survivors	Non-Survivors	p-value
Median PRISM-3 (IQR)	12 (6, 19)	11 (5, 17)	17 (10, 22)	<0.001

Table 2

Daily Clinical Variables, Stratified by Mortality

	Day 1 Values				Day 3 Values			
Variable	**n**	**Survivors**	**Non-Survivors**	**p-value**	**n**	**Survivors**	**Non-Survivors**	**p-value**
Ventilation								
PIP, mean±SD, cm H_2O	228	27.9±7.3	30.5±8.3	**0.014**	200	26±6.2	29.3±8	**0.008**
PEEP, median (IQR), cm H_2O	231	7 (5, 10)	8 (7.5, 12)	**<0.001**	200	8 (5, 10)	9 (6, 10)	0.064
Exhaled Tidal Volume, median (IQR), mL/kg	215	7.22 (6.17, 8.6)	7.21 (5.99, 7.92)	0.27	188	7 (5.8, 8.4)	7.2 (5.9, 10)	0.57
Respiratory Rate, mean±SD, breaths/min	226	28.4±11	29.1±10.1	0.72	198	29.3±11.3	29.7±13.1	0.86
Dynamic Compliance, median (IQR), mL/kg/cm H_2O	207	0.38 (0.27, 0.52)	0.35 (0.26, 0.44)	0.28	185	0.42 (0.31, 0.56)	0.39 (0.28, 0.67)	0.77
Oxygenation								
FiO_2, median (IQR)	300	0.6 (0.45, 0.91)	0.6 (0.51, 1)	0.10	276	0.45 (0.4, 0.6)	0.55 (0.41, 0.7)	**0.001**
P/F Ratio, median (IQR)	274	196 (124, 280)	129 (93, 167)	**0.005**	261	196 (124, 280)	129 (93, 167)	**<0.001**
Mean Airway Pressure, median (IQR), cm H_2O	236	13 (11, 17)	14.9 (8.1, 28)	**<0.001**	223	14 (10, 17)	16 (12.5, 20.5)	**0.022**
Oxygenation Index, median (IQR), cm H_2O/mmHg	218	9.7 (5, 18)	17 (9.1, 28)	**0.001**	210	7 (4.7, 14.4)	13.5 (9.7, 21.2)	**<0.001**
Imaging								
CXR Quadrants Infiltrated, median (IQR)	261	3 (3, 4)	4 (3, 4)	0.56	238	3 (2,4)	4 (3, 4)	0.31
Lung Injury Score, median (IQR)	261	2 (1.5, 2.5)	2 (1.5, 2.5)	0.53	238	1.75 (1.25, 2.25)	2.25 (1.75, 3.33)	**0.012**
Multi-Organ Dysfunction								
Required Vasoactive Drip, %	307	40	43	0.662	305	40	48	0.27
Cumulative Fluid Balance, mean±SD, L/m^2	264	0.86±1.2	1.1±1.6	0.26	261	1.49±2.34	2.79±3.31	**0.003**
DailyPELOD, median (IQR)	308	12 (10, 20)	12 (12, 23)	**0.016**	308	12 (2, 12)	12 (10, 22)	**0.001**
Daily Extrapulmonary PELOD, median (IQR)	308	10 (1, 12)	10 (10, 20)	**0.009**	308	10 (0, 10)	10 (1, 20)	**0.002**

Table 3

Logistic Model of Hospital Mortality, by Day 1 and Enrollment Variables

Variable	Univariate Model			Multivariable Model		
	Mortality OR	**95% CI**	**p-value**	**Mortality OR**	**95% CI**	**p-value**
Age, years	1.02	0.97–1.08	0.36	1.05	0.97–1.13	0.21
Male Sex	1.75	0.93–3.29	0.082	1.93	0.80–4.66	0.14
Race (vs. White)						
Asian/Pacific Islander	1.27	0.40–4.06	0.68	3.77	0.75–18.99	0.11
Black or African-American	1.14	0.36–3.60	0.63	2.16	0.46–10.13	0.33
Other	1.22	0.59–2.49	0.35	2.34	0.89–6.14	0.085
Latino	1.11	0.59–2.08	0.75	1.77	0.67–4.68	0.25
PRISM-3	1.05	1.01–1.08	**0.005**	0.99	0.94–1.05	0.78
Daily Extrapulmonary PELOD	1.04	1.01–1.07	**0.021**	1.03	0.98–1.08	0.26
Direct Lung Injury	0.82	0.44–1.51	0.53	0.91	0.38–2.17	0.84
Cancer/HSCT	7.04	3.53–14.05	<**0.001**	6.59	2.50–17.39	<**0.001**
Oxygenation Index, 10 cm H_2O/mmHg	1.32	1.07–1.64	**0.012**	1.43	1.08–1.91	**0.013**

Table 4

Logistic Model of Hospital Mortality, by Day 3 and Enrollment Variables

	Univariate Model			Multivariable Model		
Variable	**Mortality OR**	**95% CI**	**p-value**	**Mortality OR**	**95% CI**	**p-value**
Age	1.02	0.97–1.08	0.36	1.06	0.97–1.16	0.17
Male Sex	1.75	0.93–3.29	0.08	2.36	0.86–6.46	0.094
Race (vs. White)						
Asian/Pacific Islander	1.28	0.40–4.06	0.68	1.45	0.19–10.81	0.72
Black or African-American	1.14	0.36–3.60	0.82	3.31	0.62–17.73	0.16
Other	1.22	0.59–2.49	0.59	1.01	0.29–3.48	0.99
Latino	1.08	0.58–2.00	0.8	1.10	0.36–3.42	0.87
PRISM-3	1.05	1.02–1.08	**0.002**	1.01	0.95–1.07	0.85
Daily Extrapulmonary PELOD	1.06	1.02–1.11	**0.002**	1.03	0.95–1.11	0.5
Direct Lung Injury	0.82	0.44–1.51	0.53	0.79	0.28–2.20	0.65
Cumulative Fluid Balance (L/m^2)	1.19	1.05–1.34	**0.005**	1.05	0.88–1.26	0.56
Cancer/HSCT	7.04	3.53–14.05	**<0.001**	9.21	3.04–27.87	**<0.001**
Oxygenation Index (10 cm H_2O/mmHg)	1.74	1.26–2.42	**0.001**	2.03	1.26–3.27	**0.004**