I, Bryce RH Robinson M.D., hereby submit this original work as part of the requirements for the degree of Master of Science in Clinical and Translational Research.

It is entitled:
Implications of acute resuscitation and mechanical ventilation strategies upon pulmonary complications following injury

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Implications of acute resuscitation and mechanical ventilation strategies upon pulmonary complications following injury

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by

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ABSTRACT

Background: Hypoxemia following injury contributes significant morbidity and mortality following trauma. The identification of modifiable risk factors for the prevention of acute lung injury in trauma patients remains unclear. We hypothesize that acute crystalloid administration and tidal volume delivery from mechanical ventilation may represent novel modalities to mitigate negative pulmonary outcomes in critically injured patients.

Methods: A retrospective, case-control study was undertaken after merging of the institutional trauma registry, trauma ventilator registry and the electronic medical record data from 2/2011 to 8/2014. Patients with survival > 24 hours, at least one PaO$_2$ to FiO$_2$ (P/F) ratio recorded during the first 7 days of hospitalization, and a tidal volume recorded during the first 2 days were included in the final analyses. Multivariate logistic regression models were utilized to investigate the contributions of demographic and injury characteristics, as well as blood products, crystalloid, and tidal volume exposures to negative pulmonary outcomes. The primary outcome of interest was the development of moderate to severe hypoxemia (P/F ratio ≤ 200 mm Hg) during days 1-7. A secondary composite pulmonary outcome was created that included the development of in-hospital pneumonia, tracheostomy, moderate to severe hypoxemia, acute respiratory distress syndrome (ARDS), or early death occurring during days 1-7.

Results: Of the 661 patients within the dataset, 531 met inclusion criteria. The median age was 42 years, ISS was 24, 77% were male, 26% suffered a penetrating injury, and 57% experienced a P/F ≤ 200 mm Hg. The median tidal volume was 7.8 (7.0-8.7) mL/kg of predicted body weight and the median crystalloid exposure in the first 24 hours was 2.3 (1.4-3.4) half liters. Those with
high tidal volume exposure (>8 ml/kg, n = 224) were significantly older, female, and received less platelets. Those with high crystalloid amounts (> 3 half liters, n = 175) were significantly younger, had more penetrating injuries, were more commonly hypotensive on emergency department evaluation, had a higher Glasgow coma scale on admission, and had more crystalloid, packed red blood cell, and plasma needs. High crystalloid users also had a greater intensive care unit and hospital lengths of stay, ventilator days, and developed ARDS more often. Age (odds ratio [OR] 1.02, 95% confidence interval [CI] 1.01-1.04, p < 0.01) and chest abbreviated injury score (AIS) (OR 1.43 [CI 1.25-1.62], p < 0.01) were risk factors for a P/F ≤ 200 mm Hg. Age (OR 1.03 [1.02-1.04], p = 0.04), head AIS (OR 1.3 [CI 1.15-1.47], p < 0.01), chest AIS (OR 1.32 [OR 1.16-1.51], p < 0.01), and crystalloid during the first 24 hours (OR 1.17 [1.00-1.37], p = 0.05) were found to be risk factors for a negative composite pulmonary outcome.

**Conclusions:** Crystalloid, but not tidal volume, exposure appears to be a modifiable risk factor for pulmonary complications. Further work should focus on trauma sub-populations that may have the greatest benefit from these preventative acute interventions.
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CHAPTER I

INTRODUCTION

Injury continues to be a leading cause of death worldwide and is the leading cause of years of life lost due to premature mortality. Improvements in trauma care have resulted in the survival of patients that otherwise would have died secondary to acute hemorrhage during the initial period of care. However, patients who live are placed at a higher risk of developing “diseases of survivorship” that have the commonality of dysfunctional acute inflammation.

Hypoxemia and its more severe form, acute respiratory distress syndrome (ARDS), are the pulmonary sequelae of this pro-inflammatory state. Hypoxemia is present in over 70% of patients who initially survive major trauma. Hypoxic death may subsequently occur due to failed gas exchange at the level of alveoli units that become laden with edema and exudative fluid from cell-mediated inflammation. Because of the difficulty in recognizing the initial clinical presentation of sub-clinical lung injury, treatment strategies to rescue the patient are often initiated only after severe pulmonary damage has occurred, leading to a relatively high mortality risk that has been unchanged over the last twenty years.

Specific resuscitation and mechanical ventilation strategies may represent opportunities to mitigate the development of hypoxemia in high-risk trauma patients. Hemorrhage is one of the leading causes of death for trauma patients, with the majority of these occurring in the first 6 hours following injury. Fundamental in the prevention of hemorrhagic death is the resuscitation of trauma patients immediately following injury. Intravenous volume replacement with crystalloid fluids, specifically Ringer’s lactate or normal saline, is the initial step in resuscitation from hypovolemia. In the event that ongoing blood loss is detected, crystalloid fluids are
supplemented with blood transfusions as guided by the American College of Surgeons’ Advanced Trauma Life Support algorithms. The standard resuscitation strategy has been recently challenged in those with severe hemorrhagic shock. Termed damage control resuscitation (DCR), this new method of resuscitation aims to reduce crystalloid exposure by transfusing component therapy of packed red blood cells (pRBCs) and fresh frozen plasma (FFP) in ratios that mimic whole blood. DCR has been associated with reduced rates of early death in both military and civilian settings, but results in the increased exposure of patients to blood products. This exposure may cause harm, specifically transfusion related acute lung injury (TRALI). In trauma patients specifically, pRBCs and FFP exposures have been associated with higher rates of lung injury, even in the era of DCR. Nonetheless, work from our group has demonstrated a reduction in hypoxemia associated with the use of DCR. Furthermore, we have clarified that acute hypoxemia appears to be associated with even minimal increments of crystalloid exposure as opposed to blood products. Thus, although this remains an area of controversy, it appears that an acute resuscitation strategy that minimizes crystalloid may be a viable intervention in the prevention of ALI in high-risk bleeding patients.

Acute mechanical ventilation strategies may also play a role in the reduction of hypoxemia. Traditional ventilation practices with tidal volumes (V_T) of 10-15 mL/kg of predicted body weight have been recommended to prevent hypoxemia and atelectasis. However, ventilator-induced lung injury (VILI) is a known complication of excessive V_T. VILI occurs by the repetitive overstretching of alveoli causing interstitial protein leak into the airways and repetitive opening and closing of alveoli secondary to insufficient end-expiratory pressure. The end result of this en mass alveolar injury is pulmonary edema, leukocyte-mediated inflammation, and impaired gas exchange leading to hypoxemia. Lung protective ventilation strategies in
subjects with signs of acute hypoxemia aim to reduce VILI by applying reduced breath $V_T$ at 6-8 mL/kg of predicted body weight. The application of low $V_T$s after the diagnosis of hypoxemia significantly reduces mortality and is considered a critical care best practice.\textsuperscript{5,26,27} Controversy exists regarding the widespread application of reduced $V_T$ to all ventilated patients because low $V_T$ is associated with progressive atelectasis leading to hypercapnic respiratory acidosis with the potential for increased pulmonary infections and hemodynamic instability.\textsuperscript{28-30} Nonetheless, multiple studies have demonstrated poor pulmonary outcomes of critically ill medical patients that received $V_T$ in excess of 6 mL/kg, though its application to trauma patients during the acute phases of care remains unknown.\textsuperscript{31-37}

The object of this study was to understand the relationship and interaction of acute crystalloid exposures and $V_T$ to negative pulmonary outcomes in critically injured patients. Our central hypothesis is that specific, modifiable resuscitation and ventilation strategies exist that mitigate negative pulmonary outcomes in severely injured patients.
CHAPTER II

METHODS

Study Population

Three individual datasets, which included the University of Cincinnati Trauma Ventilator Registry, the University Hospital Trauma Registry and the University Hospital electronic medical record, were merged to create the stand-alone University of Cincinnati Acute Lung Injury (UC ALI) database. UC ALI patient inclusion criteria included having an injury with an International Classification of Diseases (ICD)-9 code from 800-959.0 (excluding codes 905-909.9, 910-924.9 and 930-939.9), classified as a hospital admission, transfer or death resulting from trauma, and having at least a single day of mechanical ventilation. A retrospective evaluation of the dataset was performed using data from 2/21/2011 to 7/31/2014. Patients with mechanical ventilation prior to injury, those with a length of stay < 24 hours and those without a PaO\textsubscript{2} to FiO\textsubscript{2} (P/F) ratio measurement were excluded from analyses. An additional a priori population of interest were those who received a transfusion of pRBC during the first 24 hours of hospitalization.

Study Variables

The primary independent variables of interest included the highest $V_T$ during the first 2 days of mechanical ventilation and crystalloid exposure recorded during the first 6 and first 24 hours after admission. Tidal volume comparisons between patients were made using predicted body weights (PBW, mL/kg). Crystalloid solutions were defined as the sum of saline, Lactated Ringer’s solutions, Normosol-R® (Hospira, Lake Forest, IL), and Plasma-Lyte A® (Baxter
Healthcare Corporation, Deerfield IL) infused. Crystalloid fluid exposure was compared using aliquots of half-liter volumes. Other demographic variables of interest included age, sex, and mechanism of injury. To adjust for injury severity and the contribution to lung injury, initial emergency department (ED) systolic blood pressure, Injury Severity Score (ISS) with individual body region scores (Abbreviated Injury Scale [AIS]), as well blood product exposures were evaluated. 38

**Definition of Pulmonary Outcomes**

The categorization of hypoxemia was based on the Berlin definition of ARDS. 4,39 Hypoxemia was categorized as severe (P/F ≤ 100 mm Hg), moderate (P/F 101-200 mm Hg), mild (P/F 201-300 mm Hg) or none (P/F > 300 mm Hg). PaO₂ to FiO₂ ratios used for analysis were limited to values collected during the first 7 days of hospitalization. If multiple values existed for a given day, the most severe value was utilized. The primary outcome of interest was the proportion of patients who had severe or moderate hypoxemia (P/F ≤ 200 mm Hg) at any time during the first 7 days of care.

Secondary outcomes of interest included the duration of hospital and ICU stay, location of discharge from the institution as well as early mortality, defined as a death occurring within the first 7 days of admission, and the in-hospital mortality rate. Specific secondary pulmonary complications of interest included the number of ventilator days, ventilator-free days in 30, rates of in-hospital performed tracheostomy, pneumonia, and occurrence of ARDS. 40

The National Trauma Data Bank’s (NTDB) definitions for pneumonia and ARDS were utilized. 41 This definition indentifies pneumonia as occurring during hospitalization and meeting at least one of the listed two criteria: (1) rales or dullness to percussion on physical exam of the
chest and least any of the following; new onset of purulent or change in character of sputum, organism isolated from the blood, or isolation of pathogen from specimens obtained by trans-tracheal aspirate, bronchial brushing or biopsy; or (2) chest radiograph with new or progression infiltrate/consolidation/cavitation/pleural effusion and any of the following; new onset of purulent or change in character of sputum, organism isolated from the blood, or isolation of pathogen from specimens obtained by trans-tracheal aspirate, bronchial brushing or biopsy, isolation or detection of respiratory virus, diagnostic single antibody titer for a respiratory pathogen, or histopathologic evidence of pneumonia. The NTDB definition of ARDS includes the occurrence of acute hypoxemia occurring within 7 days of a known clinical insult, bilateral opacities on chest imaging, respiratory failure not fully explained by a cardiac source, and a P/F ratio < 200 mm Hg (or 300 mm Hg with positive end-expiratory pressure ≥ 5 cm of H2O).

Finally, a composite pulmonary outcome (CPO) was created as a secondary outcome. Patients with any event of moderate to severe hypoxemia (P/F ≤ 200 mm Hg) during the first 7 days of hospitalization, in-hospital pneumonia, tracheostomy, ARDS, or early death were analyzed as having a negative CPO.

Data Analysis

In an effort to examine clinically meaningful outcomes from excessive crystalloid and VT exposures, threshold values were created by rounding median values to the next highest whole value. To determine the odds of severe-to-moderate hypoxemia (P/F ≤ 200 mm Hg) compared to with mild or no hypoxemia (P/F >200 mm Hg), odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using logistic regression with clinically meaningful variables. Description of continuous variables utilized median values (with interquartile ranges). Chi-square and
Wilcoxon rank-sum tests were used to compare relevant groups as applicable. Significance was defined as $p \leq 0.05$. All data analysis was performed using SAS version 9.4 (Cary, NC).
CHAPTER III

RESULTS

Overall

A total of 661 patients were identified within the UC ALI dataset. The final study cohort included 531 patients (80.3%) with mechanical ventilation use, a survival of $\geq 24$ hours and $\geq 1$ P/F ratio recorded (Figure 1). The median age for the entire cohort was 42 (27-55) years, 76.8% were male and 25.8% experienced a penetrating injury. Approximately 14.2% presented to the ED with an initial systolic blood pressure $< 90$ mmHg and 39.7% with a Glasgow coma scale (GCS) $\leq 8$. The median ISS was 24 (17-30). Those with non-zero AIS scores had median head scores of 4 (3-5), chest of 3 (2-3), and abdomen of 3 (2-4). The median length of stay (LOS) in the ICU was 9 (5-18) days and 13 (7-22) days in the hospital. Approximately 56.7% of patients experienced a non-home discharge with 23.7% having a discharge to a long-term assisted-care facility. Early death (within 7 days of admission) occurred in 8.6% of the cohort while the overall in-hospital mortality rate was 10.2%. In-hospital pneumonia occurred in 36.3%, tracheostomy in 34.2%, moderate to severe hypoxemia in 58.4%, and ARDS in 11.3%.

Patient Characteristics by $V_T$ and Crystalloid Exposure

Patients were exposed to a median of 2.3 (1.4-3.4) half-liter aliquots of crystalloid during the first 24 hours of care (Figure 2). The median maximum calculated $V_T$ mL/kg by PBW during the first 2 days was 7.8 mL/kg (7.0 – 8.7) (Figure 3). Rounding to the highest whole number for these variables produced a “cut-off” of 3 half-liters of crystalloid and 8 ml/kg by PBW for $V_T$. Comparisons between cohorts with low vs. high crystalloid ($\leq 3$ vs. $>3$ half-liters) and $V_T$ ($\leq 8$ vs.
>8 ml/kg) exposures were performed (Table 1). A significantly greater proportion of women were exposed to high (38.4% vs. 12.0%, p < 0.01) compared to low Vₜ. High tidal volume exposure was also associated with a significantly lower rate of penetrating injury (21.0% vs. 29.3%, p = 0.03), a higher rate of skilled nursing facility discharge (15.6% vs. 8.8%, p = 0.02), and greater median age (45 vs. 39, p = 0.05).

Those with a high crystalloid exposure were younger (36 vs. 44, p = 0.01), male (81.7% vs. 74.4%, p = 0.06), had a higher rate of penetrating injury (38.3% vs. 19.7%, p < 0.01), an improved GCS on presentation (proportion with GCS ≤ 8, 28.1% vs. 45.4%, p < 0.01), hypotension on admission (proportion with SBP < 90 mm Hg, 22.7% vs. 10.3%, p < 0.01), and a higher abdomen AIS (p = 0.02). This cohort experienced a significantly longer ICU (11 vs. 9 days, p < 0.01) and hospital LOS (16 vs. 12 days, p < 0.01). No differences in the location of disposition or mortality were found between crystalloid groups.

**Pulmonary Outcomes by Vₜ and Crystalloid Exposure**

The median Vₜ in those categorized as having high Vₜ was 8.8 (8.5-9.8) mL/kg of PBW while the median in the low subgroup was 7.1 (6.7-7.6, p < 0.01, Table 2). Exposure to high tidal volume was associated with a trend towards developing ARDS (14.3% vs. 9.1%, p = 0.06). Those exposed to high crystalloid had a significantly higher rate of ARDS (16.0% vs. 9.0%, p = 0.02). High fluid exposure was also associated with a larger number of ventilator days (7 vs. 5, p = 0.02) though when normalized by using ventilator-free days in 30, no difference was found between the crystalloid cohorts. No differences were seen between hypoxemia categories, pneumonia, tracheostomy and negative composite pulmonary outcomes rates between high vs. low Vₜ and crystalloid groups.
Resuscitation Characteristics by $V_T$ and Crystalloid Exposure

Exposure to platelets was significantly lower in those with $V_T > 8$ mL/kg (1 vs 2 units, $p = 0.04$, Table 3). Otherwise, blood products, crystalloid infused, and ratio of pRBC to plasma was not different at 6 or 24 hours after admission by $V_T$ category. Those with > 3 half-liters of crystalloid during the first 24 hours of care had significantly higher fluid, pRBC and plasma requirements at the 6 hour interval (1.7 vs. 0.5 half liters, $p < 0.01$; 5 vs. 4, $p < 0.01$; 5 vs. 4 units, $p = 0.02$, respectively) and at 24 hours (4.0 vs. 1.7 half-liters, $p < 0.01$; 6 vs. 4, $p < 0.01$; 6 vs. 4 units, $p < 0.01$, respectively). Platelets transfused during the first 6 hours and 24 hours were not associated with the volume of crystalloid infused. Higher proportions of patients were critical admission threshold of blood transfused (CAT+: $\geq$ 3 units of pRBC transfused during any single hour during the first 24 hours of care) positive (31.4% vs. 11.2%, $p < 0.01$) and experienced a massive transfusion (MT: $\geq$ 10 units pRBC during the first 24 hours; 16.6% vs. 3.4%, $p < 0.01$) in the high fluid cohort.\(^\text{42}\)

Determination of Modifiable Risk Factors for Hypoxemia

The association of relevant clinical variables as well as blood, crystalloid, and $V_T$ with the development of moderate to severe hypoxemia was determined (Table 4). Variable significant in univariate analysis for a P/F ratio $\leq$ 200 mm Hg during the first week of care were age, having a blunt injury, and chest AIS. Both pRBC and platelets transfused during the first 24 hours had trends towards univariate significance. Multivariable regression determined age (OR 1.02, [CI 1.01-1.04]; $p < 0.01$) and chest AIS (OR 1.43, [1.25-1.62]; $p < 0.01$) as significant risk factors for hypoxemia. Crystalloid at 24 hours and $V_T$ approached, but did not reach, significance (OR 1.13 [0.98-1.31]; $p = 0.09$ and OR 1.12 [0.97-1.28]; $p = 0.11$, respectively).
When the cohort was narrowed to only those receiving at least a single unit of pRBC during the first 24 hours of care (n = 199), univariate analysis demonstrated age, blunt injury and platelets transfused during the first 24 hours as significant (Table 5). Multivariable regression in this subpopulation yielded only age (OR 1.04, [1.02-1.06]; p < 0.01) and abdomen AIS (OR 1.25, [1.02-1.54]; p = 0.03) to be significant factors for moderate to severe hypoxemia. There was a trend for chest AIS (OR 1.21, [0.98-1.50]; p = 0.08) to be a significant risk; however, blood, crystalloid and V_T were not.

Risk factors for developing a negative pulmonary composite outcome (patients with ARDS, or moderate to severe hypoxemia, or in-hospital pneumonia, or tracheostomy, or mortality [day 1-7]) were broader (Table 6). Univariate analysis identified age, blunt injury, ED systolic blood pressure, head and chest AIS, and 24 hour platelet transfusions as risks. After multivariate modeling, age (OR 1.03, [1.02-1.04]; p = 0.04), head AIS (OR 1.30, [1.15-1.47]; p < 0.01), chest AIS (OR 1.32, [1.16-1.51]; p < 0.01), and the volume of crystalloid infused during the first 24 hours of care (OR 1.17, [1.00-1.37]; p = 0.05) were identified as risks factors for a negative composite outcome. Neither blood products transfused nor mechanical ventilator tidal volumes were identified as risk factors for negative pulmonary sequelae.
CHAPTER IV

DISCUSSION

The “two-hit” model of acute inflammation from injury followed by subsequent, multiple inflammatory insults leading to multi-organ failure is commonly cited as the common pathway for delayed morbidity and mortality following trauma.\textsuperscript{43-45} Significant tissue injury with associated hemorrhage is often viewed as the initial insult or “hit.” As resuscitation techniques continue to rapidly evolve, survivors with profound morbidities become more prevalent secondary to reduced mortality from hemorrhagic shock.\textsuperscript{46} Mitigating “secondary hits”, specifically those associated with hypoxemic respiratory failure, is a major component of care of the injured patient. Nonetheless, validated and modifiable interventions during the early phases of resuscitation to reduce negative pulmonary complications continue to elude trauma care providers. In this work, we attempt to describe the association of acute crystalloid exposure and tidal volume breath delivery in a severely injured population requiring mechanical ventilation.

Increasing age continues to be a significant risk factor for the development of hypoxemia following injury. Current and past work by our group and others consistently highlights the need for further investigation to clarify the interplay between age, injury, and pulmonary inflammation.\textsuperscript{4,47-49} Since 2000 in the United States, the largest proportional increase in crude trauma deaths (+118\%) occurred in those > 54 years of age.\textsuperscript{50} Deaths rates from cancer and heart disease have decreased nationally during this same period. Though a non-modifiable risk factor for hypoxemia, the magnitude of anticipated respiratory care following injury to the elderly in an ever-aging US population is difficult to ignore.
This work continues to strengthen the association between the magnitude of injury and the risk of developing respiratory complications.\textsuperscript{4,47,49,51-54} Worsening chest AIS was a significant predictor of moderate to severe hypoxemia and of a negative pulmonary composite outcome. Implicit in the worsening chest AIS is the relationship of direct chest injury to capillary wall leak at the level of pulmonary alveoli leading to impaired gas exchange as well as being the inciting tissue bed for local and systemic inflammation. Chest AIS had a trend ($p = 0.08$) towards being an independent risk for moderate to severe hypoxemia in those that received blood; however, abdomen AIS was associated with hypoxemia in this bleeding sub-population. The study population with abdominal injuries did demonstrate a high degree of severity: median AIS of 3 (2-4). Though not calculated, one would assume an even higher degree of overall injury with inflammation in those bleeding, needing a pRBC transfusion, and surviving > 24 hours. Alterations in systemic inflammation leading to pulmonary dysfunction due to the cumulative burden of hemorrhage with direct abdominal tissue injury have been defined in large animal studies though warrant further clinical investigation.\textsuperscript{55}

In an effort to examine modifiable risk factors for the development lung injury after trauma, the quantification of hourly crystalloid requirements during the first 24 hours and the maximum $V_T$ by PBW delivered during the first 2 days was examined. Crystalloids in half liter aliquots were used based on their statistically significant risk in previous work and the common practice to bolus such discrete volumes during the acute phases of care.\textsuperscript{4} In this work, exposure to >3 half liters of fluid within the first 24 hours of care was associated with a larger number of ventilator days and rate of ARDS. Crystalloid exposure during the first 24 hours was found to be a predictor of a negative composite pulmonary outcome and had a trend towards being a risk factor for moderate to severe hypoxemia. The practice of limiting crystalloid exposure has been
previously examined as a preventative measure for hypoxemia following injury and is based on the significant work of the ARDSnet group in patients already with the diagnosis of ARDS. \(^{56}\) In that prospective randomized trial, patients with ARDS who received a conservative strategy for fluid management were found to have significantly improved oxygenation, ventilator and ICU free days, and a reduction in lung injury. Through a combination of fluid restriction and active pharmacologic diuresis, the mean cumulative fluid balance during the first week was -136 mL in the conservative group and +6992 mL in the controls. Those in the conservative cohort received approximately 700 mL less crystalloid in comparison to controls 1 day after randomization. Nonetheless, this study was performed in those already with the diagnosis of ARDS; only 33-36% were in shock at the time of randomization, and trauma patients composed only 1.5% of those included. Though a process of active diuresis is not appropriate for trauma patients during the active phases of resuscitation, the limitation of crystalloid may be. Crystalloid infusions in the injured have been implicated as risk factors for pulmonary complications and alterations in the coagulation cascade likely secondary to their mitigation of cellular and inflammatory disturbances. \(^{4,19,54,57-60}\) Accentuated pulmonary inflammation from crystalloid exposure results in capillary leak within alveolar units leading to impaired gas exchange and clinical hypoxemia. The influence of the timing of crystalloid exposure, as well as the trauma sub-populations who are at the greatest risk, both remain unclear. \(^{61}\)

The implication of V\(_T\) exposure of trauma patients to pulmonary complications remains less clear. Tidal volume was not found to be a risk factor for moderate to severe hypoxemia in patients that required at least a single unit of pRBC during the first 24 hours of care or in the development of the composite pulmonary outcome. A trend may exists for the association of V\(_T\) to moderate to severe hypoxemia (\(p = 0.11\)); however, further work will need to be performed.
The contradictory findings of our work are likely related to the relative low $V_T$ (median 7.8 mL/kg of PBW, Figure 3) applied to our entire cohort and a population consisting solely of trauma patients. Gajic et al demonstrated retrospectively in 332 medical patients that risk factors for developing ALI included large $V_T$ in a dose response fashion ($>6$ mL per kg of predicted body weight), acidemia, a history of restrictive lung disease, and blood transfusions. However, the median tidal volume during day 1 for that cohort was $10.9 \pm 2.4$ mL/kg of PBW allowing for comparisons to those with extreme $V_T$. Similar beneficial findings of low $V_T$ were reported after the evaluation of a large, international study of mechanically ventilated patients. The authors demonstrated that exposures to large tidal volumes (odds ratio 2.6 for $TV >700$ mL) and having a traumatic injury were associated with the development of ARDS after adjusting for baseline characteristics and other risk factors for lung injury. Trauma patients only constituted approximately 8% of the cohort in an era prior to wide spread implementation of DCR strategies at civilian centers and none of the tidal volumes recorded were normalized by predicted body weight. In a recent prospective, randomized trial of intensive care unit (ICU) patients, Determann et al found that lower $V_T$ was associated with significantly lower rates of lung injury (13.5% vs. 2.6%) and IL-6 concentrations in bronchial lavage fluid in those that did not have signs of ALI at randomization. However, patients were randomized to 6 vs. 10 mL/kg of PBW, trauma patients were only 15% of this study population and the \textit{a priori} sample calculations utilized cytokine levels rather than clinical outcomes as the primary outcome of interest. The early application of low $V_T$ in trauma patients may still be an opportunity for improvement in populations with high $V_T$ (>10 ml/kg of PBW) as the standard of care or in sub-populations, specifically women, older patients with medical comorbidities (that mimic the previous beneficial studies), and those undergoing acute operative interventions.
The current study affirms the safety of transfused blood products in the trauma patient population. Our results do not suggest that the uses of blood products alone, even in very large amounts, are associated with occurrence of ARDS. Older efforts previously highlighted the association of pRBC and plasma transfusion to the development of hypoxemia, ARDS and transfusion-related lung injury.\textsuperscript{13,15-18,64,65} Neither packed red blood cells, plasma, nor platelets were found to be an independent risk factor for the development of hypoxemia or a negative pulmonary composite outcome in this study. Such findings validate previous works that crystalloid, rather than blood, independently contributes to the development of pulmonary complications following injury with resuscitation; nonetheless, controversy still exists.\textsuperscript{4,11,54,61,66}

This work does suffer from multiple shortcomings. The influence of specific ventilator settings, positive end-expiratory pressure, and plateau pressure upon outcomes could not be determined from this dataset. Further work will need to examine the passive application of \( V_T \) to ventilator induced lung injury as compared to the delivery of large, spontaneous breaths to patients that desire them, specifically those with chronic obstructive pulmonary disease. Our study was dependent on pre-assigned definitions of in-hospital pneumonia and ARDS as documented in the medical record and collected by institutional registry staff. Future work will need to adjudicate these diagnoses with blinded review of chest imaging and review of bronchoalveolar lavage culture data. Finally, survival bias is inherent in such analyses with significantly ill subjects who may or may not develop the primary outcome of interest.\textsuperscript{67} The inclusion of patients that may have died prior to day 7 may influence the evaluation of complications during said timeframe and ultimately alter the statistical analyses of these outcomes.
CHAPTER V
SUMMARY AND CONCLUSIONS

Pulmonary complications following injury are common and may lead to significant morbidity and mortality. Age and the severity of injury continue to be risk factors for the development of negative pulmonary sequelae. Minor amounts of crystalloid and not tidal volume acutely delivered appear to be modifiable risk factors for the development of hypoxemia and negative pulmonary outcomes. Trauma care providers should continue to limit the crystalloid provided to patients in excess of perceived need and further examine sub-populations that may benefit from the application of early low tidal volume mechanical ventilation.
BIBLIOGRAPHY


Figure 1.

Traumatic injury with mechanical ventilation use
n = 661

1. Survival > 24h
2. With P/F ratio (0-7 days) recorded
3. And tidal volume recorded (0-2 days)
   n = 531

Moderate to Severe Hypoxemia (P/F ≤ 200)
   n = 310 (58.4%)

In-Hospital Pneumonia
   n = 193 (36.3%)

Tracheostomy
   n = 181 (34.1%)

Acute Respiratory Distress Syndrome
   n = 60 (11.3%)

Early Death (Day 1-7)
   n = 34 (6.4%)
Figure 2.

Crystalloid infused (half-liters)
Figure 3.

[Graph showing tidal volume (mL/kg of predicted body weight) with percentage distribution.]
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<tr>
<th></th>
<th>( V_T \leq 8 ) (n = 307)</th>
<th>( V_T &gt; 8 ) (n = 224)</th>
<th>( p = )</th>
<th>( \text{Crystalloid} \leq 3 ) half liters (n = 356)</th>
<th>( \text{Crystalloid} &gt; 3 ) half liters (n = 175)</th>
<th>( p = )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>39 (27-53)</td>
<td>45 (28-57)</td>
<td>0.05*</td>
<td>44 (27-57)</td>
<td>36 (27-50)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Male sex</td>
<td>88.0%</td>
<td>61.6%</td>
<td>&lt;0.01*</td>
<td>74.4%</td>
<td>81.7%</td>
<td>0.06</td>
</tr>
<tr>
<td>Blunt injury rate</td>
<td>70.7%</td>
<td>79.0%</td>
<td>0.03*</td>
<td>80.3%</td>
<td>61.7%</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>ED SBP &lt; 90 mm Hg</td>
<td>16.3%</td>
<td>11.3%</td>
<td>0.11</td>
<td>10.3%</td>
<td>22.7%</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Initial GCS ( \leq 8 )</td>
<td>39.4%</td>
<td>40.1%</td>
<td>0.87</td>
<td>45.4%</td>
<td>28.1%</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>ISS</td>
<td>24 (16-33)</td>
<td>24 (17-29)</td>
<td>0.81</td>
<td>23 (14-30)</td>
<td>24 (17-33)</td>
<td>0.21</td>
</tr>
<tr>
<td>Head AIS score*</td>
<td>4 (3-5)</td>
<td>4 (3-5)</td>
<td>0.72</td>
<td>4 (3-5)</td>
<td>4 (3-5)</td>
<td>0.66</td>
</tr>
<tr>
<td>Chest AIS score*</td>
<td>3 (2-3)</td>
<td>3 (2-3)</td>
<td>0.39</td>
<td>3 (3-3)</td>
<td>3 (2-4)</td>
<td>0.84</td>
</tr>
<tr>
<td>Abdomen AIS score*</td>
<td>3 (2-4)</td>
<td>3 (2-4)</td>
<td>0.53</td>
<td>3 (2-4)</td>
<td>3 (2-4)</td>
<td>0.02</td>
</tr>
<tr>
<td>ICU LOS, days</td>
<td>9 (5-18)</td>
<td>10 (4-18)</td>
<td>0.63</td>
<td>9 (4-16)</td>
<td>11 (5-22)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Hospital LOS, days</td>
<td>13 (7-22)</td>
<td>13 (8-22)</td>
<td>0.54</td>
<td>12 (6.5-18)</td>
<td>16 (10-29)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Non-home discharge</td>
<td>55.2%</td>
<td>44.9%</td>
<td>0.15</td>
<td>55.1%</td>
<td>60.0%</td>
<td>0.28</td>
</tr>
<tr>
<td>LTAC discharge</td>
<td>23.1%</td>
<td>24.6%</td>
<td>0.70</td>
<td>22.5%</td>
<td>26.3%</td>
<td>0.33</td>
</tr>
<tr>
<td>Rehabilitation discharge</td>
<td>19.2%</td>
<td>16.5%</td>
<td>0.42</td>
<td>19.4%</td>
<td>15.4%</td>
<td>0.27</td>
</tr>
<tr>
<td>SNF discharge</td>
<td>8.8%</td>
<td>15.6%</td>
<td>0.02*</td>
<td>10.7%</td>
<td>13.7%</td>
<td>0.31</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>9.8%</td>
<td>10.7%</td>
<td>0.72</td>
<td>11.2%</td>
<td>8.0%</td>
<td>0.25</td>
</tr>
<tr>
<td>First-week mortality</td>
<td>6.2%</td>
<td>6.7%</td>
<td>0.81</td>
<td>7.3%</td>
<td>4.6%</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Continuous values are presented as medians (interquartile range).

\* \( P \leq 0.05 \)

+Medians represent non-zero values.

# the significantly higher value.

\( V_T \); predicted body weight tidal volume; ED, emergency department; SBP, systolic blood pressure; GCS, Glasgow Coma Scale; ISS, injury severity score; AIS, abbreviated injury score; ICU, intensive care unit; LOS, length of stay; LTAC, long term assisted care; SNF, skilled nursing facility.
### TABLE 2. Pulmonary Characteristics and Outcomes by Tidal Volume and Crystalloid Exposure

<table>
<thead>
<tr>
<th></th>
<th>$V_T \leq 8$ (n = 307)</th>
<th>$V_T &gt; 8$ (n = 224)</th>
<th>$p =$</th>
<th>Crystalloid $\leq$ 3 half liters (n = 356)</th>
<th>Crystalloid $&gt; 3$ half liters (n = 175)</th>
<th>$p =$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum $V_T$, mL/kg</td>
<td>7.1 (6.7-7.6)</td>
<td>8.8 (8.5-9.8)</td>
<td>&lt;0.01</td>
<td>7.8 (7.0-8.7)</td>
<td>7.8 (7.1-8.8)</td>
<td>0.68</td>
</tr>
<tr>
<td>Ventilator days</td>
<td>6 (2-13)</td>
<td>6 (2-14)</td>
<td>0.25</td>
<td>5 (2-13)</td>
<td>7 (3-16)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Ventilator free days in 30</td>
<td>23 (13-28)</td>
<td>22 (10-27)</td>
<td>0.17</td>
<td>23 (13.5-28)</td>
<td>21 (10-27)</td>
<td>0.15</td>
</tr>
<tr>
<td>Hypoxemia Categories</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe hypoxemia</td>
<td>14.0%</td>
<td>14.0%</td>
<td></td>
<td>14.4%</td>
<td>13.1%</td>
<td></td>
</tr>
<tr>
<td>Moderate hypoxemia</td>
<td>42.4%</td>
<td>46.9%</td>
<td></td>
<td>42.1%</td>
<td>48.6%</td>
<td></td>
</tr>
<tr>
<td>Mild hypoxemia</td>
<td>21.2%</td>
<td>24.3%</td>
<td></td>
<td>23.4%</td>
<td>20.6%</td>
<td></td>
</tr>
<tr>
<td>No hypoxemia</td>
<td>22.5%</td>
<td>14.9%</td>
<td>0.17</td>
<td>20.1%</td>
<td>17.7%</td>
<td>0.57</td>
</tr>
<tr>
<td>Moderate to severe hypoxemia</td>
<td>56.4%</td>
<td>60.9%</td>
<td>0.33</td>
<td>56.5%</td>
<td>61.7%</td>
<td>0.26</td>
</tr>
<tr>
<td>In-hospital pneumonia</td>
<td>36.2%</td>
<td>36.6%</td>
<td>0.92</td>
<td>35.5%</td>
<td>38.3%</td>
<td>0.51</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>33.2%</td>
<td>35.3%</td>
<td>0.62</td>
<td>33.2%</td>
<td>36.0%</td>
<td>0.51</td>
</tr>
<tr>
<td>ARDS</td>
<td>9.1%</td>
<td>14.3%</td>
<td>0.06</td>
<td>9.0%</td>
<td>16.0%</td>
<td>0.02*</td>
</tr>
<tr>
<td>Composite pulmonary outcome</td>
<td>69.1%</td>
<td>68.8%</td>
<td>0.94</td>
<td>69.1%</td>
<td>68.6%</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Continuous values are presented as medians (interquartile range)

*P ≤ 0.05

+Severe hypoxemia defined as a $\text{PaO}_2/\text{FiO}_2 \leq 100$ mm Hg, moderate 101 -200 mm Hg, mild 201 – 300 mm Hg, no hypoxemia > 300 mm Hg

#Composite pulmonary outcome includes patients with ARDS, or moderate to severe hypoxemia, or in-hospital pneumonia, or tracheostomy, or mortality (day 1-7)

$V_T$; predicted body weight tidal volume; ARDS, acute respiratory distress syndrome;
### TABLE 3. Resuscitation Characteristics and Outcomes by Tidal Volume and Half-Liter Crystalloid Exposure

<table>
<thead>
<tr>
<th></th>
<th>$V_T \leq 8$ (n = 307)</th>
<th>$V_T &gt; 8$ (n = 224)</th>
<th>$p =$</th>
<th>Crystalloid ≤ 3 half liters (n = 356)</th>
<th>Crystalloid &gt; 3 half liters (n = 175)</th>
<th>$p =$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystallloid (0-6 hours)</td>
<td>1.0 (0.3-1.7)</td>
<td>0.9 (0.3-1.8)</td>
<td>0.49</td>
<td>0.5 (0.2-1.0)</td>
<td>1.7 (1.2-2.3)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Crystallloid (0-24 hours)</td>
<td>2.3 (1.4-3.4)</td>
<td>2.3 (1.4-3.5)</td>
<td>0.89</td>
<td>1.7 (1.2-2.7)</td>
<td>4.0 (3.4-5.0)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>pRBC (0-6 hours)</td>
<td>5 (2-9)</td>
<td>4 (2-7)</td>
<td>0.48</td>
<td>4 (2-7)</td>
<td>5 (3-9)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>pRBC (0-24 hours)</td>
<td>5 (2-9)</td>
<td>4 (2-8)</td>
<td>0.20</td>
<td>4 (2-7)</td>
<td>6 (3-10)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Plasma (0-6 hours)</td>
<td>4 (2-8)</td>
<td>4 (2-7)</td>
<td>0.26</td>
<td>4 (2-6)</td>
<td>5 (2-10)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Plasma (0-24 hours)</td>
<td>5 (2-9)</td>
<td>4 (2-8)</td>
<td>0.20</td>
<td>4 (2-7)</td>
<td>6 (3-10)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Platelets (0-6 hours)</td>
<td>2 (1-3)</td>
<td>1 (1-2)</td>
<td>0.04*</td>
<td>2 (1-3)</td>
<td>1 (1-2)</td>
<td>0.19</td>
</tr>
<tr>
<td>Platelets (0-24 hours)</td>
<td>2 (1-4)</td>
<td>1 (1-3)</td>
<td>0.06</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
<td>0.68</td>
</tr>
<tr>
<td>pRBC to plasma ratio (0-6 hours)</td>
<td>1.0 (0.9-1.3)</td>
<td>1.0 (0.9-1.4)</td>
<td>0.87</td>
<td>1.0 (0.8-1.3)</td>
<td>1.1 (0.8-1.3)</td>
<td>0.02*</td>
</tr>
<tr>
<td>pRBC to plasma ratio (0-24 hours)</td>
<td>1.0 (0.9-1.3)</td>
<td>1.0 (0.9-1.3)</td>
<td>0.39</td>
<td>1.1 (1.0-1.4)</td>
<td>1.0 (0.9-1.4)</td>
<td>0.06</td>
</tr>
<tr>
<td>CAT+</td>
<td>16.6%</td>
<td>19.7%</td>
<td>0.37</td>
<td>11.2%</td>
<td>31.4%</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Massive transfusion</td>
<td>8.8%</td>
<td>6.3%</td>
<td>0.28</td>
<td>3.4%</td>
<td>16.6%</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

Continuous values are presented as medians (interquartile range)

*P ≤ 0.05

Medians for blood product units include those with non-zero values

$V_T$, predicted body weight tidal volume; pRBC, packed red blood cell; CAT+, critical admission threshold positive
<table>
<thead>
<tr>
<th></th>
<th>Univariate OR (95% CI)</th>
<th>Univariate p =</th>
<th>Multivariate OR (95% CI)</th>
<th>Multivariate p =</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02 (1.01 – 1.03)</td>
<td>&lt;0.01*</td>
<td>1.02 (1.01 – 1.04)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.18 (0.79 – 1.77)</td>
<td>0.43</td>
<td>1.53 (0.95 – 2.45)</td>
<td>0.08</td>
</tr>
<tr>
<td>Blunt injury</td>
<td>1.79 (1.22 – 2.64)</td>
<td>&lt;0.01*</td>
<td>1.28 (0.79 – 2.08)</td>
<td>0.31</td>
</tr>
<tr>
<td>ED SBP &lt; 90mmHg</td>
<td>1.10 (0.66 – 1.83)</td>
<td>0.71</td>
<td>0.69 (0.39 – 1.25)</td>
<td>0.22</td>
</tr>
<tr>
<td>Head AIS</td>
<td>1.01 (0.93 – 1.10)</td>
<td>0.80</td>
<td>1.05 (0.95 – 1.17)</td>
<td>0.36</td>
</tr>
<tr>
<td>Chest AIS</td>
<td>1.35 (1.21 – 1.52)</td>
<td>&lt;0.01*</td>
<td>1.43 (1.25 – 1.62)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Abdomen AIS</td>
<td>0.97 (0.87 – 1.08)</td>
<td>0.55</td>
<td>0.93 (0.82 – 1.070)</td>
<td>0.32</td>
</tr>
<tr>
<td>pRBC (0-24 hours)</td>
<td>1.03 (1.00 – 1.07)</td>
<td>0.09</td>
<td>0.98 (0.88 – 1.09)</td>
<td>0.69</td>
</tr>
<tr>
<td>Plasma (0-24 hours)</td>
<td>1.04 (1.00 – 1.08)</td>
<td>0.04*</td>
<td>1.05 (0.95 – 1.17)</td>
<td>0.32</td>
</tr>
<tr>
<td>Platelets (0-24 hours)</td>
<td>1.14 (1.00 – 1.29)</td>
<td>0.05*</td>
<td>1.07 (0.90 – 1.27)</td>
<td>0.42</td>
</tr>
<tr>
<td>Crystalloid (0-24 hours)</td>
<td>1.09 (0.97 – 1.21)</td>
<td>0.15</td>
<td>1.13 (0.98 – 1.31)</td>
<td>0.09</td>
</tr>
<tr>
<td>Maximum Vₜ, mL/kg</td>
<td>1.08 (0.96 – 1.22)</td>
<td>0.22</td>
<td>1.12 (0.97 – 1.28)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

*p ≤ 0.05

OR, odds ratio; CI, confidence interval; ED, emergency department; SBP, systolic blood pressure; AIS, abbreviated injury score; pRBC, packed red blood cell; Vₜ, predicted body weight tidal volume.
<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate OR (95% CI)</th>
<th>p =</th>
<th>Multivariate OR (95% CI)</th>
<th>p =</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (1.01 – 1.05)</td>
<td>&lt;0.01*</td>
<td>1.04 (1.02 – 1.06)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.07 (0.57 – 2.00)</td>
<td>0.84</td>
<td>1.83 (0.82 – 4.08)</td>
<td>0.14</td>
</tr>
<tr>
<td>Blunt injury</td>
<td>2.05 (1.12 – 3.72)</td>
<td>0.02*</td>
<td>1.32 (0.60 – 2.95)</td>
<td>0.49</td>
</tr>
<tr>
<td>ED SBP &lt; 90mmHg</td>
<td>0.93 (0.48 – 1.82)</td>
<td>0.84</td>
<td>0.52 (0.23 – 1.19)</td>
<td>0.12</td>
</tr>
<tr>
<td>Head AIS</td>
<td>1.13 (0.96 – 1.31)</td>
<td>0.13</td>
<td>1.14 (0.95 – 1.38)</td>
<td>0.16</td>
</tr>
<tr>
<td>Chest AIS</td>
<td>1.17 (0.98 – 1.41)</td>
<td>0.08</td>
<td>1.21 (0.98 – 1.50)</td>
<td>0.08</td>
</tr>
<tr>
<td>Abdomen AIS</td>
<td>1.05 (0.90 – 1.24)</td>
<td>0.52</td>
<td>1.25 (1.02 – 1.54)</td>
<td>0.03*</td>
</tr>
<tr>
<td>pRBC (0-24 hours)</td>
<td>1.05 (1.00 – 1.10)</td>
<td>0.06</td>
<td>1.07 (0.92 – 1.26)</td>
<td>0.38</td>
</tr>
<tr>
<td>Plasma (0-24 hours)</td>
<td>1.05 (1.00 – 1.09)</td>
<td>0.06</td>
<td>0.97 (0.85 – 1.16)</td>
<td>0.69</td>
</tr>
<tr>
<td>Platelets (0-24 hours)</td>
<td>1.26 (1.03 – 1.56)</td>
<td>0.03*</td>
<td>1.15 (0.79 – 1.67)</td>
<td>0.47</td>
</tr>
<tr>
<td>Crystalloid (0-24 hours)</td>
<td>1.02 (0.86 – 1.22)</td>
<td>0.79</td>
<td>1.04 (0.84 – 1.30)</td>
<td>0.70</td>
</tr>
<tr>
<td>Maximum Vₜ, mL/kg</td>
<td>1.01 (0.82 – 1.25)</td>
<td>0.90</td>
<td>1.06 (0.81 – 1.38)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

*P ≤ 0.05

OR, odds ratio; CI, confidence interval; ED, emergency department; SBP, systolic blood pressure; AIS, abbreviated injury score; pRBC, packed red blood cell; Vₜ, predicted body weight tidal volume
<table>
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<tr>
<th>Predictor</th>
<th>Univariate OR (95% CI)</th>
<th>p =</th>
<th>Multivariate OR (95% CI)</th>
<th>p =</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (1.02 – 1.04)</td>
<td>&lt;0.01*</td>
<td>1.03 (1.02 – 1.04)</td>
<td>&lt;0.04*</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.90 (0.58 – 1.39)</td>
<td>0.62</td>
<td>0.92 (0.56 – 1.53)</td>
<td>0.76</td>
</tr>
<tr>
<td>Blunt injury</td>
<td>2.17 (1.46 – 3.24)</td>
<td>&lt;0.01*</td>
<td>1.32 (0.81 – 2.15)</td>
<td>0.27</td>
</tr>
<tr>
<td>ED SBP &lt; 90mmHg</td>
<td>1.24 (0.71 – 2.15)</td>
<td>0.45</td>
<td>0.97 (0.51 – 1.86)</td>
<td>0.93</td>
</tr>
<tr>
<td>Head AIS</td>
<td>1.21 (1.10 – 1.34)</td>
<td>&lt;0.01*</td>
<td>1.30 (1.15 – 1.47)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Chest AIS</td>
<td>1.23 (1.10 – 1.40)</td>
<td>&lt;0.01*</td>
<td>1.32 (1.16 – 1.51)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Abdomen AIS</td>
<td>0.90 (0.80 – 1.00)</td>
<td>0.05*</td>
<td>0.92 (0.80 – 1.06)</td>
<td>0.25</td>
</tr>
<tr>
<td>pRBC (0-24 hours)</td>
<td>1.03 (0.99 – 1.07)</td>
<td>0.15</td>
<td>0.97 (0.86 – 1.09)</td>
<td>0.56</td>
</tr>
<tr>
<td>Plasma (0-24 hours)</td>
<td>1.04 (1.00 – 1.09)</td>
<td>0.05*</td>
<td>1.06 (0.95 – 1.19)</td>
<td>0.30</td>
</tr>
<tr>
<td>Platelets (0-24 hours)</td>
<td>1.19 (1.01 – 1.40)</td>
<td>0.03*</td>
<td>1.14 (0.93 – 1.40)</td>
<td>0.22</td>
</tr>
<tr>
<td>Crystalloid (0-24 hours)</td>
<td>1.04 (0.92 – 1.16)</td>
<td>0.56</td>
<td>1.17 (1.00 – 1.37)</td>
<td>0.05*</td>
</tr>
<tr>
<td>Maximum Vₜ, mL/kg</td>
<td>1.00 (0.88 – 1.13)</td>
<td>0.94</td>
<td>0.96 (0.84 – 1.11)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Composite pulmonary outcome includes patients with ARDS, or moderate to severe hypoxemia, or in-hospital pneumonia, or tracheostomy, or mortality (day 1-7).

*P ≤ 0.05

OR, odds ratio; CI, confidence interval; ED, emergency department; SBP, systolic blood pressure; AIS, abbreviated injury score; pRBC, packed red blood cell; Vₜ, predicted body weight tidal volume