HHS Public Access

Author manuscript

J Trauma Acute Care Surg. Author manuscript; available in PMC 2018 March 14.

Published in final edited form as:

J Trauma Acute Care Surg. 2016 June ; 80(6): 989–997. doi:10.1097/TA.0000000000000982.

THE ACUTE RESPIRATORY DISTRESS SYNDROME FOLLOWING ISOLATED SEVERE TRAUMATIC BRAIN INJURY

Carolyn M Hendrickson, MD MPH[§], **Benjamin M Howard, MD MPH**[*], **Lucy Z Kornblith, MD**[*], **Amanda S Conroy, BA**[*], **Mary F Nelson, RN MPA**[*], **Hanjing Zhuo, MD MPH**[§], **Kathleen D. Liu, MD PhD**, **Geoffrey Manley, MD PhD**, **Michael M. Matthay, MD**[§], **Carolyn S Calfee, MD MAS**, and **Mitchell Jay Cohen, MD**

[§]Division of Pulmonary and Critical Care Medicine, Departments of Medicine and Anesthesia, University of California San Francisco; San Francisco, California

[*]Department of Surgery, University of California San Francisco and San Francisco General Hospital

[ϒ]Divisions of Nephrology and Critical Care Medicine, Departments of Medicine and Anesthesia, University of California San Francisco; San Francisco, California

[Ψ]Department of Neurological Surgery, University of California San Francisco and San Francisco General Hospital

STRUCTURED ABSTRACT

BACKGROUND—Acute respiratory distress syndrome (ARDS) is common after Traumatic Brain Injury (TBI) and is associated with worse neurologic outcomes and longer hospitalization. However, the incidence and associated causes of ARDS in isolated TBI have not been well studied.

METHODS—We performed a subgroup analysis of 210 consecutive patients with isolated severe TBI enrolled in a prospective observational cohort at a Level 1 Trauma Center between 2005 and 2014. Subjects required endotracheal intubation and had isolated severe TBI defined by an Abbreviated Injury Score (AIS) Head ≥3 and AIS <3 in all other categories. ARDS within the first 8 days of admission was rigorously adjudicated using Berlin Criteria. Regression analyses were used to test the association between predictors of interest and ARDS.

RESULTS—The incidence of ARDS in the first eight days after severe isolated TBI was 30%. Patients who developed ARDS were administered more crystalloids (4.3 *vs.* 3.5 L, p= 0.005) and blood products in the first 12 hours of admission. Patients with ARDS had significantly worse clinical outcomes measured at 28 days, including longer median lengths of ICU and hospital stays (4 *vs.* 13 days, $p<0.001$, and 7.5 *vs.* 14.5 days, $p<0.001$, respectively). In unadjusted logistic

Corresponding author: Mitchell Jay Cohen MD, Department of Surgery Ward 3A, San Francisco General Hospital, 1001 Potrero Ave, San Francisco CA 94110, mcohen@sfghsurg.ucsf.edu.

Conflicts of Interest: The authors have no relevant conflicts of interest to disclose.

Meetings: Poster at the American Thoracic Society Conference, May 2014, San Diego, CA

AUTHOR CONTRIBUTIONS:

C.M.H., B.M.H., L.Z.K., H.Z., K.D.L., G.M., M.A.M., C.S.C., and M.J.C. contributed to study design, data collection, data analysis, data interpretation, writing, and critical revision. A.S.C. and M.F.N. contributed to study design, data collection, and critical revision.

regression analyses, the odds of developing ARDS were significantly associated with AIS Head score (OR 1.8, p=0.018), male sex (OR 2.9, p=0.012), and early transfusion of platelets 2.8 (p=0.003). These associations were similar in a multivariate logistic regression model.

CONCLUSIONS—In the era of balanced hemostatic resuscitation practices, severity of head injury, male sex, early crystalloids and early transfusion of platelets are associated with a higher risk of ARDS after severe isolated TBI. Early transfusion of platelets after severe TBI may be a modifiable risk factor for ARDS, and these findings invite further investigation into causal mechanisms driving this observed association.

LEVEL OF EVIDENCE—Level III; Epidemiologic

Keywords

Traumatic Brain Injury (TBI); Acute Respiratory Distress Syndrome (ARDS); Platelet Transfusion; Crystalloid

INTRODUCTION

Each year in the United States (US) 1.7 million people sustain Traumatic Brain Injury (TBI) and 52,000 of these people die. TBI is a contributing factor to over 30% of all injury-related deaths in the US(1, 2). Pulmonary complications are common in this population (3–9). The development of Acute Respiratory Distress Syndrome (ARDS) after TBI is associated with low partial pressure of oxygen in brain tissue(10), worse neurologic outcomes, and higher health-care costs(5, 8, 11, 12). Despite the clinical importance of ARDS after TBI, little is known about the factors driving this association or how to predict which patients are at highest risk for ARDS (7, 13, 14).

In the general trauma population, administration of crystalloid fluids and transfusion of blood products after injury have been strongly associated with ARDS(15–24). Although the optimal ratio of blood products for trauma resuscitation is under investigation(25), changes in transfusion and crystalloid resuscitation practices and may explain the decreasing incidence of ARDS described in some recently published studies(24). While many studies describe risk factors for ARDS after polytrauma, there is a paucity of work studying ARDS after TBI. Isolated TBI is a distinct clinical phenotype within the general trauma population, and it is important to study the clinical and biological pathways leading to ARDS in a well-defined cohort of isolated TBI patients.

In this subgroup analysis of 210 patients with severe isolated TBI enrolled in a prospective cohort study, we describe the differences in patient characteristics, transfusion practices, and fluid management between those who developed rigorously adjudicated ARDS and those patients who did not. In the larger trauma cohort that gave rise to this subgroup, we previously studied predictors of ARDS versus hypoxemia without ARDS(26). The earlier study (n= 603) included 194 of the 210 subjects described here and found that head injury was an independent predictor of ARDS in the general trauma cohort. This subgroup analysis builds on these findings and describes risk factors for ARDS after severe TBI in the absence of other serious injuries. This study represents a novel approach to understanding the relationship between TBI and ARDS for two reasons: the restricted cohort of isolated TBI

limits confounding by other injuries, and the association of transfusion of specific blood products with ARDS after TBI is rigorously tested.

MATERIALS AND METHODS

We studied 210 patients with isolated severe TBI enrolled in a larger prospective observational cohort study at San Francisco General Hospital, a Level 1 trauma center affiliated with the University of California San Francisco (UCSF) between 2005 and 2014. Data collection methods have been described in detail previously(27). Comprehensive demographic and clinical data were prospectively collected on critically injured patients with the highest-level trauma activation. All included subjects included in this sub-study required intubation and mechanical ventilation, and survived at least six hours from time of admission; data was collected for 28 days following admission. Subjects had an AIS Head Score ≥ 3 with confirmed findings of TBI on head computed tomography scans obtained on the day of admission. Subjects with severe injuries in any other body region, defined as AIS score ≥3 in any other category, were excluded. Massive transfusion was defined as ≥ 10 units of packed red blood cells (pRBCs) transfused in 24 hours. Multi-organ failure was defined using the Denver Postinjury Multiple Organ Failure Score (28). A rigorous two-physician ARDS adjudication protocol was used to identify cases according to the Berlin definition in the first 8 days of admission (26, 29).

Data are presented as mean ± standard deviation, median (interquartile range), or *n* (percentage). Univariate comparisons were made using Student's *t* test for normally distributed data and Wilcoxon rank sum for skewed data. In exploratory univariate analyses, $\alpha < 0.2$ was considered significant for further investigation with regression models. In all other analyses, $\alpha < 0.05$ was considered significant. Univariate logistic regression models were used to test the association between all biologically plausible predictors and ARDS. An *a priori* data analysis plan used univariate logistic regression models to test for differential risk of ARDS by patient characteristics and process of care variables. One subject had an AIS Head score of 6, a non-survivable injury, and was excluded from the multivariable logistic regression analyses to facilitate modeling comparisons of AIS Head scores in the other three categories (AIS 3–5). Multivariate models included interaction terms between blood products. Two period effects were considered in the models. First, the American Association of Blood Banks policies eliminated plasma and platelets from previously pregnant female donors in 2007 and 2008(30). Second, a randomized controlled trial of two blood product ratios for trauma resuscitation enrolled patients at this center from August 2012 through November 2013(25). This was a negative study but could have influenced clinical practice patterns. A sensitivity analysis was performed to address potential bias introduced by errors in time ordering of exposure to blood product and ARDS outcomes by excluding 14 subjects who developed ARDS in the first 24 hours of admission. A multivariable model included all variables found with biologic plausibility, and backwards elimination was performed using likelihood ratio testing to establish the final model presented in this manuscript. Area under the receiver operator curve (AUROC) was calculated as a measure of model fit. Evaluation for survival bias was performed by excluding subjects who died and using a composite outcome for of ARDS or death in the first seven days after admission for both univariate and multivariate models [(Table 5.,

Supplemental Digital Content (SDC)]. Additionally, survival bias was evaluated with Kaplan-Meir curves [(Figure 3., Supplemental Digital Content (SDC)] and Cox-proportional Hazard Models for ARDS in the first seven days of hospitalization accounting for censoring by death. We conducted post-hoc analyses to better understand the relationship between platelet transfusion and ARDS. We compared the clinical characteristics, including hematologic parameters and the incidence of ventilator associated pneumonia (VAP), adjudicated by the Infectious Diseases Division, between subjects who received early platelet transfusions and those who did not. To explore potential immunomodulatory activity, we tested the association between platelet transfusion and VAP using the same logistic regression modeling protocol outlined above. All analyses were performed using STATA version 13 (StataCorp, College Station, TX).

RESULTS

Demographics and Clinical Characteristics by ARDS Status

The cohort demographics and clinical characteristics are representative of a standard severely injured trauma population, 75% male, with a median age of 43 years (IQR 27–64 years), and predominantly bluntly injured patients (85%). The incidence of ARDS in the first eight days after severe isolated TBI was 30%. Of the 62 cases of ARDS, 20 (32%) were mild, 30 (49%) were moderate, and 12 (19%) were severe by Berlin Criteria. There were no significant differences in the admission GCS score, race, ethnicity, or BMI between subjects who developed ARDS and those who did not (Table 1). Subjects who developed ARDS were more likely to be male (87% *vs.* 70%, *p*-value= 0.010), more likely to have a base deficit of <-6 in the first 12 hours (26% *vs.* 1%, *p*-value= 0.005), and there was a trend toward a more positive fluid balance on the day of admission among those who developed ARDS [median +2.3L (IQR −300– +4440) *vs.* +1.0L(IQR −190– +2320), *p*-value= 0.06]. There were no significant differences in AIS Chest, Abdomen, or Extremity scores between those who developed ARDS and those who did not. AIS Head scores were significantly higher in subjects who developed ARDS. There was a trend towards higher rates of neurosurgical interventions, craniotomy or craniectomy, among those who developed ARDS (53% *vs.* 43%, *p*-value=0.066). There was no significant difference in median admission platelet counts among patients who developed ARDS compared with those who did not [251 (IQR 198–307) *vs.* 272 (IQR 222–323)) 10^3/μL, (*p*-value =0.13)]. Prior diagnoses of chronic respiratory and cardiac illnesses were uncommon in this cohort: asthma, 7%, chronic obstructive pulmonary disease, 1%, coronary artery disease, 5%, congestive heart failure, 1%, and no patients with interstitial lung disease.

Clinical Outcomes by ARDS Status

Although the mortality rate was not significantly different between those who developed ARDS and those who did not (42% *vs.* 36%, *p*-value=0.46), patients with ARDS had significantly longer lengths of ICU and hospital stays (median 13 *vs.* 4 days and 14.5 *vs.* 7.5 days, respectively) (Table 1). Patients with ARDS required longer duration of mechanical ventilation among survivors (median 14.5 *vs.* 3 days). There were fewer ventilator-free days among patients with ARDS compared to those without (median 0 *vs.* 16.5). Because

respiratory failure is included in the definition of multiorgan failure, it is expected that patients with ARDS had higher rates of multiorgan failure (47% *vs.* 6%).

Transfusion of Blood Products by ARDS Status

All crystalloid exposures and transfusion of specific blood products presented here occurred in the first 12 hours of admission and are heretofore referred to as early. Transfusion of blood products was common in this cohort, and 51% of subjects received at least one transfusion. Subjects who developed ARDS received larger volumes of early crystalloid infusions than those who did not develop ARDS [median 4.3L (IQR 2.5–6.5L) *vs.* 3.5L (IQR 2.0–4.5L), *p*-value =0.005](Table 2). Subjects who developed ARDS were more likely to have received early transfusion platelets (34% *vs.* 16%, *p*-value =0.003), and massive transfusion, defined as ≥ 10 units of pRBCs in the first 24 hours, (19% *vs.* 5%, *p*-value =0.002). In the time-ordering sensitivity analyses, we excluded 14 subjects with ARDS diagnosed in the first 24 hours of admission who made up 23% of all ARDS cases, and this did not change the results substantially [(Table 6., Supplemental Digital Content (SDC)]. Notably, in a balanced approach to hemostatic resuscitation all subjects who received massive transfusions also received early platelet transfusions. Conversely, 20 (45%) of patients who received early transfusion of platelets received massive transfusion. Although there is significant covariate overlap between early platelet transfusion and other markers for severity of injury this overlap is incomplete (**3**): 80% of patients who received early platelet transfusion underwent neurosurgical interventions, but only 36% of patients who underwent neurosurgical interventions received early platelet transfusions.

Univariate Logistic Regression Models

In univariate logistic regression, severity of head injury measured by AIS Head, male sex, massive transfusion, early platelet transfusion, and crystalloid fluid administration conferred significantly higher odds of ARDS ($p<0.05$, Table 4). The association between platelet transfusion and ARDS was significant for both the 0–6 hour interval [OR 2.9 (95%CI 1.3–6.3, *p*-value=0.009] and the 7–24 hour interval [OR 11.7 (95%CI 1.3–106, *p*-value=0.03] and there were no patients who received platelets in the 7–24 hours interval but not in the 0–12 hour interval. After excluding patients with massive transfusion, the odds of ARDS after early platelet transfusion was 1.9 and the variable still met the met *a priori* cut off for inclusion in the multivariate model (*p*-value=0.171).

Multivariate Logistic Regression Model

A multivariate logistic regression model incorporated variables with significant univariate associations with ARDS ($p<0.2$ considered significant or model building), along with *a priori* designated characteristics, including age (Table 4). The final multivariable model included severity of head injury (AIS score), male sex, early platelet transfusion, and crystalloid infusion (AUROC =0.72, n of 208 and 61 patients with ARDS). In the final adjusted model, early transfusion of platelets conferred a 2.5 fold increase in the odds of ARDS (95%CI 1.2–5.3) and men had a 2.9 fold increase in the odds of ARDS (95%CI 1.2–6.9). Adjusting for severity of head injury, sex, and early transfusion of platelets, each liter of crystalloid infused did not substantively change the point estimate of the odd ratio for

ARDS. However, the deleterious effects of crystalloid resuscitation are well documented, and although the logistic regression coefficient on this variable is very close to 1.0, in part because of the wide range of values (0–17 liters), it was included in the final model because it improved the fit and changed the point estimates on other variables (31).

Evaluation for Survival Bias

There is no evidence of survival bias influencing the observed association between early platelet transfusion and ARDS [(Table 5., Supplemental Digital Content (SDC)]. In regression models excluding subjects who died, the odds of ARDS were significantly higher among those who received early platelet transfusion in both the univariate and multivariate models (OR 3.7, p= 0.001 and OR 3.7 p= 0.02, respectively). Regression models using a composite outcome of ARDS or death showed similar results. In a Cox model accounting for censoring by death, the unadjusted hazard ratio for ARDS after early platelet transfusion was 2.6 (95%CI 1.5–4.4, *p*-value=<0.001). Adjusting for male sex, AIS Head score, and crystalloid infusion, the hazard ratio for ARDS after early platelet transfusion was 1.9 (95%CI 1.1–3.3, *p*-value<0.02).

Effect Modification, Covariate Overlap, and Period Effects

The interaction terms between early platelet and FFP transfusions and early platelet and PRBC transfusion included in the multivariate model were not significant [*p*-value = 0.58 and 0.90, respectively, (Table 7., Supplemental Digital Content (SDC)].). Co-administration of blood products is common in this cohort because of balanced transfusion practices for trauma resuscitation: 39 (89%) of subjects receiving early platelets were also transfused with early pRBCS, 36 (81%) were transfused with early FFP, and 20 (45%) received massive transfusion. This covariate overlap was considered in evaluation of the final multivariate model. Early transfusion of pRBCs and FFP did not improve the fit of the multivariate logistic regression model, did not substantively change the pointe estimate of the platelet variable, and were eliminated.

To address concerns that platelet transfusion may simply be a marker for patients undergoing neurosurgical interventions or those receiving massive transfusion, separate models were created substituting craniectomy and craniotomy for AIS Head and massive transfusion without specific adjustment for platelet transfusion [(Table 8., Supplemental Digital Content (SDC)]. Because massive transfusion may be a marker for more severe injury not captured by AIS, the multivariate analyses were repeated after excluding patients with massive transfusion and the estimate of the effect of early platelet transfusion on the odds of ARDS was mildly attenuated [(Table 9., Supplemental Digital Content (SDC)]. Adjusting for platelet count on emergency department arrival did not improve the multivariate model (likelihood ratio test *p*-value =0.32) Neither of the period effects described in the methods section substantially changed the magnitude, direction, or precision of the estimates of these associations in the multivariate model.

Clinical Characteristics Associated with Early Platelet Transfusion

Admission platelet counts were significantly lower in subjects who received any platelet transfusions in the first 12 hours of hospital admission (222 ± 83 *vs.* 279± 81 k/μL, *p*

<0.001) (Figure 1). Only 4 (9%) of the 44 subjects who received early platelet transfusions had admission platelet counts <100,000/μL) and 14 (32%) of these 44 subjects had platelet counts <100,000/μL on any lab value measured in the first 12 hours after admission. Among subjects who were given early platelet transfusions, there was no difference in admission platelet counts among those who went on to develop ARDS and those who did not develop ARDS (212 ± 87 *vs.* 229 ± 80 k/μL, p =0.28). Excluding subjects who did not get massive transfusion, admission platelet counts were significantly lower among those who got platelets in the first 12 hours of admission (198 ± 82 *vs.* 279 ± 81 k/μL, p =<0.001), and 3 (12%) of the patients given platelet transfusion but not massive transfusion had admission platelet counts < 100,000/μL. Of the 44 patients who received early platelet transfusions, 5 were known to be taking aspirin prior to admission and 3 of these were also on clopidogrel. Partial thromboplastin time (PTT) on ED arrival was significantly higher among subjects who went on to receive early platelet transfusion compared to those who did not receive platelets [30 (IQR 26–35) seconds *vs.* 28 (IQR 26–30) seconds, p-value=0.02). International normalized ratio (INR) on arrival to the ED was significantly higher among patients who received early platelet transfusions compared to those who did not [1.2 (IQR 1.1–1.3) *vs.* 1.1 (IQR 1.0–1.2), p-value=0.0014]. Admission hemoglobin concentration was significantly lower in subjects who received any early platelet transfusions (13.2±2.3 *vs.* 14.1 ± 1.7, p =0.0015).

Platelet Transfusion and Ventilator Associated Pneumonia (VAP

VAP rates were higher among patients who received early platelet transfusion compared to those who did not (23% *vs.* 8.1%, p-value =0.0o8). In univariate logistic regression, the odds of VAP were higher among patients who received early platelet transfusions compared to those who did not (OR 3.2 95%CI 1.2–7.25 p-value 0.011). A low incidence of VAP (11%, 24 cases) limits meaningful multivariate logistic regression modeling.

DISCUSSION

Our findings demonstrate that in the era of modern hemostatic resuscitation practices, male sex and severity of head injury, as well as early administration of crystalloids and platelets after severe isolated TBI are associated with a higher risk of developing ARDS (Figure 2). Male sex could confer a higher risk of ARDS because it is a surrogate for behaviors that are more common among men, such as tobacco or alcohol use, or it could represent a differential response to injury or processes of care between sexes(32–34). Consistent with findings from earlier studies, our analyses show that more severe head injury confers a higher risk of ARDS(5, 6). The association between crystalloids and ARDS is not unique to this cohort of isolated TBI and also reported in the larger cohort of intubated trauma patients that gave rise to this subgroup(26). The deleterious effects of crystalloid fluid resuscitation on many organ systems are well established(31).

After adjusting for severity of head injury, sex, and crystalloid infusion, transfusion of platelets in the first 12 hours is associated with increased risk of ARDS (OR 2.5, 95%CI 1.2–5.3, p-value =0.015). This risk is not a surrogate for massive transfusion and is independent of platelet count upon arrival to the ED. The high degree of covariate overlap

between platelet transfusions and transfusion of other blood products contributes to the ability of the platelet variable to explain the effects of massive transfusion and early transfusion of any pRBCs or FFP. However, these other variables did not improve the fit of the regression model and there was no evidence of effect modification between blood products. Taken together, these findings support the hypothesis that this variable captures specific pathogenic pathways causing ARDS after TBI. Furthermore, the effects of early platelet transfusion were only mildly attenuated when patients who received massive transfusion were excluded from the analysis [(Table 9., Supplemental Digital Content (SDC)]. There is no evidence of survival bias [(Table 5., Supplemental Digital Content (SDC)].

One potential explanation for the association of platelet transfusion and ARDS after TBI is that administered platelets themselves could have adverse effects possibly involving innate immune responses such as neutrophil extracellular traps or soluble mediators (35–37). Some studies have shown an association between platelet transfusion and infection in other surgical populations(38, 39). The association between platelet transfusion and VAP is consistent with the possibility that transfused platelets may have an adverse effect on the immune system after TBI.

An alternative, but not mutually exclusive, explanation for the observed association of platelet transfusion and ARDS is confounding by indication. Platelet transfusions may be prescribed to a subset of isolated TBI patients who are more severely injured or ill in ways that are not captured by AIS and ISS scores, neurosurgical interventions, or other factors included in the regression models. Early transfusion of platelets could identify patients with a more severe systemic response to brain injury including sequestration of platelets in the lungs, or platelet dysfunction or coagulopathy that is not reflected in platelet counts, PTT or INR on ED arrival (36, 40, 41). Because the physicians at this study site do not use functional platelet testing for clinical decision-making, platelet transfusion in this cohort was not in response to un-reported laboratory values that quantify platelet function. Given that greater than 80% of subjects who received early platelet transfusion also received FFP and pRBCs early, it is likely that many platelet transfusions were given as part of a balanced approach to hemostatic resuscitation.

Previously, the effects of ARDS on clinical outcomes after TBI have been separately reported from studies of the association between transfusion of blood products and clinical outcomes after TBI(5, 6, 42–44). Interpreting our findings in the context of existing literature on TBI and transfusions is challenging because many of these studies either exclude isolated TBI or do not distinguish between TBI with and without polytrauma. In the largest pertinent study, Anglin *et al.* analyzed data combined from three prospective cohort studies to describe the relationship transfusion of specific blood products and long-term functional outcomes among patients with TBI and coagulopathy, thrombocytopenia, or anemia, with and without other injuries(42). In adjusted models, transfusion of FFP, but not platelets, was associated with worse clinical outcomes. Similarly, an earlier study of trauma patients with hemorrhagic shock, excluding patients with isolated TBI, found an association between FFP and worse clinical outcomes, but no association between transfusion of platelets and ARDS (18). Interestingly, a propensity matched retrospective study found no

difference in the rate of hemorrhage progression or mortality between patients who received co-administration of platelets and desmopressin compared to patients who received neither after traumatic intracranial hemorrhage(43). The variable effects of transfusion of specific blood products on clinical outcomes may be attributed to the heterogeneous populations enrolled in these studies as well as differences in the outcome of interest.

Coagulopathy of trauma is common after isolated TBI, and hematologic dysfunction is part a systemic response to injury that results in multiorgan failure and is associated with poor clinical outcomes(9, 45–47). Early transfusion of platelets may be necessary for survival and control of bleeding, but also have untoward effects on the systemic response to injury including ARDS(48). A better understanding of the biology driving ARDS after TBI is needed to balance the benefits of managing coagulopathy while mitigating adverse effects of transfused blood products. Platelet transfusion may be a potentially modifiable risk factor for ARDS after severe TBI. However, the benefits of balanced transfusion practices may well outweigh the risks of complications such as ARDS. Even so, identifying risks associated with transfusion is important as it may lead to improved clinical outcomes through co-interventions. For example, protocols implementing lung protective ventilation strategies and closer monitoring for detection of pulmonary edema in patients who require platelets transfusions could help clinicians identify and treat ARDS after TBI more effectively and thereby avoid prolonged hypoxemia and secondary brain injury.

The strengths of this study include the prospective data collection and rigorous adjudication of ARDS outcomes a homogenous cohort of isolated TBI with limited confounding due to concomitant traumatic injuries(26, 29, 49). To our knowledge ours is the first study to describe the relationship of transfusions of blood products and the risk of ARDS after severe isolated TBI. Careful attention to both time ordering of exposure to blood products and adjudication of ARDS strengthen the rationale for a causal interpretation of the association between early platelet transfusion and ARDS after severe isolated TBI. From the data presented here, we cannot conclude that the platelets caused the lung injury. Rather, we propose that platelet transfusion is a marker for several potential mechanisms of lung injury after TBI. This study has several limitations. Although the data for this study was prospectively collected, this avenue of investigation is a secondary data analysis and not part of the main study objective. There is limited data available about clinician decisions for transfusion and insufficient data on functional testing for platelet-driven coagulopathy to facilitate meaningful analyses. As a single-center study, these findings may be less generalizable. Additionally, the AIS classification does not capture the subtlety of differences in injury severity that may have important clinical implications. Intracranial hypertension has been associated with ARDS after TBI, but we do not have data from invasive monitoring on enough subjects of this cohort to study the relationship of ICP to the other variables presented here(50).

In this nested cohort study we describe important epidemiologic findings that may guide translational research to prevent and treat ARDS after TBI, and thereby improve clinical outcomes in this vulnerable population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: Supported by NIH GM-085689 and DoD W911NF-10-1-0384 (MJC), NIH HL090833 and HL110969 (CSC), PICORI ME-1306-02735 (GM), R37 HL51856 (MAM & KDL), and NIH 5T32HL007185-37 and 1F32HL124911-01 (CMH)

References

1. Prevention CfDCa. Injury Prevention & Control: Traumatic Brain Injury. 2013. Available from: http://www.cdc.gov/traumaticbraininjury/statistics.html - 3
2. Faul, MXL., Wald, MM., Coronado, VG. Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002–2006. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.
3. Demling R, Riessen R. Pulmonary dysfunction after cerebral injury. Crit Care Med. 1990 Jul; 18(7): 768–74. [PubMed: 2194747]
4. Kemp CD, Johnson JC, Riordan WP, Cotton BA. How we die: the impact of nonneurologic organ dysfunction after severe traumatic brain injury. The American surgeon. 2008 Sep; 74(9):866–72. [PubMed: 18807680]
5. Holland MC, Mackersie RC, Morabito D, Campbell AR, Kivett VA, Patel R, Erickson VR, Pittet JF. The development of acute lung injury is associated with worse neurologic outcome in patients with severe traumatic brain injury. J Trauma. 2003 Jul; 55(1):106–11. [PubMed: 12855888]
6. Bratton SL, Davis RL. Acute lung injury in isolated traumatic brain injury. Neurosurgery. 1997 Apr; 40(4):707–12. discussion 12. [PubMed: 9092843]
7. Mascia L. Acute lung injury in patients with severe brain injury: a double hit model. Neurocritical care. 2009 Dec; 11(3):417–26. [PubMed: 19548120]
8. Rincon F, Ghosh S, Dey S, Maltenfort M, Vibbert M, Urtecho J, McBride W, Moussouttas M, Bell R, Ratliff JK, et al. Impact of acute lung injury and acute respiratory distress syndrome after traumatic brain injury in the United States. Neurosurgery. 2012 Oct; 71(4):795–803. [PubMed: 22855028]
9. Zygun DA, Kortbeek JB, Fick GH, Laupland KB, Doig CJ. Non-neurologic organ dysfunction in severe traumatic brain injury. Crit Care Med. 2005 Mar; 33(3):654–60. [PubMed: 15753760]
10. Rosenthal G, Hemphill JC, Sorani M, Martin C, Morabito D, Meeker M, Wang V, Manley GT. The role of lung function in brain tissue oxygenation following traumatic brain injury. J Neurosurg. 2008 Jan; 108(1):59–65. [PubMed: 18173311]
11. Salim A, Martin M, Brown C, Inaba K, Browder T, Rhee P, Teixeira PG, Demetriades D. The presence of the adult respiratory distress syndrome does not worsen mortality or discharge disability in blunt trauma patients with severe traumatic brain injury. Injury. 2008 Jan; 39(1):30–5. [PubMed: 17920066]
12. Mascia L, Andrews PJ. Acute lung injury in head trauma patients. Intensive care medicine. 1998 Oct; 24(10):1115–6. [PubMed: 9840251]
13. Mascia L, Sakr Y, Pasero D, Payen D, Reinhart K, Vincent JL. Sepsis Occurrence in Acutely Ill Patients I. Extracranial complications in patients with acute brain injury: a post-hoc analysis of the SOAP study. Intensive care medicine. 2008 Apr; 34(4):720–7. [PubMed: 18175107]
14. Mascia L, Zavala E, Bosma K, Pasero D, Decaroli D, Andrews P, Isnardi D, Davi A, Arguis MJ, Berardino M, et al. High tidal volume is associated with the development of acute lung injury after severe brain injury: an international observational study. Crit Care Med. 2007 Aug; 35(8):1815–20. [PubMed: 17568331]
15. Marik PE, Corwin HL. Acute lung injury following blood transfusion: expanding the definition. Crit Care Med. 2008 Nov; 36(11):3080–4. [PubMed: 18824899]

16. Croce MA, Tolley EA, Claridge JA, Fabian TC. Transfusions result in pulmonary morbidity and death after a moderate degree of injury. J Trauma. 2005 Jul; 59(1):19–23. discussion -4. [PubMed: 16096534]

17. Silverboard H, Aisiku I, Martin GS, Adams M, Rozycki G, Moss M. The role of acute blood transfusion in the development of acute respiratory distress syndrome in patients with severe trauma. The Journal of trauma. 2005 Sep; 59(3):717–23. [PubMed: 16361918]

18. Watson GA, Sperry JL, Rosengart MR, Minei JP, Harbrecht BG, Moore EE, Cuschieri J, Maier RV, Billiar TR, Peitzman AB. Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. J Trauma. 2009 Aug; 67(2):221–7. discussion 8-30. [PubMed: 19667872]

19. Holena DN, Netzer G, Localio R, Gallop RJ, Bellamy SL, Meyer NJ, Shashaty MG, Lanken PN, Kaplan S, Reilly PM, et al. The association of early transfusion with acute lung injury in patients with severe injury. The journal of trauma and acute care surgery. 2012 Oct; 73(4):825–31. [PubMed: 23034528]

20. Chaiwat O, Lang JD, Vavilala MS, Wang J, MacKenzie EJ, Jurkovich GJ, Rivara FP. Early packed red blood cell transfusion and acute respiratory distress syndrome after trauma. Anesthesiology. 2009 Feb; 110(2):351–60. [PubMed: 19164959]

21. Christie JD, Kotloff RM, Pochettino A, Arcasoy SM, Rosengard BR, Landis JR, Kimmel SE. Clinical risk factors for primary graft failure following lung transplantation. Chest. 2003 Oct; 124(4):1232–41. [PubMed: 14555551]

22. Miller PR, Croce MA, Kilgo PD, Scott J, Fabian TC. Acute respiratory distress syndrome in blunt trauma: identification of independent risk factors. The American surgeon. 2002 Oct; 68(10):845–50. discussion 50-1. [PubMed: 12412708]

23. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF Jr, Hite RD, et al. National Heart L, Blood Institute Acute Respiratory Distress Syndrome Clinical Trials N. Comparison of two fluid-management strategies in acute lung injury. New Engl J Med. 2006 Jun 15; 354(24):2564–75. [PubMed: 16714767]

24. Plurad D, Martin M, Green D, Salim A, Inaba K, Belzberg H, Demetriades D, Rhee P. The decreasing incidence of late posttraumatic acute respiratory distress syndrome: the potential role of lung protective ventilation and conservative transfusion practice. J Trauma. 2007 Jul; 63(1):1–7. discussion 8. [PubMed: 17622861]

25. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, del Junco DJ, Brasel KJ, Bulger EM, Callcut RA, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA : the journal of the American Medical Association. 2015 Feb 3; 313(5):471–82. [PubMed: 25647203]

26. Howard BM, Kornblith LZ, Hendrickson CM, Redick BJ, Conroy AS, Nelson MF, Callcut RA, Calfee CS, Cohen MJ. Differences in degree, differences in kind: Characterizing lung injury in trauma. J Trauma Acute Care Surg. 2015 Apr; 78(4):735–41. [PubMed: 25742257]

27. Brohi K, Cohen MJ, Ganter MT, Matthay MA, Mackersie RC, Pittet JF. Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? Annals of surgery. 2007 May; 245(5):812–8. [PubMed: 17457176]

28. Sauaia A, Moore EE, Johnson JL, Ciesla DJ, Biffl WL, Banerjee A. Validation of postinjury multiple organ failure scores. Shock. 2009 May; 31(5):438–47. [PubMed: 18838942]

29. Hendrickson CM, Dobbins S, Redick BJ, Greenberg MD, Calfee CS, Cohen MJ. Misclassification of acute respiratory distress syndrome after traumatic injury: The cost of less rigorous approaches. J Trauma Acute Care Surg. 2015 Sep; 79(3):417–24. [PubMed: 26307875]

30. Toy P, Gajic O, Bacchetti P, Looney MR, Gropper MA, Hubmayr R, Lowell CA, Norris PJ, Murphy EL, Weiskopf RB, et al. Transfusion-related acute lung injury: incidence and risk factors. Blood. 2012 Feb 16; 119(7):1757–67. PubMed PMID: 22117051. Pubmed Central PMCID: PMC3286351. Epub 2011/11/26. eng. [PubMed: 22117051]

31. Cotton BA, Guy JS, Morris JA Jr, Abumrad NN. The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. Shock (Augusta, Ga). 2006 Aug; 26(2): 115–21.

32. Lingappan K, Jiang W, Wang L, Couroucli XI, Barrios R, Moorthy B. Sex-specific differences in hyperoxic lung injury in mice: implications for acute and chronic lung disease in humans. Toxicology and applied pharmacology. 2013 Oct 15; 272(2):281–90. [PubMed: 23792423]
33. Schmidt ME, Matochik JA, Goldstein DS, Schouten JL, Zametkin AJ, Potter WZ. Gender differences in brain metabolic and plasma catecholamine responses to alpha 2-adrenoceptor blockade. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 1997 Apr; 16(4):298–310. [PubMed: 9094148]
34. Roof RL, Duvdevani R, Braswell L, Stein DG. Progesterone facilitates cognitive recovery and reduces secondary neuronal loss caused by cortical contusion injury in male rats. Experimental neurology. 1994 Sep; 129(1):64–9. [PubMed: 7925843]
35. Shaz BH, Stowell SR, Hillyer CD. Transfusion-related acute lung injury: from bedside to bench and back. Blood. 2011 Feb 3; 117(5):1463–71. [PubMed: 20944069]
36. Ortiz-Munoz G, Mallavia B, Bins A, Headley M, Krummel MF, Looney MR. Aspirin-triggered 15-epi-lipoxin A4 regulates neutrophil-platelet aggregation and attenuates acute lung injury in mice. Blood. 2014 Oct 23; 124(17):2625–34. [PubMed: 25143486]
37. Vlaar APJ, Hofstra JJ, Kulik W, van Lenthe H, Nieuwland R, Schultz MJ, Levi MM, Roelofs JJTH, Tool ATJ, de Korte D, et al. Supernatant of stored platelets causes lung inflammation and coagulopathy in a novel in vivo transfusion model. Blood. 2010; 116(8):1360–8. [PubMed: 20479286]
38. Spiess BD, Royston D, Levy JH, Fitch J, Dietrich W, Body S, Murkin J, Nadel A. Platelet transfusions during coronary artery bypass graft surgery are associated with serious adverse outcomes. Transfusion. 2004; 44(8):1143–8. [PubMed: 15265117]
39. Wu B, Wang Y, Wang C, Cheng Y, Rong R. Intraoperative platelet transfusion is associated with increased postoperative sternal wound infections among type A aortic dissection patients after total arch replacement. Transfusion medicine (Oxford, England). 2014 Dec; 24(6):400–5.
40. Castellino FJ, Chapman MP, Donahue DL, Thomas S, Moore EE, Wohlauer MV, Fritz B, Yount R, Ploplis V, Davis P, et al. Traumatic brain injury causes platelet adenosine diphosphate and arachidonic acid receptor inhibition independent of hemorrhagic shock in humans and rats. J Trauma Acute Care Surg. 2014 May; 76(5):1169–76. [PubMed: 24747445]
41. Chi X, Zhi L, Gelderman MP, Vostal JG. Host Platelets and, in Part, Neutrophils Mediate Lung Accumulation of Transfused UVB-Irradiated Human Platelets in a Mouse Model of Acute Lung Injury. PloS One. 2012; 7(9):e44829. [PubMed: 23028636]
42. Anglin CO, Spence JS, Warner MA, Paliotta C, Harper C, Moore C, Sarode R, Madden C, Diaz-Arrastia R. Effects of platelet and plasma transfusion on outcome in traumatic brain injury patients with moderate bleeding diatheses. Journal of neurosurgery. 2013 Mar; 118(3):676–86. [PubMed: 23259827]
43. Kim D, O'Leary M, Nguyen A, Kaji A, Bricker S, Neville A, Bongard F, Putnam B, Plurad D. The effect of platelet and desmopressin administration on early radiographic progression of traumatic intracranial hemorrhage. J Neurotrauma. 2015 Nov 15; 32(22):1815–21. [PubMed: 25604812]
44. Brasel KJ, Vercruysse G, Spinella PC, Wade CE, Blackbourne LH, Borgman MA, Zarzabal LA, Du F, Perkins JG, Maegele M, et al. The association of blood component use ratios with the survival of massively transfused trauma patients with and without severe brain injury. J Trauma. 2011 Aug; 71(2 Suppl 3):S343–52. [PubMed: 21814102]
45. Wafaisade A, Lefering R, Tjardes T, Wutzler S, Simanski C, Paffrath T, Fischer P, Bouillon B, Maegele M. Acute coagulopathy in isolated blunt traumatic brain injury. Neurocritical care. 2010 Apr; 12(2):211–9. [PubMed: 19806475]
46. Lustenberger T, Talving P, Kobayashi L, Inaba K, Lam L, Plurad D, Demetriades D. Time course of coagulopathy in isolated severe traumatic brain injury. Injury. 2010 Sep; 41(9):924–8. [PubMed: 20471013]
47. Talving P, Lustenberger T, Lam L, Inaba K, Mohseni S, Plurad D, Green DJ, Demetriades D. Coagulopathy after isolated severe traumatic brain injury in children. J Trauma. 2011 Nov; 71(5): 1205–10. [PubMed: 21427617]

48. Larsen AM, Leinoe EB, Johansson PI, Larsen R, Wantzin P, Birgens H, Ostrowski SR. Haemostatic function and biomarkers of endothelial damage before and after platelet transfusion in patients with acute myeloid leukaemia. Transfusion Med. 2015 Jun; 25(3):174–83.

49. Calfee CS, Matthay MA, Eisner MD, Benowitz N, Call M, Pittet JF, Cohen MJ. Active and passive cigarette smoking and acute lung injury after severe blunt trauma. American journal of respiratory and critical care medicine. 2011 Jun 15; 183(12):1660–5. [PubMed: 21471091]

50. Contant CF, Valadka AB, Gopinath SP, Hannay HJ, Robertson CS. Adult respiratory distress syndrome: a complication of induced hypertension after severe head injury. J Neurosurg. 2001 Oct; 95(4):560–8. [PubMed: 11596949]

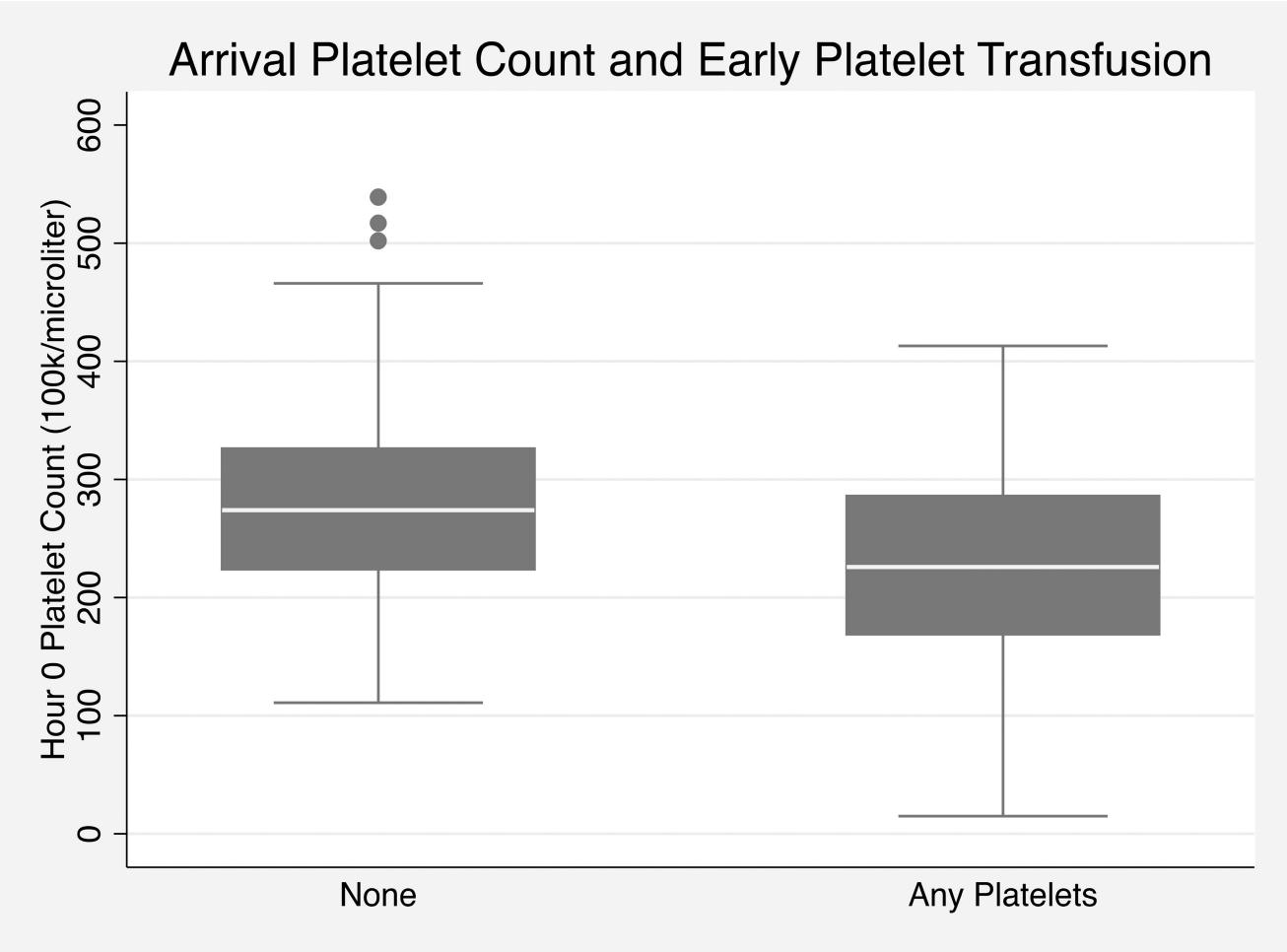

Figure 1.

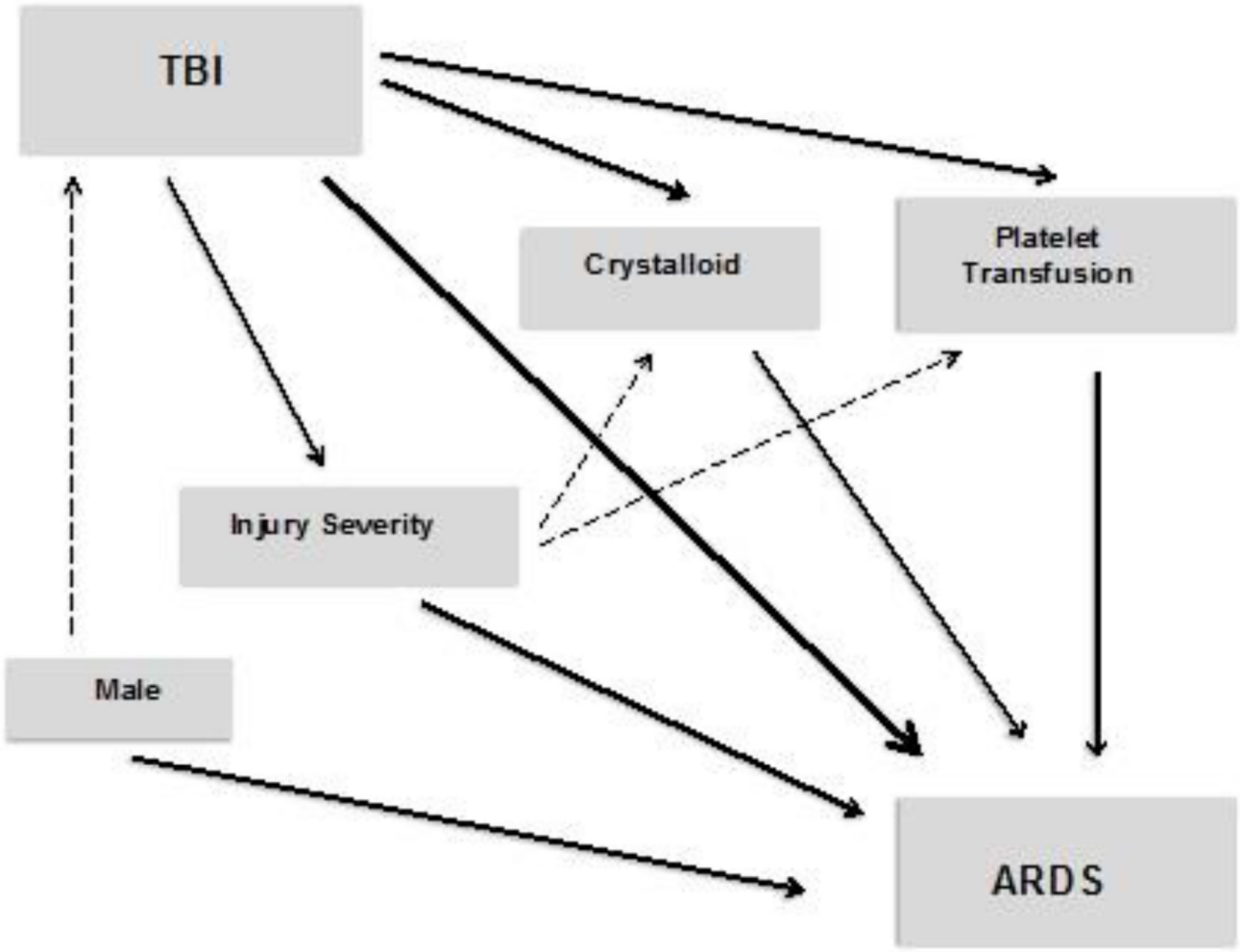

Figure 2.

Table 1

Demographic and Clinical Features of 210 Patients with Isolated Severe Traumatic Brain Injury With and Without ARDS

	Without ARDS (n = 148)	With ARDS (n= 62)	*p*-value*
Patient Characteristics			
Age (years)	47 ± 22	45 ± 21	0.6
Male sex	104 (70)	54 (87)	**0.01**
Blunt injury	125 (84)	53 (85)	0.85
Admission GCS	7 (3–10)	6 (3–10)	0.69
Head AIS	5 (4–5)	5 (5–5)	**0.018**
Head AIS >3	123 (83)	58 (94)	**0.045**
Craniotomy or Craniectomy	63 (43)	35 (56)	0.066
Chest AIS>0	18 (12)	8 (13)	0.88
Any Rib Fractures	13(9)	7 (11)	0.57
Skin AIS>0	125 (85)	35 (73)	**0.013**
Injury Severity Score (ISS)‡	26 (19–30)	26 (25–30)	0.43
ISS Excluding Head and Face AIS Scores‡	1 (1–2)	1 (0–2)	**0.04**
Base Deficit <−6 in first 12h	15 (11)	16 (26)	**0.005**
Platelet Count (k/μL) Ψ	272 (222–323)	251 (198–307)	0.13
PTT (seconds) Ψ	28 (26–31)	28 (26–32)	0.38
INR Ψ	1.1±0.2	1.2±0.2	0.46
Hemoglobin (g/dL) Ψ	13.7±1.8	13.8±2.1	0.41
Clinical Outcomes at 28 days			
Multi-organ failure	9 (6)	29 (47)	**<0.001**
Length of ICU Stay	4 (2–8)	13 (7–24)	**<0.001**
Length of Hospital Stay	7.5 (3–17)	14.5 (8–28)	**<0.001**
Ventilator Days Among Survivors	3 (2–8)	14.5 (7.5–25.5)	**<0.001**
Ventilator Free Days	16.5 (0–26)	0 (0–13)	**<0.001**
All cause mortality	54 (36)	26 (42)	0.46

Definitions of abbreviations: GCS= Glasgow Coma Scale; AIS= Abbreviated Injury Score; ISS= Injury Severity Score; PTT=partial thromboplastin time, INR=International normalized ratio

Findings presented as mean ± SD, n(%), and median (IQR) as appropriate

*p-value refers to unpaired t-test for age, Wilcoxon rank-sum test for all other continuous variables, and unordered χ^2 tests for all dichotomous predictors

†Dichotomized variable of presence or absence of any rib fractures on chest radiographs on the day of admission

‡ISS calculated as the sum of the squares of the three most severely injured body regions determined by AIS scores

ΨLaboratory values obtained on arrival to the Emergency Department

Table 2

Early Resuscitation and ARDS in After Isolated Severe Traumatic Brain Injury

Transfused 0–12 hrs[†]	**Without ARDS (n = 148)**	**With ARDS (n= 62)**	***p*-value**[*]
Any blood product[†]	68 (46)	37 (60)	0.069
Massive Transfusion[‡]	8 (5)	12 (19)	**0.002**
Any pRBC[†]	60 (41)	34 (55)	0.057
Any platelet[†]	23 (16)	21 (34)	**0.003**
Any FFP[†]	44 (30)	27 (44)	0.053
Any cryoprecipitate[†]	7 (5)	3 (5)	0.97
Crystalloid 0–12hrs (L)	3.5 (2.0–4.5)	4.3 (2.5–6.5)	**0.005**

Definitions of abbreviations: pRBC = packed red blood cells; FFP = fresh frozen plasma;

Data presented as n (%) for all transfusion related variables and median (IQR) for crystalloid data.

[*] *p*-value refers to a rank-sum test for crystalloid and unordered χ^2 tests for all transfusion variables

[†] "Any" refers to at least one unit of specified blood product administered in the first 12 hours of hospital admission

[‡] Massive transfusion is defined as ≥ 10 units of packed red blood cells in the first 24 hours of admission

Table 3

Overlap of Early Platelet[†] Transfusion with Massive Transfusion, Severity of Head Injury, and Neurosurgical Interventions

	Any Platelet[†] Transfusion *n*(%)
Craniotomy or Craniectomy (n=98)	35 (36)
AIS Head = 3 (n=29)	2 (7)
AIS Head = 4 (n=37)	4 (11)
AIS Head = 5 (n=143)	38 (27)
AIS Head = 6 (n=1)	0
Massive Transfusion[‡](n=20)	20 (100) [Ψ]
Any Early pRBC[†] (n=94)	39 (41)

[†]Early transfusion defined as at least one unit administered in the first 12 hours of hospital admission

[‡]Massive transfusion is defined as ≥ 10 units of packed red blood cells in the first 24 hours of admission.

[Ψ]24(55%) of patients who received early platelets, did not receive massive transfusion.

Table 4

Logistic Regression Analyses of ARDS after Isolated Severe TBI

Predictor	Odds Ratio	95% CI	*p*-value	AUROC
Univariate Models				
AIS Head > 3	2.9	1.0–8.9	0.054	0.55
AIS Head [Ψ]	1.8	1.1–2.9	**0.018**	0.59
Craniectomy or Craniotomy	1.7	1.0–3.2	0.067	0.57
Male	2.9	1.3–6.5	**0.012**	0.58
Any blood product 0–12h [†]	1.7	1.0–3.2	0.071	0.57
Massive transfusion [‡]	4.2	1.7–11.1	**0.003**	0.57
Any platelets 0–12h	2.8	1.4–5.5	**0.004**	0.54
Any platelets 0–12h, excluding massive transfusion	1.9	0.7–4.4	0.171	0.57
Any pRBCs 0–12h	1.8	1.0–3.2	0.059	0.57
Any FFP 0–12h	1.8	1.0–3.4	0.055	0.57
Crystalloid fluids 0–12h (per L)	1.0	1.0–1.0	**0.007**	0.62
Full Multivariate Model				0.71
AIS Head [Ψ]	1.4	0.9–2.4	0.18	
Male	2.9	1.2–6.9	0.015	
Crystalloid fluids 0–12h (per L)	1.0	1.0–1.0	0.15	
Any platelets 0–12h	2.5	1.2–5.3	0.015	
Nested Multivariate Model				0.68
AIS Head [Ψ]	1.5	0.9–2.6	0.103	
Male	2.6	1.1–6.0	0.026	
Crystalloid fluids 0–12h (per L)	1.0	1.0–1.0	0.056	
Likelihood ratio test: *p*=0.015				

Definitions of abbreviations: AUROC= area under receiver operator curve, pRBC = packed red blood cells; FFP = fresh frozen plasma; h=hours from Emergency Department arrival, L= liter

[Ψ] AIS Head per 1 unit change can take on the potential values of 3, 4, 5, or 6 in this analysis, test for departure from linear trend is not significant

[†] Any transfusion includes specified blood product administered in the first 12 hours of hospital admission

[‡] Massive transfusion is defined as ≥ 10 units of packed red blood cells in the first 24 hours of admissionn