Title

Predictors of postinjury acute respiratory distress syndrome: Lung injury persists in the era of hemostatic resuscitation.

Journal

Journal of Trauma and Acute Care Surgery, 87(2)

ISSN

2163-0755

Authors

Kornblith, Lucy Z
Robles, Anamaria J
Conroy, Amanda S
et al.

Publication Date

2019-08-01

DOI

10.1097/ta.0000000000002331

Peer reviewed

HHS Public Access

Author manuscript

J Trauma Acute Care Surg. Author manuscript; available in PMC 2020 August 01.

Published in final edited form as:

J Trauma Acute Care Surg. 2019 August ; 87(2): 371–378. doi:10.1097/TA.0000000000002331.

PREDICTORS OF POST-INJURY ARDS: LUNG INJURY PERSISTS IN THE ERA OF HEMOSTATIC RESUSCITATION

Lucy Z Kornblith, MD[1], **Anamaria J Robles, MD**[1], **Amanda S Conroy, BA**[1], **Brittney J Redick, BA**[1], **Benjamin M Howard, MD**[1], **Carolyn M Hendrickson, MD MPH**[2], **Sara Moore, BA MA**[3], **Mary F Nelson, RN**[1], **Farzad Moazed, MD**[2], **Rachael A Callcut, MD MSPH**[1], **Carolyn S Calfee, MD MAS**[2], **Mitchell Jay Cohen, MD**[4]

[1]Department of Surgery, Zuckerberg San Francisco General Hospital and the University of California, San Francisco; San Francisco, California

[2]Department of Medicine, University of California, San Francisco; San Francisco, California

[3]Department of Biostatistics, University of California, Berkeley; Berkeley, California

[4]Department of Surgery, Denver Health Medical Center and the University of Colorado; Denver, Colorado

Abstract

BACKGROUND—Acute respiratory distress syndrome (ARDS) following trauma is historically associated with crystalloid and blood product exposure. Advances in resuscitation have occurred over the last decade, but their impact on ARDS is unknown. We sought to investigate predictors of post-injury ARDS in the era of hemostatic resuscitation.

METHODS—Data were prospectively collected from arrival to 28d for 914 highest-level trauma activations who required intubation and survived >6h from 2005-2016 at a Level 1 Trauma Center. Patients with PaO2:FiO2 ratio (PF) of ≤300mgHg during the first 8d were identified. Two blinded expert clinicians adjudicated all chest radiographs for bilateral infiltrates in the first 8d. Those with left heart failure detected were excluded. Multivariate logistic regression was used to define predictors of ARDS.

RESULTS—Of the 914 intubated patients, 63% had a PF≤300 and 22% developed ARDS; among the ARDS cases, 57% were diagnosed *early* (in the first 24h) and 43% *later*. ARDS patients diagnosed *later* were more severely injured (ISS 32 vs. 20, p=0.001) with higher rates of blunt injury (84% vs. 72%, p=0.008), chest injury (58% vs. 36%, p<0.001), and TBI (72% vs. 48%, p<0.001) compared with the no ARDS group. In multivariate analysis, head/chest AIS scores,

Corresponding author: Lucy Z Kornblith, MD, Department of Surgery, Ward 3A, Zuckerberg San Francisco General Hospital, 1001 Potrero Avenue, Room 3C-38, San Francisco, CA 94110, Phone: (415) 206-3764, Fax: (415) 206-5484, lucy.kornblith@ucsf.edu.

AUTHOR CONTRIBUTIONS:

LZK, AJR, BJR, BMH, CMH, SM, ASC, RAC, CSC, and MJC contributed to design and conduct of the study, collection, management, analysis, and interpretation of the data, and preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication

MFN contributed to design and conduct of the study, collection, management, analysis, and interpretation of the data, and preparation, review, or approval of the manuscript

Conflicts of interest: None

Meetings: Presented at the Pacific Coast Surgical Association 89th Annual Meeting, February 19, 2018, in Napa, California

crystalloid from 0-6h, and platelet transfusion from 0-6h and 7-24h were independent predictors of ARDS developing after 24h.

CONCLUSION—Blood and plasma transfusion were not independently associated with ARDS. However, platelet transfusion was a significant independent risk factor. The role of platelets warrants further investigation but may be mechanistically explained by lung injury models of pulmonary platelet sequestration with peripheral thrombocytopenia.

LEVEL OF EVIDENCE—Level IV; prognostic

Keywords

ARDS; Berlin criteria; platelet transfusion; hemostatic resuscitation

BACKGROUND

Injury remains a leading cause of death in the young (1). The majority of late deaths after injury are due to multiple organ failure (MOF) (2–4), most commonly involving the lung (5). Lung injury is a major cause of morbidity and mortality in trauma, surgical, and medical patients. Following decades of recognition as a clinical entity, lung injury was more precisely defined as acute respiratory distress syndrome (ARDS) at the American-European Consensus Conference in 1994 (6) and revised with gradation of hypoxemia in the Berlin Definition in 2012 (7).

The etiology of lung injury after trauma remains debated, but many groups have reported associations with crystalloid administration and transfusion of blood products (8–13). Over the past decade however, transfusion practices have dramatically evolved as a result of the discovery and understanding of trauma-induced coagulopathy (14–16) coupled with the improved clinical outcomes realized with decreased crystalloid use and hemostatic blood product resuscitation in both military and civilian populations (17–19). The effect of our changing resuscitation practices has resulted in a debate regarding the incidence of post-injury ARDS, as studies published after these landmark changes in the standard of care for trauma resuscitation report highly variable incidence of ARDS after injury. Some studies demonstrate that post-injury ARDS is almost non-existent with rates as low as 10%, while others report an incidence as high as 40% (13, 20–23). Additionally, multifactorial heterogeneity across studies particularly with respect to different criteria for the classification of ARDS as an outcome, the change in consensus definitions of ARDS, and emerging knowledge of phenotypic variation in ARDS has led to an unclear understanding of the true incidence and risk factors for development of post-injury ARDS. Given this, we sought to examine the incidence and predictors of ARDS after injury in the era of hemostatic resuscitation using rigorous adjudication of ARDS as the outcome of interest and strict adherence to the Berlin criteria. We hypothesized that ARDS after injury remains common despite hemostatic resuscitation practices.

METHODS

During the study period, there were 8762 highest-level activations, of which 1671 were enrolled for prospective study at a Level 1 Trauma Center (exclusions: pediatric, pregnant,

in-custody, burns >20% body surface area, transferred from another facility, did not require ICU level care, or atraumatic). Following exclusions, comprehensive injury, demographic, clinical, and outcome data were prospectively collected on arrival and out to 28 days for 914 highest-level trauma activation subjects who required intubation and survived for more than 6 hours after injury from 2005-2016 (Figure 1) under a waiver-of-consent approved by the University of California Institutional Review Board. ARDS was defined in the cohort by Berlin Definition (7). Two blinded expert critical care boarded physician investigators reviewed all chest x-rays (CXRs) ordered for clinical reasons on subjects with a documented PaO2:FiO2 (PF) ratio of ≤300mgHg during the first 8 days of admission and classified subjects as "positive" or "negative" for the presence of bilateral infiltrates in the first 8 days. Studies were classified as "equivocal" if the CXR was of poor quality and/or could not be confidently interpreted by the expert clinicians (24). These patients were excluded entirely from analysis. Confirmation of PF ratio of ≤300mgHg at time of positive CXR was performed. Left heart failure was adjudicated for description of moderate-severely reduced ejection fraction or volume overload by blinded expert critical care boarded physician investigators from echocardiogram reports if performed for clinical care within 24 hours of the qualifying film for ARDS. Chart review of admission, discharge, and ICU notes for diagnosis of heart failure or volume overload was used when echocardiogram was not performed. Multi-organ failure (MOF) was defined using the Denver Postinjury Multiple Organ Failure Score (25) and an adjusted non-pulmonary multi-organ failure (NP-MOF) score based on the Denver guidelines was defined excluding the pulmonary contribution to the overall score. Crystalloid volumes were reported in ½ liter increments per prior literature (13). Ventilator-associated pneumonia (VAP) was defined by hospital reporting via the National Healthcare Safety Network Ventilator Associated Event Surveillance Algorithm (26, 27). Thrombocytopenia was defined as a platelet count $<150 \times 10^9$/L. There were no reported cases of transfusion-related acute lung injury and transfusion-associated circulatory overload.

Data are presented as mean (standard deviation), median (interquartile range), or percentage; univariate comparisons were made using Student's *t* test for normally distributed data, Wilcoxon rank sum or Kruskal Wallis testing for skewed data, and Fisher's exact test for proportions. Multivariate logistic regression was performed to identify independent predictors of the development of *later* ARDS. In order to accommodate limitations in the granularity of the treatment times of blood product and crystalloid administration to ensure exposure preceded outcome, our models compared subjects with *later* ARDS to those with no ARDS and excluded subjects who developed ARDS in the first 24 hours or died within the first 24 hours. The multivariate model included relevant univariate variables that reached statistical significance, and all variables included in multivariate model were continuous measures. An [alpha] = 0.05 was considered significant. All analysis was performed by the authors using Stata version 12 (StataCorp, College Station, TX).

RESULTS

Whole cohort

During the study period, 914 subjects were intubated and survived at least 6h from injury (Figure 1). Analysis confirmed adherence to hemostatic resuscitation methods (mean blood: plasma ratio 0.73, mean blood: platelet ratio 0.38; Table 1). 63% (572/914) met the PF ratio of ≤300mgHg and underwent CXR adjudication. Nineteen subjects were equivocal for bilateral infiltrates by CXR and were excluded entirely from analysis. 38% (218/572) were adjudicated to have bilateral infiltrates on CXR. Of these 218 subjects with bilateral infiltrates on CXR, 14 were ultimately excluded entirely from analysis: twelve subjects were adjudicated to have cardiogenic pulmonary edema, and two subjects had bilateral infiltrates on CXR, but the PF ratio ≤300mgHg did not occur within 24 hours of the presence of bilateral infiltrates. Ultimately, 22% (204/914) of the cohort had ARDS by Berlin Definition: of these, 25% (n=52) had severe hypoxemia (PF≤100), 43% (n=88) had moderate hypoxemia (PF 101-200), and 31% (n=64) had mild hypoxemia (PF 201-300) (Figure 1). The incidence of new diagnosis of ARDS by day following injury is demonstrated in the eFigure.

ARDS vs. no ARDS

Compared to the 677 subjects without ARDS, the 204 subjects who developed ARDS had a larger burden of overall injury (median Injury Severity Score [ISS] 30 vs. 20, $p<0.001$), a higher prevalence of blunt injury (84% vs. 72%, $p<0.001$), and had more chest injury (mean number of rib fractures 2.6 vs. 0.28, $p<0.001$; median chest abbreviated injury score [AIS] 3 vs. 0, $p<0.001$; percent with chest AIS ≥3 51% vs. 26%, $p<0.001$; Table 2). Those who developed ARDS had higher rates of brain injury (67% vs. 48%, $p<0.001$; Table 2), and isolated brain injury (51% vs. 39%, $p=0.02$; Table 2).

The subjects who developed ARDS received significantly more crystalloid, blood, plasma, and platelets in the first 24 hours (all $p=0.001$; Table 2), and higher ratios of blood to plasma/platelets compared to those who did not (mean blood: plasma ratio 0.96 vs. 0.87; mean blood: platelet ratio 0.70 vs. 0.26; all $p=0.001$; Table 2). On admission, those who developed ARDS had a significantly lower platelet count than those who did not (180 vs. 222 × 10^9/L, $p<0.001$; Table 2) and went on to have worse outcomes including increased mortality ($p<0.001$; Table 2). However, of note, mortality occurred later in those with ARDS than those without ARDS, likely due to survival bias (median hours to death 158.7 vs. 32.6 hours $p=0.001$; Table 2). 67% were ventilated with lung protective ventilation (28) tidal volumes <8mL/kg on their day of ARDS (eTable 1).

Early ARDS vs. Later ARDS

We next stratified ARDS into those who developed ARDS within 24 hours (*early*, median time to development 6 hours) and those who developed ARDS beyond 24 hours of injury (*later*, median time to development 84 hours). 43% (88/204) developed ARDS *early*, and 57% (116/204) developed ARDS *later* (Table 3). There were few statistically or clinically significant differences in the demographics or injury characteristics between the two groups. The subjects who developed ARDS *early* were more likely to be in shock (SBP<90mmHg

on presentation: 20% vs. 10%, p=0.03; base excess −8.5 vs. −5.5, p=0.002; Table 3). Surprisingly, there were no significant differences in overall injury or chest injury burden between the groups (ISS, median chest AIS, percent with AIS≥3, percent with rib fractures, percent with direct lung injury [pulmonary contusion, pulmonary laceration, pneumothorax, hemothorax, or subcutaneous emphysema]; all p>0.05; Table 3). There was a significantly lower admission platelet count in the subjects who developed ARDS *early* (median platelet counts 129 vs. 188 × 10^9/L, p=0.0043; Table 3).

Despite the lack of major differences in injury characteristics and severity, those who developed ARDS *early* received more crystalloid, blood, plasma, and platelets early (within 6 hours) after injury (all p<0.05; Table 3). In addition, they received a higher mean blood: platelet ratio transfusion in the first 24 hours (0.85 vs. 0.57; all p=0.03; Table 3). Those who developed ARDS *early* had shorter ICU and hospital stays and lower rates of MOF (all p<0.01: Table 3), but no difference in NP-MOF rates, likely due to survival bias. Lung protective ventilation (28) was used in at least 60% of both groups on their day of confirmed ARDS (mean tidal volume: *early* 8.8ml/kg vs. *later* 7.7 ml/kg, p=0.25; eTable 2).

Predictors of Development of Later ARDS

Lastly, we performed a multivariate logistic regression to define predictors of the development of ARDS. In a multivariate model (AUC 0.80), the only independent predictors for development of *later* ARDS were head injury (head AIS; odds ratio [OR] 1.38, confidence interval [CI] 1.21-1.57, p<0.001), chest injury (chest AIS; OR 1.35, CI 1.17-1.55, p<0.001), early crystalloid administration (crystalloid half liter 0-6 hours; OR 1.10, CI 1.04-1.15, p<0.001), and early and late platelet administration (platelet units 0-6 hours; OR 2.34, CI 1.04-5.25, p=0.04; platelet units 7-24 hours; OR 5.40, CI 2.58-11.31, p<0.01; Table 4). Most notably, for every one unit of additional platelets transfused from 7-24 hours after injury, there was a five-fold increase in the odds of developing ARDS past 24 hours from injury.

DISCUSSION

ARDS plays a pivotal role in mortality after injury (3, 5–7, 29–31) and is independently associated with a 3-fold increase in death (32). Thus, significant interest exists in defining modifiable factors that contribute to the development of ARDS. Classically, the primary physician modifiable risk factors for the development of ARDS after severe trauma have been crystalloid administration and transfusion of blood products; however, the majority of these associations were defined prior to the current hemostatic resuscitation era (8–12, 33–35). In addition, there is significant variability in research methods for identifying and defining lung injury following trauma; ARDS in trauma literature is often identified solely based on the partial pressure of oxygen (PaO2): fraction of inspired oxygen (FiO2) (PF) ratio (23), either ignoring the importance of the presence of bilateral infiltrates by chest radiography (CXR) (which diagnostically defines ARDS) or by relying on a radiographic report. We previously identified that only 46% of patients with hypoxemia after injury have ARDS by Berlin criteria with CXR adjudication (36). In addition, emerging studies have begun to identify phenotypic variation of lung injury (37, 38) after injury. Using latent class

analysis, Reilly *et al.* have identified three independent temporal classes of lung injury after trauma (within 24 hours, 2-3 days, and 4-5 days) that were associated with distinct injury characteristics and outcomes (38). This plausible heterogeneity of ARDS after injury may account for additional variability in reported incidence and defined predictors of ARDS in trauma. The inconsistent approaches used for identifying ARDS for study makes understanding the true prevalence and physiologic mechanisms problematic.

Recently Robinson *et al.* studied ARDS subjects from the Pragmatic Randomized Optimal Platelet and Plasma Ratios study (defining ARDS as a PF ratio <200 with CXR confirmed bilateral pulmonary infiltrates, adjudicated by investigators) identifying that ARDS was associated with blunt injury, chest injury, and crystalloid given in the first 6 hours, but was not associated with blood transfusion. Due to inclusion criteria (patients predicted to receive massive transfusion and PF<200), these study results may not be generalizable to patients who are less injured, have received less transfusion, or have mild ARDS by Berlin criteria (13). Given the immense heterogeneity across post-injury ARDS studies, we sought to examine post-injury ARDS during the modern era of hemostatic resuscitation and using complete Berlin Definition (development in first 7 days post-injury, presence of physician adjudicated bilateral infiltrates, absence of cardiac failure as primary cause of respiratory compromise, and positive end-expiratory pressure (PEEP) of 5 cm H_20 or more) (7).

Our study confirms that despite modern hemostatic resuscitation, ARDS remains prevalent following injury and is seen in 22% of severely injured and intubated subjects (peak of 44% at the beginning of the study period). Over half (57%) of the subjects in our study developed ARDS *later*, at least 24 hours from injury. However, a large percentage (43%) developed ARDS *early*, or within 24 hours from injury. Although a recent study identified a phenotype of *early* ARDS to be associated with more severe chest injury, initial hypotension, and early blood transfusion (39), we found no significant difference in overall injury, degree of hypotension, or in any markers of chest injury including pulmonary contusion between our *early* and *later* ARDS groups in our cohort despite the similar distribution of subjects who developed *early* and *later* ARDS and similar sample size. Interestingly, despite the lack of difference in overall injury severity, there is a clear unmeasured burden of injury present in those who developed ARDS *early*.

Similarly, those who developed ARDS *early* had peripheral thrombocytopenia on admission compared to those who developed ARDS *later*. This observation echoes findings from basic science studies and cellular investigations on the role of platelets in lung injury. The pathogenesis of ARDS has been attributed to both direct and indirect lung injury with increased permeability of the epithelial alveolar-capillary barrier and increased endothelial vascular permeability leading to fluid accumulation in the air spaces (40). Investigations of lung injury in human and animal models have identified a phenomena of platelet aggregation leading to peripheral thrombocytopenia and pulmonary sequestration of platelets (41, 42). In our study, it may be that due to unmeasurable injury characteristics, those who developed *early* ARDS had peripheral thrombocytopenia immediately after injury, triggering transfusion of platelets that became sequestered in the pulmonary circulation. Alternatively, perhaps circulating platelets are sequestered in the pulmonary circulation leading to peripheral thrombocytopenia. In either case, the finding of relative thrombocytopenia in the

whole ARDS cohort compared to the non-ARDS cohort, as well as in those who developed ARDS *early* compared to *later*, and the independent association of late platelet transfusion with development of *later* ARDS exposes a plausible measurable role of platelets in the development of post-injury ARDS.

Finally, in the multivariate model of independent predictors of the development of *later* ARDS, head and chest injury, early crystalloid administration, and platelet transfusions (0-6 hours and 7-24 hours) were the only independent predictors of development of ARDS at least 24 hours after injury. This finding is supportive of known frequent concordance of ARDS and traumatic brain injury (TBI) with associated dismal outcomes (43, 44) which is critical given the divergent therapeutic priorities in the respiratory management of TBI compared to ARDS (44). Additionally, thoracic trauma remains an independent predictor of ARDS (23, 35, 45) and early crystalloid administration continues to appear to play a formal role in the development of ARDS (46). Lastly, as previously addressed, the transfusion of late platelets may be a primer to pulmonary sequestration of platelets or may be in response to low circulating platelets due to sequestration in the lungs. The potential causal order of this relationship in trauma remains to be decoded.

We acknowledge several limitations of our study. This study cannot identify inflammatory driven lung injury from direct lung injury, but our multivariate analysis controls for direct lung injury (chest AIS) in order to identify predictors of *later* ARDS. Due to the critical importance of rigorous time-ordering of the cardinal exposures of crystalloid and blood products prior to the outcome of ARDS, we were unable to define independent predictors of development of *early* ARDS, and we have accounted for this ambiguity in our targeted logistic regression models of *later* ARDS to ensure exposures preceded outcomes. In addition, without a true baseline (or follow-up) echocardiogram, there is no way to completely rule out cardiogenic edema. Furthermore, we do not have data on overall rates of sepsis in this population and do not know time ordering of the development of VAP compared to ARDS. We do not have cause-of death or long term outcome data in this cohort. In the future, further elucidation of the post-injury temporal phenotypes of ARDS needs to be defined. If differences exist between *early* and *later* ARDS as suggested by our results and others (39), there may be modifiable risk factors that are unique to *early* ARDS that we were not able to identify. In addition, we did not collect aspiration rates in this population and cardiac function was retrospectively assessed. As with all prospective studies, we recognize the presence of survival bias, which may account for some differences in outcome measures for subjects living long enough to develop ARDS. Similarly, the subjects who developed ARDS had higher rates of complications, which could be partially due to their longer survival. Additionally, due to the observational structure of our study, we cannot elucidate any causal relationships between platelets and lung injury, only intriguing associations.

In the era of hemostatic resuscitation, ARDS remains common after injury. We found that blood and plasma transfusion were not associated with the development of ARDS in severely injured subjects. However, platelet transfusion was a significant independent predictor of the development of ARDS. This role of platelets warrants further investigation but may be mechanistically explained by lung injury models of neutrophil mediated

pulmonary platelet sequestration with peripheral thrombocytopenia, and may expose a potential modifiable risk factor for the development of ARDS. The future exploration of post-injury phenotypes of ARDS may assist in risk stratification and modifiable therapeutic targets for the varying populations of *early* versus *later* ARDS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: Dr. Cohen is supported by DoD W911QY-15-C-0044 and NIH UM1HL120877, Dr. Callcut is supported by NIH K01ES026834 and DoD W911QY-15-C-0044, Dr. Hendrickson is supported by K23 HL133495. Dr. Calfee was supported by NHLBI R01HL110969 and NHLBI R35HL140026. Dr. Kornblith is supported by NIGMS K23GM130892-01.

REFERENCES:

1. Norton R, Kobusingye O. Injuries. N Engl J Med. 2013;368(18):1723–30. [PubMed: 23635052]
2. Trunkey DD. Trauma. Accidental and intentional injuries account for more years of life lost in the U.S. than cancer and heart disease. Among the prescribed remedies are improved preventive efforts, speedier surgery and further research. Scientific American. 1983;249(2):28–35. [PubMed: 6623052]
3. Cothren CC, Moore EE, Hedegaard HB, Meng K. Epidemiology of urban trauma deaths: a comprehensive reassessment 10 years later. World J Surg. 2007;31(7):1507–11. [PubMed: 17505854]
4. Oyeniyi BT, Fox EE, Scerbo M, Tomasek JS, Wade CE, Holcomb JB. Trends in 1029 trauma deaths at a level 1 trauma center: Impact of a bleeding control bundle of care. Injury. 2017;48(1):5–12. [PubMed: 27847192]
5. Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A. The role of the lung in postinjury multiple organ failure. Surgery. 2005;138(4):749–57; discussion 57-8. [PubMed: 16269305]
6. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, LeGall JR, Morris A, Spragg R. Report of the American-European Consensus conference on acute respiratory distress syndrome: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Consensus Committee. J Crit Care. 1994;9(1):72–81. [PubMed: 8199655]
7. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526–33. [PubMed: 22797452]
8. Croce MA, Tolley EA, Claridge JA, Fabian TC. Transfusions result in pulmonary morbidity and death after a moderate degree of injury. J Trauma Acute Care Surg. 2005;59(1):19–23; discussion -4.
9. 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 Acute Care Surg. 2009;67(2):221–7; discussion 8-30.
10. 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. J Trauma Acute Care Surg. 2012;73(4):825–31. [PubMed: 23034528]
11. 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;124(4):1232–41. [PubMed: 14555551]

12. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF Jr, Hite RD, Harabin AL Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354(24):2564–75. [PubMed: 16714767]
13. Robinson BRH, Cohen MJ, Holcomb JB, Pritts TA, Gomaa D, Fox EE, Branson RD, Callcut RA, Cotton BA, Schreiber MA, et al. Risk Factors for the Development of Acute Respiratory Distress Syndrome Following Hemorrhage. Shock. 2017.
14. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma Acute Care Surg. 2003;54(6):1127–30.
15. Cohen MJ, Call M, Nelson M, Calfee CS, Esmon CT, Brohi K, Pittet JF. Critical role of activated protein C in early coagulopathy and later organ failure, infection and death in trauma patients. Ann Surg. 2012;255(2):379–85. [PubMed: 22133894]
16. MacLeod JB, Lynn M, McKenney MG, Cohn SM, Murtha M. Early coagulopathy predicts mortality in trauma. J Trauma Acute Care Surg. 2003;55(1):39–44.
17. Holcomb JB, Wade CE, Michalek JE, Chisholm GB, Zarzabal LA, Schreiber MA, Gonzalez EA, Pomper GJ, Perkins JG, Spinella PC, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg. 2008;248(3): 447–58. [PubMed: 18791365]
18. Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, Sebesta J, Jenkins D, Wade CE, Holcomb JB. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma Acute Care Surg. 2007;63(4):805–13.
19. Spinella PC, Perkins JG, Grathwohl KW, Beekley AC, Niles SE, McLaughlin DF, Wade CE, Holcomb JB. Effect of plasma and red blood cell transfusions on survival in patients with combat related traumatic injuries. J Trauma Acute Care Surg. 2008;64(2 Suppl):S69–77; discussion S-8.
20. 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 Acute Care Surg. 2007;63(1):1–7; discussion 8.
21. Martin M, Salim A, Murray J, Demetriades D, Belzberg H, Rhee P. The decreasing incidence and mortality of acute respiratory distress syndrome after injury: a 5-year observational study. J Trauma Acute Care Surg. 2005;59(5):1107–13.
22. 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. Am J Respir Crit Care Med. 2011;183(12):1660–5. [PubMed: 21471091]
23. Robinson BR, Cotton BA, Pritts TA, Branson R, Holcomb JB, Muskat P, Fox EE, Wade CE, del Junco DJ, Bulger EM, et al. Application of the Berlin definition in PROMMTT patients: the impact of resuscitation on the incidence of hypoxemia. J Trauma Acute Care Surg. 2013;75(1 Suppl 1):S61–7. [PubMed: 23778513]
24. Shah CV, Lanken PN, Localio AR, Gallop R, Bellamy S, Ma SF, Flores C, Kahn JM, Finkel B, Fuchs BD, et al. An alternative method of acute lung injury classification for use in observational studies. Chest. 2010;138(5):1054–61. [PubMed: 20576730]
25. Sauaia A, Moore EE, Johnson JL, Ciesla DJ, Biffl WL, Banerjee A. Validation of postinjury multiple organ failure scores. Shock. 2009;31(5):438–47. [PubMed: 18838942]
26. Allen-Bridson K, Gross C, Hebden JN, Morrell GC, Wright MO, Horan T. Healthcare-associated infections studies project: an American Journal of Infection Control and National Healthcare Safety Network data quality collaboration-Ventilator-associated event 1, 2013. Am J Infect Control. 2013;41(11):1085–6. [PubMed: 23972519]
27. Magill SS, Rhodes B, Klompas M. Improving ventilator-associated event surveillance in the National Healthcare Safety Network and addressing knowledge gaps: update and review. Curr Opin Infect Dis. 2014;27(4):394–400. [PubMed: 24945615]
28. Acute Respiratory Distress Syndrome N, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1301–8. [PubMed: 10793162]

29. Sauaia A, Moore FA, Moore EE, Moser KS, Brennan R, Read RA, Pons PT. Epidemiology of trauma deaths: a reassessment. J Trauma Acute Care Surg. 1995;38(2):185–93.
30. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med. 1995;23(10):1638–52. [PubMed: 7587228]
31. Sauaia A, Moore FA, Moore EE, Haenel JB, Read RA, Lezotte DC. Early predictors of postinjury multiple organ failure. Arch Surg. 1994;129(1):39–45. [PubMed: 8279939]
32. Shah CV, Localio AR, Lanken PN, Kahn JM, Bellamy S, Gallop R, Finkel B, Gracias VH, Fuchs BD, Christie JD. The impact of development of acute lung injury on hospital mortality in critically ill trauma patients. Crit Care Med. 2008;36(8):2309–15. [PubMed: 18664786]
33. Marik PE, Corwin HL. Acute lung injury following blood transfusion: expanding the definition. Crit Care Med. 2008;36(11):3080–4. [PubMed: 18824899]
34. 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. J Trauma Acute Care Surg. 2005;59(3):717–23.
35. Miller PR, Croce MA, Kilgo PD, Scott J, Fabian TC. Acute respiratory distress syndrome in blunt trauma: identification of independent risk factors. Am Surg. 2002;68(10):845–50; discussion 50-1. [PubMed: 12412708]
36. 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;78(4):735–41. [PubMed: 25742257]
37. Croce MA, Fabian TC, Davis KA, Gavin TJ. Early and late acute respiratory distress syndrome: two distinct clinical entities. J Trauma Acute Care Surg. 1999;46(3):361–6; discussion 6-8.
38. Reilly JP, Bellamy S, Shashaty MG, Gallop R, Meyer NJ, Lanken PN, Kaplan S, Holena DN, May AK, Ware LB, et al. Heterogeneous Phenotypes of the Acute Respiratory Distress Syndrome after Major Trauma. Ann Am Thorac Soc. 2014.
39. Reilly JP B S, Shashaty MGS, Localio AR, Gallop R, Meye NJ, Kaplan S, Holena D, Lanken PN, Christ JD. Early Hypotension, Severity of Thoracic Trauma, and Blood Transfusion are Associated with an Early Onset Endophenotype of Acute Lung Inury after Major Trauma. Am J Respir Crit Care Med. 2012.
40. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med. 2000;342(18): 1334–49. [PubMed: 10793167]
41. Blaisdell WF L F. Respiratory Distress Syndrome of Shock and Trauma: Post-Traumatic Respiratory Failure. Paul A Ebert MD, editor. Philadelphia, London, Toronto: W.B. Saunders Company; 1977.
42. HJ R Role of Pulmonary Microembolism in the Hemodynamics of Endotoxin Shock. Surg Gynecol Obstet. 1972.
43. 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 Acute Care Sur. 2003;55(1):106–11.
44. Mascia L Acute lung injury in patients with severe brain injury: a double hit model. Neurocrit care. 2009;11(3):417–26. [PubMed: 19548120]
45. Watkins TR, Nathens AB, Cooke CR, Psaty BM, Maier RV, Cuschieri J, Rubenfeld GD. Acute respiratory distress syndrome after trauma: development and validation of a predictive model. Crit Care Med. 2012;40(8):2295–303. [PubMed: 22809905]
46. Alam HB, Austin B, Koustova E, Rhee P. Resuscitation-induced pulmonary apoptosis and intracellular adhesion molecule-1 expression in rats are attenuated by the use of Ketone Ringer's solution. J Am Coll Surg. 2001;193(3):255–63. [PubMed: 11548795]

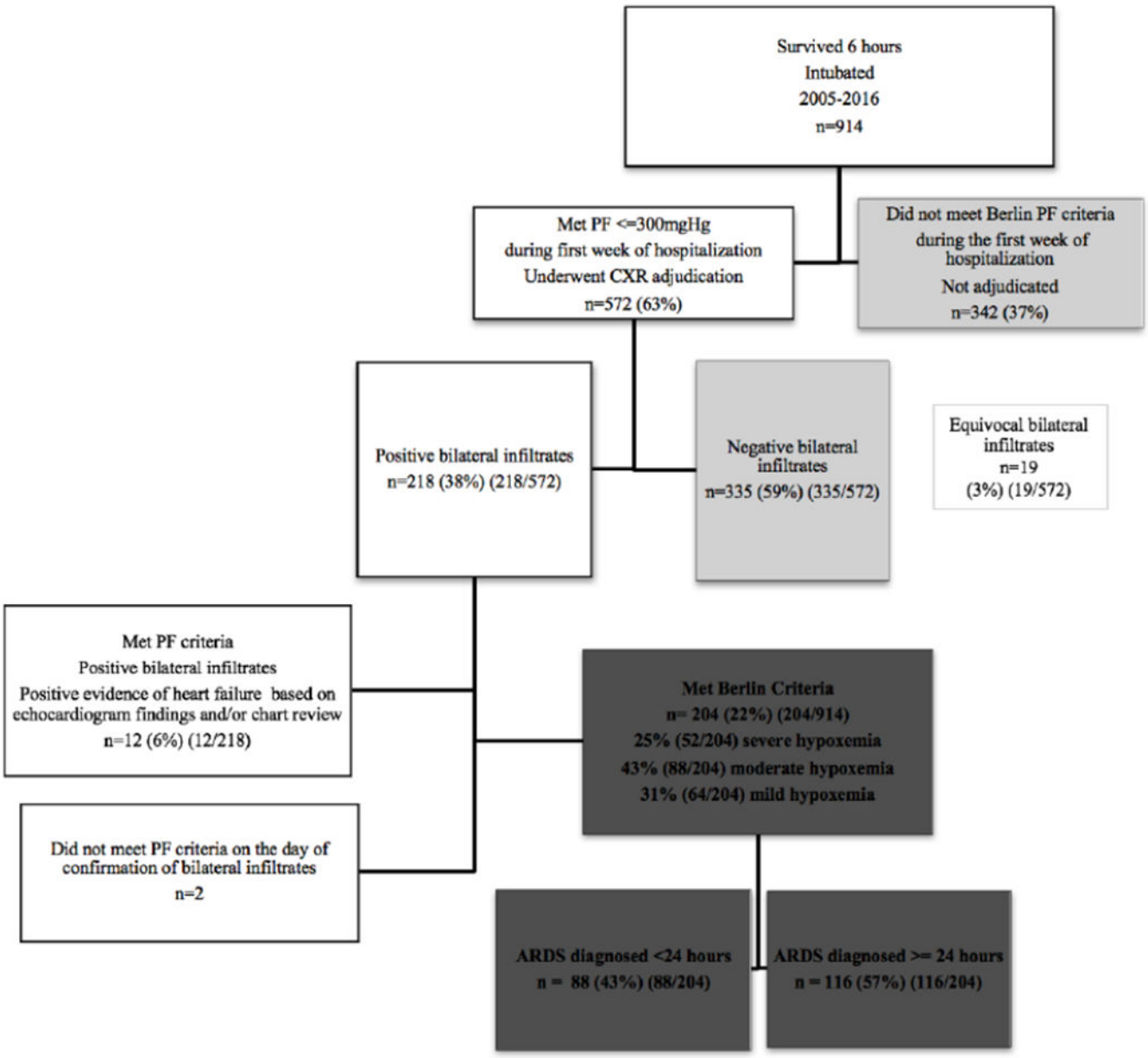

Figure 1. Flowchart of subject selection.

Light gray=no ARDS. Dark gray=ARDS. PF=partial pressure of oxygen: fraction inspired oxygen. CXR=chest radiography. Severe hypoxemia (PF≤100), moderate hypoxemia (PF 101-200), and mild hypoxemia (PF 201-300).

Table 1.

Demographics and outcomes

	n = 914
Age (years)	40 (27-55)
Male gender, n (%)	730/914 (80)
White, n (%)	549/913 (60)
Black, n (%)	164/913 (18)
Latino, n (%)	220/863 (25)
BMI (kg/m2)	26.8 (± 5.3)
Blunt injury rate, n (%)	686/911 (75)
Admit GCS	8 (4-14)
Admit SBP <90 mm Hg, n (%)	105/900 (12)
Admit HR >110 BPM, n (%)	282/886 (32)
Injury severity score (ISS)	25 (10-33)
Head abbreviated injury score (AIS)	3 (0-5)
Chest abbreviated injury score (AIS)	0 (0-3)
Abdomen abbreviated injury score (AIS)	0 (0-2)
Percent with chest injury (AIS>0), n (%)	389/913 (43)
Percent with severe chest injury (AIS≥3), n (%)	296/913 (32)
Percent with rib fracture(s), n (%)	232/865 (27)
Number of rib fractures	1.3 +/− 2.9
Percent with traumatic brain injury, n (%)	482/914 (53)
Percent with isolated traumatic brain injury, n (%)	284/682 (42)
Admit base excess	−5.0 +/− 6.1
Admit platelet count (× 10^9/L)	203 (148-265)
Crystalloid (half liters) 0-6h	6.4 +/− 5.8
Blood (units) 0-6h	3.7 +/− 7.6
Plasma (units) 0-6h	2.5 ± 5.5
Platelets (units) 0-6h	0.3 ± 0.9
Crystalloid (half liters) 7-24h	3.0 +/− 2.1
Blood (units) 7-24h	0.8 +/− 2.6
Plasma (units) 7-24h	0.7 ± 2.2
Platelets (units) 7-24h	0.1 +/− 0.5
Blood to Plasma ratio, 0-24h	0.73 +/− 1.0
Blood to Platelets ratio, 0-24h	0.38 +/− 0.67
Percent transfused Blood 0-24h, n (%)	489/911 (54)
Percent transfused Plasma 0-24h, n (%)	382/910 (42)
Percent transfused Platelets 0-24h, n (%)	205/910 (23)
Ventilator free days (to 28 days)	23 (0-26)
Acute respiratory distress syndrome (ARDS), n (%)	204/914 (22)
Ventilator-associated pneumonia (VAP), n (%)	64/912 (7)
Multi-organ failure (MOF), n (%)	142/914 (16)

	n = 914
Non-pulmonary multi-organ failure (NP-MOF), n (%)	56/914 (6)
ICU days	4.5 (2-13)
Hospital days	10 (4-24)
Mortality at discharge, n (%)	215/914 (24)
Hours to death	56.5 (20.6-195.5)

*Patient demographics for the 914 patients. Data are mean +/− SD, median (inter-quartile range), or n (%) as indicated. Data for skewed variables reported as median with inter-quartile ranges. Ventilator free days are counted for the first 28 days of hospitalization. Patients who expired received 0 ventilator free days.

Table 2.

Demographics and outcomes of patients without and with ARDS

	No ARDS n=677 (77%)	ARDS n=204 (23%)	*p*-value
Age (years)	39 (27-55)	40.5 (27-54)	0.26
Male gender, n (%)	539/677 (80)	168/204 (82)	0.42
BMI (kg/m2)	26.6 +/− 5.1	27.5 +/− 5.8	0.05
Blunt injury rate, n (%)	486/676 (72)	170/202 (84)	**<0.001**
Admit GCS	9 (4-14)	8 (3-14)	0.09
Admit SBP <90 mm Hg, n (%)	74/669 (11)	28/201 (14)	0.26
Admit HR >110 BPM, n (%)	179/656 (27)	89/199 (45)	**0.001**
Injury severity score (ISS)	20 (9-29)	30 (25-41)	**<0.001**
Head abbreviated injury score (AIS)	3 (0-5)	4 (2-5)	**<0.001**
Chest abbreviated injury score (AIS)	0 (0-3)	3 (0-4)	**<0.001**
Abdomen abbreviated injury score (AIS)	0 (0-2)	0 (0-2)	**0.001**
Percent with chest injury (AIS>0), n (%)	245/677 (36)	124/204 (61)	**<0.001**
Percent with severe chest injury (AIS≥3), n (%)	176/677 (26)	104/204 (51)	**<0.001**
Percent with rib fracture(s), n (%)	137/642 (21)	83/194 (43)	**<0.001**
Number of rib fractures	0.28 (± 2.3)	2.6 (± 4.0)	**<0.001**
Percent with traumatic brain injury, n (%)	324/677 (48)	137/204 (67)	**<0.001**
Percent with isolated traumatic brain injury, n (%)	213/545 (39)	60/117 (51)	**0.02**
Admit base excess	−4.3 +/− 5.9	−6.73 +/− 6.23	**<0.001**
Admit platelet count (x 10^9/L)	222 +/− 97	180 +/− 98	**<0.001**
Crystalloid (half liters) 0-6h	5.6 +/− 4.7	8.5 +/− 7.1	**0.001**
Blood (units) 0-6h	2.8 +/− 6.1	6.4 +/− 10.2	**0.001**
Plasma (units) 0-6h	1.8 +/− 4.6	4.5 +/− 7.0	**0.001**
Platelets (units) 0-6h	0.2 +/− 0.7	0.7 +/− 1.3	**0.001**
Crystalloid (half liters) 7-24h	5.5 +/− 3.5	7.6 +/− 5.9	**0.001**
Blood (units) 7-24h	0.5 +/− 1.7	1.9 +/− 4	**0.001**
Plasma (units) 7-24h	0.4 +/− 1.6	1.5 +/− 3.2	**0.001**
Platelets (units) 7-24h	0.1 +/− 0.3	0.4 +/− 0.8	**0.001**
Blood to Plasma ratio, 0-24h	0.6 +/− 1.0	0.96 +/− 0.87	**0.001**
Blood to Platelets ratio, 0-24h	0.26 +/− 0.6	0.7 +/− 0.73	**0.001**
Ventilator free days (to 28 days)	25 (10-26)	3 (0-17)	**0.001**
Percent transfused Blood 0-24h, n (%)	323/676 (48)	145/202 (72)	**<0.001**
Percent transfused Plasma 0-24h, n (%)	241/675 (36)	124/202 (61)	**<0.001**
Percent transfused Platelets 0-24h, n (%)	102/675 (15)	88/202 (44)	**<0.001**
Ventilator-associated pneumonia (VAP), n (%)	13/675 (2)	48/204 (24)	**<0.001**
Multi-organ failure (MOF), n (%)	44/677 (7)	84/204 (41)	**<0.001**
Non-pulmonary multi-organ failure (NP-MOF), n (%)	21/677 (3)	28/204 (14)	**<0.001**
ICU days	3 (2-7)	14 (6-23)	**0.001**
Hospital days	8 (3-18)	18 (9-40.5)	**0.001**
Mortality at discharge, n (%)	129/677 (19)	73/204 (36)	**<0.001**

	No ARDS n=677 (77%)	ARDS n=204 (23%)	*p*-value
Hours to death	33 (17-74)	159 (66-312)	**0.001**

*

Patient demographics for the 677 patients without ARDS and the 204 patients with ARDS. 19 excluded for equivocal bilateral infiltrates, 12 excluded for heart failure (out of 208 patients who had echocardiography performed), and 2 did not meet P/F criteria on the day of confirmation of bilateral infiltrates. Data are mean +/− SD, median (inter-quartile range), or n (%) as indicated. Data for skewed variables reported as median with inter-quartile ranges. Ventilator free days are counted for the first 28 days of hospitalization. Patients who expired received 0 ventilator free days. ARDS=Acute respiratory distress syndrome.

Table 3.

Demographics and outcomes of patients with ARDS *early* and *later*

	ARDS *early* n=88 (43%)	ARDS *later* n=116 (57%)	*p*-value
Age (years)	40 (29.5-59)	41 (26-53)	0.19
Male gender, n (%)	72/88 (82)	96/116 (83)	0.86
BMI (kg/m2)	28.5 +/− 5.4	27 +/− 6.0	**0.043**
Blunt injury rate, n (%)	73/86 (85)	97/116 (84)	0.85
Admit GCS	7.5 (3-14)	8 (4-14)	0.49
Admit SBP <90 mm Hg, n (%)	17/85 (20)	11/116 (9)	**0.03**
Admit HR >110 BPM, n (%)	44/85 (52)	45/114 (39)	0.09
Injury severity score (ISS)	29 (21-43)	30 (26-38)	0.75
Head abbreviated injury score (AIS)	4 (0-5)	5 (3-5)	1.00
Chest abbreviated injury score (AIS)	3 (0-4)	2 (0-3)	0.10
Abdomen abbreviated injury score (AIS)	0 (0-3)	0 (0-2)	0.40
Percent with chest injury (AIS>0), n (%)	57/88 (65)	67/116 (58)	0.39
Percent with severe chest injury (AIS≥3), n (%)	49/88 (56)	55/116 (47)	0.26
Percent with rib fracture(s), n (%)	38/81 (47)	45/113 (40)	0.38
Number of rib fractures	2.9 +/− 4.2	2.3 +/− 4.0	0.28
Direct lung injury, n (%)	42/88 (48)	47/116 (41)	0.32
Percent with traumatic brain injury, n (%)	54/88 (61)	83/116 (72)	0.14
Percent with isolated traumatic brain injury, n (%)	23/53 (43)	37/64 (58)	0.14
Admit base excess	−8.48 +/− 6.24	−5.48 +/− 5.93	**0.002**
Admit platelet count (× 10^9/L)	129 (87-184)	188 (133-256)	**0.004**
Crystalloid (half liters) 0-6h	10.05 +/− 9.00	7.30 +/− 5.00	**0.030**
Blood (units) 0-6h	9.85 +/− 13.61	3.73 +/− 5.32	**<0.001**
Plasma (units) 0-6h	6.74 +/− 8.92	2.88 +/− 4.50	**0.003**
Platelets (units) 0-6h	1.05 +/− 1.72	0.37 +/− 0.81	**<0.001**
Crystalloid (half liters) 7-24h	8.62 +/− 7.93	6.88+/− 3.66	0.77
Blood (units) 7-24h	2.74 +/− 5.47	1.20 +/− 2.10	0.14
Plasma (units) 7-24h	2.25 +/− 4.31	0.87 +/− 1.91	0.07
Platelets (units) 7-24h	0.48 +/− 0.91	0.29 +/− 0.63	0.24
Blood to Plasma ratio, 0-24h	1.1 +/− 1.0	0.9 +/− 0.8	0.13
Blood to Platelets ratio, 0-24h	0.85 +/− 0.75	0.57 +/− 0.68	**0.03**
Percent transfused Blood 0-24h, n (%)	65/87 (75)	80/115 (70)	0.44
Percent transfused Plasma 0-24h, n (%)	58/87 (67)	66/115 (57)	0.19
Percent transfused Platelets 0-24h, n (%)	46/87 (53)	42/115 (37)	**0.02**
Ventilator free days (to 28 days)	2.5 (0-18)	3.5 (0-16)	0.86
Ventilator-associated pneumonia (VAP), n (%)	18/88 (20)	30/116 (26)	0.41
Multi-organ failure (MOF), n (%)	27/88 (31)	57/116 (49)	**0.010**
Non-pulmonary multi-organ failure (NP-MOF), n (%)	13/88 (15)	15/116 (13)	0.84
ICU days	9 (3-20.5)	14 (9-24)	**<0.001**
Hospital days	14 (5-32)	22.5 (13-44.5)	**0.002**

	ARDS *early* n=88 (43%)	ARDS *later* n=116 (57%)	*p*-value
Mortality at discharge, n (%)	39/88 (44)	34/116 (29)	**0.04**
Hours to death	78 (30-279)	237 (120-385)	**0.005**
Hours to ARDS	6 (3-12)	84 (56-104)	**<0.001**

*Patient demographics for the 88 patients diagnosed with ARDS within the first 24 hours (*early*) and the 116 patients diagnosed with ARDS after 24 hours (*later*). Data are mean +/− SD, median (inter-quartile range), or n (%) as indicated. Data for skewed variables reported as median with inter-quartile ranges. Ventilator free days are counted for the first 28 days of hospitalization. Patients who expired received 0 ventilator free days. ARDS=Acute respiratory distress syndrome. *p*-values bolded for <0.05

Table 4.

Multivariate predictors of ARDS development *later*

	Univariate OR	CI			*p*	Multivariate OR	CI			*p*
Age (years)	1.00	0.99	-	1.01	0.8720					
Male gender	1.23	0.73	-	2.06	0.4340					
BMI (kg/m2)	1.01	0.97	-	1.05	0.6680					
Blunt injury rate	2.00	1.19	-	3.36	0.0090	1.79	0.91	-	3.53	0.09
Head AIS	1.32	1.19	-	1.47	<0.001	**1.38**	**1.21**	-	**1.57**	**<0.001**
Chest AIS	1.34	1.20	-	1.51	<0.001	**1.35**	**1.17**	-	**1.55**	**<0.001**
Abdomen AIS	1.14	1.00	-	1.30	0.0480	1.12	0.92	-	1.33	0.28
Crystalloid (half liters) 0-6h	1.08	1.04	-	1.12	<0.001	**1.10**	**1.04**	-	**1.15**	**<0.001**
Blood (units) 0-6h	1.03	1.01	-	1.07	0.0220	0.89	0.80	-	1.01	0.07
Plasma (units) 0-6h	1.06	1.02	-	1.10	0.0040	1.14	0.91	-	1.44	0.23
Platelet (units) 0-6h	1.30	1.03	-	1.64	0.0260	**2.34**	**1.04**	-	**5.25**	**0.04**
Crystalloid (half liters) 7-24h	1.11	1.05	-	1.16	<0.001	1.05	0.99	-	1.12	0.11
Blood (units) 7-24h	1.25	1.12	-	1.39	<0.001	0.99	0.78	-	1.27	0.97
Plasma (units) 7-24h	1.18	1.05	-	1.32	0.0040	0.86	0.67	-	1.10	0.24
Platelet (units) 7-24h	4.12	2.45	-	6.93	<0.001	**5.40**	**2.58**	-	**11.31**	**<0.001**

*
Bolded: $p<0.05$ for multivariate predictors. AIS=abbreviated injury score. AUC=0.80. All variables included in multivariate model are continuous measures.