Published in final edited form as:

Crit Care Med. 2007 October ; 35(10): 2243–2250.

Trauma-associated lung injury differs clinically and biologically from acute lung injury due to other clinical disorders*

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Abstract

Objective—Patients with trauma-associated acute lung injury have better outcomes than patients with other clinical risks for lung injury, but the mechanisms behind these improved outcomes are unclear. We sought to compare the clinical and biological features of patients with trauma-associated lung injury with those of patients with other risks for lung injury and to determine whether the improved outcomes of trauma patients reflect their baseline health status or less severe lung injury, or both.

Design, Setting, and Patients—Analysis of clinical and biological data from 1,451 patients enrolled in two large randomized, controlled trials of ventilator management in acute lung injury.

Measurements and Main Results—Compared with patients with other clinical risks for lung injury, trauma patients were younger and generally less acutely and chronically ill. Even after adjusting for these baseline differences, trauma patients had significantly lower plasma levels of intercellular adhesion molecule-1, von Willebrand factor antigen, surfactant protein-D, and soluble tumor necrosis factor receptor-1, which are biomarkers of lung epithelial and endothelial injury previously found to be prognostic in acute lung injury. In contrast, markers of acute inflammation, except for interleukin-6, and disordered coagulation were similar in trauma and nontrauma patients. Trauma-associated lung injury patients had a significantly lower odds of death at 90 days, even after adjusting for baseline clinical factors including age, gender, ethnicity, comorbidities, and severity of illness (odds ratio, 0.44; 95% confidence interval, 0.24 – 0.82; $p = .01$).

Conclusions—Patients with trauma-associated lung injury are less acutely and chronically ill than other lung injury patients; however, these baseline clinical differences do not adequately explain their improved outcomes. Instead, the better outcomes of the trauma population may be explained, in part, by less severe lung epithelial and endothelial injury.

*See also p. 2431.

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The authors have not disclosed any potential conflicts of interest.

Keywords

respiratory distress syndrome; adult; multiple trauma; biological markers

Acute lung injury (ALI) and its more severe form, acute respiratory distress syndrome (ARDS), may result from a variety of different initial insults, including sepsis, aspiration, pneumonia, multiple transfusions, and trauma (1). The recognition that patients with ALI are a heterogeneous group has led to significant advances in understanding the pathogenesis of the syndrome (2). An increasing body of literature strongly suggests that the pathogenesis of ALI may vary with the clinical risk factor that precedes the development of ALI. Multiple studies have reported that trauma-related ALI has a lower mortality than ALI owing to other clinical risk factors (3–7). Moreover, a recent study found that ALI does not increase mortality in patients with trauma (8), in contrast to other studies that have shown that ALI significantly increases mortality in septic patients (9,10).

Prior studies also have suggested that trauma-related ALI may differ pathophysiologically from nontrauma-related ALI. Previous studies of biological specimens from patients with ALI have demonstrated the utility of plasma biomarkers both for predicting patient outcomes and for providing important insights into disease pathogenesis (11–14). Patients with trauma-related ALI had lower levels of biomarkers that reflect endothelial activation—von Willebrand factor antigen (vWF), intercellular adhesion molecule-1 (ICAM-1), and E-selectin—than patients with sepsis as a risk factor for ALI, even after controlling for severity of illness (15). Similarly, previous studies of patients from the ARDS Network's trial of low tidal volume ventilation noted that levels of vWF were significantly lower in trauma patients than in patients with other risks for lung injury (16).

Although these prior studies have suggested clinical and biological differences between trauma-related ALI and other risk groups, many of the clinical characteristics of trauma-related ALI patients have not been fully described, and many of the biomarkers found to be prognostic in ALI have not been specifically analyzed in trauma patients. Furthermore, it remains unclear whether the biological features and clinical outcomes of trauma-related ALI reflect unique characteristics of this subgroup, or whether they simply reflect baseline differences presumed to exist between trauma patients and nontrauma patients with respect to age, comorbidities, and severity of illness. If trauma-related ALI has unique clinical and biological features, and particularly if its clinical outcomes differ beyond what would be expected based on demographic characteristics, our understanding of the pathogenesis of ALI may be expanded, and future trial designs may be altered.

To address these issues, we analyzed clinical and biological data from 1,451 patients enrolled in two ARDS Network trials of ventilation strategies in ALI/ARDS: the landmark trial of low tidal volume ventilation published in 2000 and the Assessment of Low Tidal Volume and Increased End-Expiratory Volume to Obviate Lung Injury (ALVEOLI) trial of low vs. high levels of positive end-expiratory pressure (PEEP) (17,18). Our study had three aims: a) to compare the clinical features of trauma-associated ALI with those of ALI owing to other clinical risk factors; b) to compare the biomarker profile of trauma-associated ALI with that in ALI owing to other clinical risk factors; and c) to determine whether differences in clinical outcomes between patients with trauma-related ALI and nontrauma-related ALI are attributable to the differences in baseline characteristics of these two groups, or to differences in severity of lung injury, or both.

METHODS

Data for this study were obtained from patients enrolled in two of the large randomized clinical trials of ventilation strategy conducted by the ARDS Network (17,18). Inclusion and exclusion criteria were similar in the two trials and are described in the original publications (17,18). The institutional review boards of all involved hospitals approved both trials, and all patients or surrogates provided informed consent with the exception of those enrolled in the low tidal volume trial at one hospital, where the requirement was waived (17).

Original Studies

The first study, referred to as the low tidal volume trial, enrolled 861 patients to test the hypothesis that ventilation with a low tidal volume, plateau pressure-limited strategy would reduce mortality in patients with ALI (17). Details of the trial have been published in full (17). Briefly, patients were randomized to ventilation with a tidal volume of either 6 or 12 mL/kg predicted body weight; once the benefit of the lower tidal volume strategy had been demonstrated, an additional 41 patients were assigned to the lower tidal volume to complete a trial of lisofylline vs. placebo and also are included in this analysis (19). Clinical data and plasma samples for biomarker measurements were collected at baseline before randomization; all patients were followed until death, day 180, or discharge home with unassisted breathing. The trial demonstrated a significant reduction in 180-day mortality in the low tidal volume treatment group (31% vs. 40%; $p = .007$). In a factorial design, ketoconazole (20) and lisofylline (19) also were administered to subsets of patients as investigational therapies for acute lung injury, neither of which affected mortality.

The second study, referred to as ALVEOLI, enrolled 549 patients to test the hypothesis that higher levels of PEEP would reduce mortality in patients with ALI (18). Details of the trial have been published in full (18). Briefly, patients were randomized to ventilation with either a lower PEEP or higher PEEP strategy. Clinical data and plasma samples for biomarker measurements were collected at baseline before randomization; patients were followed until death, day 90, or discharge home with unassisted breathing. The data safety and monitoring board terminated the trial after enrollment of 549 patients on the basis of futility. The trial found no difference in 90-day mortality and no modulation of circulating interleukin (IL)-6, surfactant protein D (SP-D), or ICAM-1 with higher vs. lower levels of PEEP.

The etiology of ALI was determined in both trials by the site investigator; in cases in which more than one potential cause of ALI was present, the site investigator determined which was the principal cause.

Plasma Biomarkers

We analyzed baseline (day 0) plasma levels of eight biomarkers found in previous studies to be associated with severity and outcomes in ALI to determine whether levels differed significantly in trauma patients as compared with nontrauma patients. The eight biomarkers—ICAM-1, vWF, protein C, plasminogen activator inhibitor-1 (PAI-1), SP-D, soluble tumor necrosis factor receptor 1 (sTNFr-1), and ILs-6 and -8—reflect different aspects of the pathophysiology of ALI and are described in more detail in the Discussion section. Biomarker measurements were performed using identical assay techniques by the same laboratories for both studies. Details of the methods used to measure the biomarkers have been published in full elsewhere (16,21–26). Biomarkers were missing in some patients, primarily in patients from the low tidal volume study. In that cohort, plasma was not available on all patients, primarily those patients in the ketoconazole or lisofylline arms of the study because of the additional plasma required to measure drug levels in these patients.

Statistical Methods

Statistical analysis was performed with Stata 8.2 (Stata, College Station, TX). To compare the baseline characteristics of trauma patients with those of nontrauma patients, we used the chi-square and Fisher's exact tests for categorical variables, Student's *t*-test with the unequal variance assumption for normally distributed variables, and Mann-Whitney U tests for variables not normally distributed. Normality was assessed by quantile-quantile plots and other qualitative graphical methods, and all *p* values are two-tailed.

To compare baseline levels of the biomarkers, none of which were normally distributed, we used Mann-Whitney U tests. We then natural log-transformed the biomarker data to perform multivariable linear regression to control for baseline clinical features that differed between trauma and nontrauma patients such as age, comorbidities, and severity of illness. This analysis was designed to determine whether biomarker levels differed between trauma and nontrauma patients because of preexisting characteristics of the patient populations such as baseline health status, demographic differences, or chronic disease. Model checking was performed using residual-based diagnostics. To examine the impact of missing biomarker data, we performed a sensitivity analysis using sampling weights. We first developed linear regression models to predict the probability of each biomarker being measured for each patient. The original linear regression models (in which log-transformed biomarker levels were the outcome variable) were then refitted using the inverse predicted probabilities as sampling weights; in this way, patients who had a particular biomarker measured but whose clinical characteristics suggested they would have been likely to have missing data would be heavily weighted. With these sampling weights included in the original linear models, the results were substantively unchanged for all the biomarkers, and the unweighted results are reported.

We performed logistic regression to determine the odds of mortality in patients with trauma-related ALI compared with those with other clinical risks for ALI. We chose 90-day mortality as the primary outcome because data through 90 days was available for patients in both trials. To determine whether outcome differences were determined primarily by the patients' baseline health status, we then constructed a multivariable logistic model to adjust for baseline differences in demographics, comorbidities found on bivariate analysis to differ between the two groups, use of low tidal volume ventilation, Acute Physiology, Age and Chronic Health Evaluation (APACHE) III score (27), and PaO₂/F_{IO}₂ ratio. These covariates were selected on the basis of the bivariate analysis results and on face validity (28). As a sensitivity analysis, we also performed a manual backward-selection procedure incorporating all of the predictors that were statistically significant (*p* < .05) on bivariate analysis (29) with stepwise exclusion of covariates with *p* > .20 and serial iterations of the likelihood ratio test; the results obtained with this model did not differ significantly from those obtained with the first model. The model fit was analyzed with the Hosmer-Lemeshow goodness-of-fit test and the linktest for specification errors in the logistic model (28).

RESULTS

Clinical Characteristics

Trauma patients comprised approximately 10% of the overall population of patients in the two trials (Fig. 1). The demographic characteristics and comorbidities of the patients, stratified by trauma, are summarized in Table 1. As compared with patients with other clinical risk factors for ALI, trauma patients were younger and more likely to be white. Trauma patients also were significantly less likely to have a history of acquired immunodeficiency syndrome, recent immunosuppression, diabetes, and end-stage renal disease requiring dialysis. Furthermore, trauma patients had significantly lower APACHE III scores than nontrauma patients (mean score, 67 ± 25 in trauma vs. 89 ± 30; *p* < .001).

Compared with nontrauma patients, trauma patients had a higher mean arterial pressure (mean, 70 mm Hg compared with 61 mm Hg in nontrauma patients; $p < .001$) and a lower incidence of vasopressor administration (odds ratio [OR], 0.38 comparing trauma to nontrauma patients; 95% confidence interval [CI], 0.24 – 0.62), suggesting a lower prevalence of hypotension in the trauma group (Table 2). In addition, trauma patients had a higher urine output in the 24 hrs preceding enrollment than nontrauma patients (median urine output, 2300 vs. 1843 mL; $p < .001$).

Baseline measures of respiratory physiology and ventilator settings before trial enrollment are summarized in Table 3. Trauma patients had a lower mean respiratory rate (18 vs. 21; $p < .001$) and minute ventilation (11.6 vs. 12.8 L/min; $p < .001$) than nontrauma patients. The $Pa_{O_2}/F_{I_{O_2}}$ ratio was significantly higher in trauma patients (median, 164 vs. 114; $p < .001$). Baseline tidal volume and tidal volume expressed in mL/kg predicted body weight did not differ between trauma and nontrauma patients. Peak, plateau, and end-expiratory pressures were significantly higher in trauma than nontrauma patients. However, the difference in plateau pressure likely was linked to the difference in PEEP; both were 2 cm.

Relevant laboratory values and radiographic findings are detailed in Table 4. Trauma patients had a significantly lower hematocrit, platelet count, and white blood cell count than nontrauma patients. Furthermore, trauma patients had lower creatinine and albumin and higher bicarbonate than nontrauma patients. As expected, trauma patients had a higher rate of pneumothorax, subcutaneous emphysema, and tube thoracostomy than nontrauma patients.

Biomarkers

We compared baseline (day 0) plasma levels of eight biomarkers in patients with trauma-related ALI with patients with other clinical risks for lung injury (Table 5). On bivariate analysis, trauma patients had significantly lower baseline levels of ICAM-1, SP-D, vWF, PAI-1, IL-8, and sTNFr-1 than nontrauma patients. Levels of IL-6 and protein C were not significantly different. In a multivariable model that controlled for age, ethnicity, significant baseline comorbidities (acquired immunodeficiency syndrome, immunosuppression, diabetes, and end-stage renal disease), APACHE III score, and $Pa_{O_2}/F_{I_{O_2}}$, trauma remained significantly associated with lower levels of ICAM-1, SP-D, vWF, and sTNFr-1 (Table 5). Figure 2 shows the magnitude of differences in these four key biomarkers. Although levels of IL-6 did not significantly differ between trauma and nontrauma patients in an unadjusted analysis, levels were statistically higher among trauma patients in the multivariate analysis.

Outcomes

In an analysis that controlled only for treatment with low tidal volume ventilation, the odds of mortality at 90 days for trauma patients were significantly lower than those for nontrauma patients (Table 6) (OR, 0.21; 95% CI, 0.12–0.38; $p < .001$). After adjusting for age, gender, ethnicity, significant comorbidities (acquired immunodeficiency syndrome, immunosuppression, diabetes, and end-stage renal disease), use of the low tidal volume strategy, APACHE III score, and $Pa_{O_2}/F_{I_{O_2}}$, the odds of death for trauma patients were still significantly lower than those for nontrauma patients (OR, 0.44; 95% CI, 0.24 – 0.82; $p = .01$). Additional adjustments for initial study group (low tidal volume trial vs. ALVEOLI) and ketoconazole and lisofylline use had no impact on the results, nor did an additional adjustment for sepsis as the etiology of ALI (in model including sepsis: OR, 0.44 for impact of trauma on mortality; $p = .01$; p value for sepsis covariate, 0.50). Likewise, it did not significantly impact the results when we included all chronic medical conditions in the model or when we restricted the analysis to patients without a history of chronic illness.

We then added the biomarkers that were significantly lower in trauma patients (ICAM-1, SP-D, vWF, and sTNFr-1) as covariates in the multivariable model, in order to determine whether decreased biological activity of the pathways these markers reflect may mediate the observed difference in mortality. Adding the biomarkers to the model notably attenuated the difference in mortality between trauma-associated ALI and nontrauma-associated ALI, such that the difference was no longer statistically significant (OR, 0.66; 95% CI, 0.31–1.43).

Trauma patients also had significantly more ventilator-free days than nontrauma patients in an unadjusted analysis (median, 17 ventilator-free days for trauma patients vs. 14 ventilator-free days for nontrauma patients; $p = .03$). Given the unusual distribution of this variable (i.e., the large number of patients with 0 ventilator-free days, generating a very abnormal distribution even with log-transformation), we did not apply multivariable linear models to this comparison.

DISCUSSION

We found that patients with trauma-associated ALI had markedly different clinical characteristics than patients with other clinical risks for ALI in a population enrolled in two ARDS Network randomized, controlled trials. Specifically, compared with patients with other risks for ALI, trauma patients were younger and less chronically ill, and their acute illness was generally less severe. In addition, patients with trauma-associated ALI had lower plasma levels of several biomarkers previously found to be associated with poor clinical outcomes in ALI, including ICAM-1, SP-D, sTNFr-1, and vWF; these differences persisted even after adjusting for the patients' baseline clinical differences. Finally, we found that patients with trauma-associated ALI had strikingly better clinical outcomes than patients with other risks for ALI, even after adjusting for baseline clinical differences.

Our work expands on previous findings in several ways. First, this study comprehensively describes the clinical features of trauma-associated ALI in a large cohort and confirms that these patients are younger, healthier, and generally less acutely ill than others with ALI. Second, this study demonstrates that plasma levels of biomarkers of endothelial and lung epithelial injury are significantly lower in trauma patients, even after adjusting for clinical differences, in contrast to markers of acute inflammation and disordered coagulation. Third, we found that the baseline clinical characteristics of trauma patients in this study population do not adequately explain their improved clinical outcomes. Our results suggest that trauma patients have on average less severe lung epithelial and endothelial injury than patients with other clinical risks for ALI, a finding that may be partially responsible for their better clinical outcomes.

The biomarker data presented here also provide insight into the pathophysiology of trauma-related ALI. The eight biomarkers studied—ICAM-1, vWF, protein C, PAI-1, SP-D, sTNFr-1, IL-6, and IL-8—have been shown in prior studies to reflect the severity of ALI. ICAM-1 and vWF are both considered markers of endothelial injury and have been associated with poor outcomes in ALI patients (12,16,30,31). Protein C and PAI-1 are markers of disordered coagulation and fibrinolysis previously demonstrated to predict clinical outcomes in patients with lung injury (24,26). SP-D reflects lung epithelial cell injury and is similarly prognostic in patients with ALI (23). sTNFr-1 is released both by the lung epithelium and by neutrophils binding to the endothelium during acute inflammation; elevated levels have been associated with increased mortality in ALI patients (21). Finally, IL-6 and IL-8 are cytokines that reflect acute systemic inflammation and are prognostic of poor clinical outcomes in patients with ALI (22). Several of these markers (IL-6, IL-8, SP-D, and sTNFr1) also have been demonstrated to be decreased over time by a lung-protective ventilation strategy (21–23), confirming their critical role in the pathogenesis and outcomes of ALI. The lower levels of ICAM-1, vWF, SP-D, and sTNFr-1 in trauma patients in this study may reflect less severe endothelial (vWF, ICAM-1) and epithelial (SP-D, sTNFr-1) injury in the lungs of patients with trauma-related

ALI (13,32–36). Instead, the primary insult in trauma-related ALI may be one of systemic inflammation and disordered coagulation, as reflected by levels of IL-6, IL-8, protein C, and PAI-1 that were similar to (or higher than, in the case of IL-6) those in other causes of ALI (22,37).

The finding that adjusting for baseline levels of ICAM-1, SP-D, vWF, and sTNFr-1 attenuated the reduced mortality of trauma patients may be explained by one of several mechanisms, any of which may account for the loss of independent association between trauma and improved survival. It may be that decreased activity of the pathways reflected by these biological markers mediates part of the observed difference in mortality—in other words, that trauma patients have less severe endothelial and lung epithelial injury, which leads to a lower risk of death. Alternatively, these biomarkers may reflect different aspects of severity of illness than those captured by APACHE III or those included in our backward selection model. It is also possible that adding these four additional variables primarily increased the variance of the trauma parameter; however, it should be noted that the addition of each one of the biomarkers alone to the model resulted in significant attenuation of the odds ratio for trauma, such that the effect of trauma on mortality was no longer statistically significant (data not shown). In contrast, adding the other four biomarkers (IL-6, IL-8, PAI-1, and protein C) to the logistic model as a sensitivity analysis did not significantly impact the coefficient or variance of the trauma parameter. This analysis suggests that increased variance alone is unlikely to explain the effect of including these markers in the model.

This study has several limitations. First, we do not have information on the rates of direct chest trauma vs. indirect trauma-related lung injury. Tube thoracostomy may be a surrogate marker for direct chest trauma, and was not found to be a significant covariate in any of our multivariate analyses; nevertheless, we cannot rule out significant differences between patients with direct vs. indirect pulmonary trauma (38). Likewise, injury severity scores, commonly used to grade the severity of traumatic injury, were not collected (39). Second, we do not have complete data on either the overall volume of fluids received by patients in the trial or on their central venous or pulmonary artery occlusion pressures. Third, biomarkers were not measured in all patients. Biomarker measurements were made purely on the basis of plasma availability; within trauma patients, there were no differences in age, gender, ethnicity, APACHE III score, or significant comorbidities between patients who did and did not have all biomarkers measured. In addition, we performed a sensitivity analysis using sampling weights, described in the methods section, which did not significantly impact the results. Nevertheless, we cannot rule out some degree of selection bias in the biomarker measurements. Fourth, patients with trauma-associated ALI likely were cared for by different physicians than patients with nontrauma-associated ALI (i.e., surgical vs. medical intensivists); thus, practice variation may be in part responsible for some of the observed differences between these two groups of patients. Finally, we studied patients enrolled in randomized, controlled trials, which tend to select patients healthier than the overall population of all patients with disease.

CONCLUSIONS

In summary, in a study sample of patients enrolled in two ARDS Network randomized, controlled trials, we found that patients with trauma-related lung injury were younger and less acutely and chronically ill than their counterparts with other clinical risks for lung injury. The trauma patients had lower levels of plasma markers of lung epithelial and endothelial injury (ICAM-1, vWF, SP-D, and sTNFr-1), indicating that the pathophysiology of trauma-related ALI may be different from that of the broader population of lung injury patients. Perhaps most importantly, patients with trauma-related ALI had a lower odds of death than those with nontrauma-related ALI, even after controlling for baseline demographic and clinical

differences. Given these results, future trials in acute lung injury should consider stratifying by trauma.

APPENDIX

National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network

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Figure 1. Primary etiology of acute lung injury in patients in the low tidal volume (n = 902) and Assessment of Low Tidal Volume and Increased End-Expiratory Volume to Obviate Lung Injury (n = 549) trials. Patients with trauma-associated lung injury comprised approximately 10% (n = 141) of the overall study population.

Figure 2.

Trauma-associated acute lung injury patients have lower levels of plasma biomarkers of endothelial and epithelial injury than patients with other clinical risk factors for acute lung injury. * $p < .001$ for all comparisons in unadjusted model; $p \leq .001$ for all comparisons in multivariable model using natural log-transformed biomarkers that adjusts for age, gender, race and ethnicity, comorbidities, severity of illness, and $\text{PaO}_2/\text{F}_{\text{IO}_2}$ ratio. Median values are depicted; error bars represent 25% to 75% interquartile range.

Table 1

Baseline patient characteristics and comorbidities of patients with trauma-related and nontrauma-related acute lung injury

Characteristic	Trauma (n = 141)	Nontrauma (n = 1307)	<i>p</i> Value
Age, mean (SD), yrs	44 (17)	52 (17)	<.001
Female gender, no. (%)	89 (63)	750 (57)	.18
Race-ethnicity, no. (%) ^a			.036
White	118 (84)	955 (73)	
Black	10 (7)	222 (17)	
Latino	7 (5)	79 (6)	
Asian	3 (2)	41 (3)	
AIDS, no. (%)	1 (0.7)	83 (6.4)	.003
Leukemia, no. (%)	0 (0)	27 (2.1)	.10
Lymphoma, no. (%)	0 (0)	16 (1.2)	.39
Solid tumor with metastases, no. (%)	0 (0)	24 (1.8)	.16
Immunosuppression within past 6 mos, no. (%) ^b	2 (1.5)	180 (13.8)	<.001
Liver failure plus coma or encephalopathy, no. (%)	1 (0.7)	12 (0.9)	1.0
Cirrhosis, no. (%)	2 (1.5)	43 (3.3)	.31
Diabetes, no. (%)	5 (3.7)	204 (15.7)	<.001
Chronic dialysis, no. (%)	0 (0)	38 (2.9)	.044
Enrolled in the low tidal volume trial	96	806	—
Low tidal volume arm of ARMA, no. (%)	59 (61)	414 (51)	.06
Enrolled in ALVEOLI	45	504	—
Low PEEP arm of ALVEOLI, no. (%)	26 (58)	247 (49)	.26
APACHE III score, mean (SD)	67 (25)	89 (30)	<.001

AIDS, acquired immunodeficiency syndrome; ALVEOLI, Assessment of Low Tidal Volume and Increased End-Expiratory Volume to Obviate Lung Injury; PEEP, positive end-expiratory pressure; APACHE, Acute Physiology, Age, and Chronic Health Evaluation.

^aTotal may not equal 100% because of additional categories with very small numbers of patients

^bimmunosuppression defined as radiation, chemotherapy, or prednisone at doses ≥ 0.3 mg/kg per day. Comparisons by Student's *t*-test, chi-square, or Fisher's exact test.

Table 2

Baseline nonrespiratory physiologic measurements in trauma and nontrauma patients with acute lung injury

Parameter	Trauma (n = 141)	Nontrauma (n = 1307)	p Value
Maximum temperature, °C	38.5 (0.75)	38.5 (0.95)	.72
Minimum temperature, °C	36.9 (0.95)	36.7 (0.97)	.06
Lowest MAP, mm Hg	70 (12)	61 (13)	<.001
Highest MAP, mm Hg	107 (16)	101 (20)	<.001
Highest heart rate, mm Hg	128 (22)	126 (23)	.48
Urine output, median (IQR), mL	2300 (1754–3530)	1843 (1112–2930)	<.001
Vasopressors required, no. (%) ^a	21 (17.6)	393 (35.8)	<.001
Net fluid balance during 24 hrs before enrollment (no. of liters) ^b	+1.799	+1.731	.69

MAP, mean arterial pressure; IQR, interquartile range.

^aOdds ratio for use of any vasopressor within prior 24 hrs in trauma patients compared with nontrauma patients: 0.38 (0.24–0.62)

^bdata available for subjects enrolled in the low tidal volume trial only. All values represent mean (sd) except where indicated; all values from within 24 hrs before enrollment. Comparisons using Student's *t*-test with unequal variance assumption or Mann-Whitney U test where appropriate.

Table 3
Baseline respiratory physiology and ventilatory parameters in trauma versus nontrauma lung injury patients

Parameter	Trauma (n = 141)	Nontrauma (n = 1307)	p Value
Respiratory rate, total	18 (7)	21 (7)	<.001
Minute ventilation, L	11.6 (3.9)	12.8 (4.1)	<.001
Tidal volume, mL	663 (184)	635 (173)	.09
Tidal volume/PBW, mL/kg	9.8 (2.7)	10.0 (2.7)	.39
PEEP, median (IQR), cm H ₂ O	10 (5–12)	8 (5–10)	.038
Plateau pressure, cm H ₂ O ^a	30.7 (8.0)	28.7 (7.7)	.018
Peak pressure, cm H ₂ O	39.8 (11.0)	35.1 (9.4)	<.001
PaO ₂ /FIO ₂ ratio, median (IQR)	164 (108–202)	114 (82–157)	<.001
Clinical Lung Injury score, median (IQR) ^b	2.75 (2.25–3)	2.75 (2.5–3.25)	.10
Quasistatic compliance, mL/cm H ₂ O	32.0 (15.7)	32.7 (26.0)	.70
Mean airway pressure, cm H ₂ O	16.5 (5.8)	15.6 (5.2)	.11
Paco ₂ , mm Hg	40.5 (7.1)	37 (8.7)	<.001
Arterial pH	7.41 (0.06)	7.39 (0.08)	.03

PBW, predicted body weight; PEEP, positive end-expiratory pressure; IQR, interquartile range.

^aTrauma patients were more likely to be missing plateau pressure: 41/141 (29%) vs. 273/1310 (21%); odds ratio 1.56 (1.06–2.29)

^bcalculated as Murray et al (30). All values represent mean (SD) except where indicated; all values from within 24 hrs before enrollment. Comparisons made with Student's *t*-test with unequal variance assumption or Mann-Whitney U test where appropriate.

Table 4

Baseline laboratory and radiographic data in trauma and nontrauma patients with acute lung injury

Parameter	Trauma (n = 141)	Nontrauma (n = 1307)	p Value
Hematocrit, %	28.1 (4.7)	30.0 (5.9)	<.001
Platelets, median (IQR), thousands/ μ L	89 (67–130)	147 (84–233)	<.001
White blood cells, median (IQR), thousands/ μ L	11.5 (8.2–15.1)	13 (8.9–18.5)	.004
Creatinine, median (IQR), mg/dL ^a	0.9 (0.8–1.1)	1.2 (0.8–2.0)	<.001
Bicarbonate, mEq/L ^b	23.6 (4.3)	21.3 (5.6)	<.001
Bilirubin, median (IQR), mg/dL ^c	0.9 (0.6–1.6)	0.9 (0.5–1.8)	.29
Albumin, g/dL ^d	2.0 (0.5)	2.2 (0.6)	.006
Radiographic lung injury score, median (IQR)	4 (3–4)	4 (4–4)	.18
Pneumothorax, no. (%)	10 (7.1)	32 (2.4)	.0018
Subcutaneous emphysema, no. (%)	22 (15.8)	20 (1.5)	<.001
Pneumomediastinum, no. (%)	5 (3.6)	19 (1.5)	.06
Pneumatoceles, no. (%)	5 (3.5)	33 (2.5)	.47
Tube thoracostomy, no. (%)	76 (53.9)	113 (8.6)	<.001

IQR, interquartile range.

^aTo convert to μ mol/L, multiply by 88.4^bequivalent to mmol/L^cto convert to μ mol/L, multiply by 17.1^dto convert to g/L, multiply by 10. All values represent mean (sd) except where indicated. Comparisons made with chi-square test, Student's *t*-test with unequal variance assumption, or Mann-Whitney U test where appropriate.

Bivariate and multivariate analysis of baseline biomarker levels in patients with acute lung injury

Table 5

Biomarker, Day 0	n	Median Value, Trauma	Median Value, Nontrauma	Unadjusted <i>p</i> Value	Multivariable <i>p</i> Value
ICAM-1, ng/mL	1307	410 (272–738)	765 (480–1223)	<.001	<.001
SP-D, ng/mL	1075	58 (37–94)	95 (45–211)	<.001	.001
Protein C, % of control	1308	58 (45–78)	53 (35–84)	.07	.14
vWF, % of control	1088	226 (142–331)	355 (215–551)	<.001	<.001
PAI-1, ng/mL	1304	56 (36–104)	70 (37–157)	.045	.95
IL-6, pg/mL	1302	300 (128–674)	259 (100–850)	.44	.047
IL-8, pg/mL	1309	21 (20–59)	44 (20–103)	.002	.30
sTNF-1, pg/mL	1091	2535 (1945–3332)	3748 (2340–7661)	<.001	.004

ICAM, intercellular adhesion molecule; SP-D, surfactant protein D; vWF, von Willebrand factor antigen; PAI, plasminogen activator inhibitor; IL, interleukin; sTNF, soluble tumor necrosis factor receptor.

All biomarker values represent median (interquartile range) with bivariate comparison using Mann-Whitney U test. Multivariable linear model (using natural log-transformed biomarker levels) controls for age, gender, ethnicity, presence of significant comorbidities (acquired immunodeficiency syndrome, immunosuppression, diabetes, and end-stage renal disease), severity of injury, and Pao₂/Fio₂ ratio.

Table 6

Odds of death at 90 days for patients with trauma-associated acute lung injury (ALI) compared to patients with other clinical risks for ALI

Model	Odds Ratio	95% CI	<i>p</i> Value
Adjusted for low tidal volume strategy only	0.21	0.12–0.38	<.001
Adjusted for age, gender, ethnicity, low tidal volume strategy, comorbidities, ^a APACHE III score, and PaO ₂ /FIO ₂ ratio ^b	0.44	0.24–0.82	.01

CI, confidence interval; APACHE, Acute Physiology, Age, and Chronic Health Evaluation.

^a Comorbidities included were those that were significant on bivariate analysis: acquired immunodeficiency syndrome, immunosuppression, diabetes, and end-stage renal disease

^b model fit by Hosmer-Lemeshow test $p = .18$; linktest for specification errors “hatsq” $p = .55$.