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LOWER SERUM ENDOCAN LEVELS ARE ASSOCIATED WITH THE DEVELOPMENT OF ACUTE LUNG INJURY AFTER MAJOR TRAUMA

Mark E. Mikkelsen, M.D., M.S.C.E.[1], **Chirag V. Shah, M.D., M.S.C.E.**[1,2], **Arnaud Scherpereel, M.D., Ph.D.**[3], **Paul N. Lanken, M.D.**[1], **Philippe Lassalle, M.D., Ph.D.**[3], **Scarlett L. Bellamy, Sc.D.**[2], **A. Russell Localio, Ph.D.**[2], **Steven M. Albelda, M.D.**[1], **Nuala J. Meyer, M.D.**[1], and **Jason D. Christie, M.D., M.S.C.E.**[1,2]

[1]Pulmonary, Allergy, and Critical Care Division Department of Medicine University of Pennsylvania School of Medicine

[2]Center for Clinical Epidemiology and Biostatistics University of Pennsylvania School of Medicine

[3]Inserm, Pasteur Institute of Lille, CHRU of Lille, France

Abstract

Purpose—Endocan is a proteoglycan expressed by endothelial cells in the lung which may inhibit leukocyte recruitment and thus prevent the development of acute lung injury (ALI). We tested the association of serum endocan levels with subsequent development of ALI after major trauma.

Materials and Methods—Single-center nested case control study within a prospective cohort study of major trauma patients. Using an ELISA test, we measured endocan levels from admission serum in 24 controls (no ALI) and 24 cases (ALI within 5 days of trauma). Multivariable logistic regression was used to test the association of admission serum endocan levels with subsequent ALI.

Results—Patients who developed ALI had lower levels of endocan on admission (mean 3.5 ± 1.4 ng/mL vs. 4.9 ± 2.6 ng/mL in controls, p=0.02). For each 1-unit increase in serum endocan level, the odds ratio for ALI development decreased (0.69, 95% confidence interval (CI): 0.49, 0.97, p=0.03). Lower endocan levels remained associated with a higher incidence of ALI after adjustment for age and illness severity.

Conclusions—Lower levels of serum endocan on admission are associated with subsequent development of ALI in trauma patients. These observations may be explained by endocan-mediated blockade of leukocyte recruitment in the lung.

Corresponding author: Mark E. Mikkelsen, M.D., M.S.C.E. Pulmonary, Allergy, and Critical Care Division 836 W. Gates Pavilion 3400 Spruce Street Philadelphia, PA 19104 mark.mikkelsen@uphs.upenn.edu Phone: (215) 615-5416 Fax: (215) 614-0869.

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Keywords

Trauma; acute respiratory distress syndrome; acute lung injury; biomarkers; endothelium

1. Introduction

The development of acute lung injury (ALI) is a major complication of critical illness, affecting approximately 200,000 adults annually with a case-fatality rate which approaches 40% (1). In trauma-associated ALI, the development of ALI impacts significantly upon the overall mortality (2). Endothelial dysfunction is central to the alveolar-capillary membrane injury that characterizes ALI (3-4). Therefore, markers of endothelial dysfunction may be different in ALI subjects compared to those without ALI.

Endocan, a dermatan sulfate proteoglycan, is expressed by endothelial cells in lung and kidney (5); circulating levels are stable and can be measured in serum (6-7). *In vitro*, endocan regulates the interaction between leukocyte function-associated antigen-1 and intercellular adhesion molecule-1 (ICAM-1) (8). By blocking ICAM-1, endocan may inhibit leukocyte recruitment into the lung and thus prevent the development of ALI (9-10).

We hypothesized that serum endocan levels measured at initial Emergency Department (ED) presentation would be associated with the subsequent development of ALI after major trauma. The primary aim of our study was to test whether serum endocan levels were associated with the development of ALI in critically ill trauma patients requiring mechanical ventilation.

2. Materials and Methods

The Institutional Review Board of the University of Pennsylvania approved the study with an informed consent exemption.

2.1 Setting and Patient Population

This was a single-center nested case-control study (11) within a prospective observational cohort study of acutely injured trauma patients at the Hospital of the University of Pennsylvania, a Level 1 trauma center. We prospectively identified patients with major trauma admitted through the emergency department (ED) between 1999 and 2002. We included trauma patients with an Injury Severity Score (ISS) ≥ 16 (12). We excluded patients who were discharged or died within 24 hours of admission and those patients who suffered from isolated head trauma. We randomly selected 24 ALI cases and 24 controls (non-ALI) from within the cohort. For this hypothesis-generating study, no *a priori* power calculation was performed.

2.2 Data Collection

A trained research nurse abstracted data prospectively from the medical record using a pre-drafted case report form. Data recorded included: sociodemographic information, comorbid conditions, mechanism of injury and extent of injury on initial survey, vital signs and laboratory measurements in the emergency department, operating room, and during the initial 24 hours in the Intensive Care Unit, and crystalloid (mL) and packed red blood cell (RBC) transfusions administered in the emergency department and operating room during the initial resuscitation. We evaluated packed RBC transfusions as both a dichotomous variable (any transfusion during the initial resuscitation) and a linear variable (total number of units). The Injury Severity Score (12) and the Acute Physiology and Chronic Health

Evaluation (APACHE) III score (13) were calculated based on abstracted data from the initial survey or initial 24 hours in the ICU, as appropriate.

2.3 Serum Endocan

We used a sandwich-based enzyme-linked immunosorbent assay (ELISA) to measure serum endocan levels (ng/mL) from stored serum samples drawn in the ED prior to ICU admission (6). Serum endocan levels were measured at the Pasteur Institute of Lille, France by investigators (AS, PL) unaware of clinical information other than a unique identifier. Based on prior studies of healthy subjects, we defined normal serum endocan levels as less than 1 ng/mL (14).

2.4 Outcome

Our primary outcome was the development of ALI requiring mechanical ventilation over the initial 5 hospital days. We defined ALI according to the American-European Consensus Conference criteria as bilateral pulmonary infiltrates on chest radiograph, acute hypoxemia (ratio of partial pressure of arterial oxygen to fraction of inspired oxygen concentration ≤ 300), in the absence of left atrial hypertension (3). Two blinded physician reviewers independently reviewed each case for the development of ALI, with adjudication, if necessary, by a third independent physician reviewer. Cases were drawn randomly from those patients with a definite ALI classification and controls were drawn randomly from patients with a definite non-ALI classification; equivocal cases were excluded from the study (15). The details of our trauma cohort have been published previously (2).

2.5 Statistical Analysis

We used the Student's T-test to compare continuous variables and the chi-squared statistic or Fisher's exact test to compare categorical variables between ALI cases and controls. We tested for associations between serum endocan levels and baseline patient characteristics and severity of illness measures (ISS, APACHE III). We used Pearson's product-moment correlation coefficient to assess for an association between two continuous variables (e.g., serum endocan levels and APACHE III). We used a linear regression model to depict the fitted relationship between serum endocan levels and predicted probability of ALI.

We used multivariable logistic regression to adjust for potential confounding in the association between initial serum endocan levels and the development of ALI. Based on hypotheses from prior studies or plausible biologic mechanisms for ALI association, we considered age, gender, race, comorbid conditions (e.g., diabetes mellitus), therapy received (e.g., packed RBC transfusion), cause of traumatic injury and extent of injury (e.g., pulmonary contusion), and severity of illness (e.g., ISS, APACHE III) as potential confounders (2-4, 12-13, 16-20).

We used variance inflation factors to assess for multicollinearity (21). Variables detected to be collinear with APACHE III which are included in the calculation of the APACHE III score were not included separately (e.g., heart rate, mean arterial pressure, white blood cell count, and serum creatinine level). To avoid over-fitting, we adjusted for each potential confounder one covariate at-a-time (22).

2.6 Stratified Analyses

We tested whether the association between serum endocan levels and the development of ALI was independent of mechanism of injury (blunt vs. penetrating). Further, given the potential that having received a blood transfusion in the ED impacted the serum endocan level measured in the ED, and to assess whether the association was independent of transfusion-related ALI (23-24), we tested whether serum endocan levels were associated

with the development of ALI in the 22 patients who did not receive a blood transfusion in the ED. We used Stata SE 10.0 software for our statistical analyses (State Datacorp, College Station, TX) and used a p-value of < 0.05 to signify statistical significance.

3. Results

3.1 Study Cohort

We studied 48 acutely injured trauma patients with an ISS ≥ 16. Of the 48 trauma patients, 37 (77%) required operative intervention. As reported in Table 1, the 24 patients who developed ALI were more severely ill, as measured by higher ISS (p=0.04), higher APACHE III scores (p<0.001), lower platelet counts (p=0.02), and higher serum creatinine levels, and received significantly more units of packed red blood cells (p<0.001). Serum endocan levels were elevated in all 48 patients with severe trauma (mean 4.2 ng/mL, standard deviation 2.2, range 1.3, 12.6).

3.2 Association between Endocan Levels and Clinical Variables

At hospital admission, serum endocan levels were not associated with age (p=0.62), gender (p=0.60), admission vital signs or laboratory values, mechanism of injury (p=0.15), nor severity of illness as measured by the ISS (p=0.76) or APACHE III score (p=0.96). Serum endocan levels appeared higher in blunt trauma, compared to penetrating trauma (mean 4.7 ± 2.6 ng/mL vs. 3.7 ± 1.7 ng/mL, p=0.12), and appeared higher in non-survivors, compared to survivors, (mean 5.2 ± 3.1 ng/mL vs. 4.0 ± 1.9 ng/mL, p=0.12), although these differences did not achieve statistical significance.

3.3 Association between Endocan Levels and Development of ALI

Patients who developed ALI had lower levels of endocan in the ED prior to ICU admission compared to those who did not develop ALI (N=48, mean 3.5 ± 1.4 ng/mL vs. 4.9 ± 2.6 ng/mL, p=0.02) (see Figure 1). We present the fitted relationship between the observed development of ALI on the log-odds scale and serum endocan levels in Figure 2. For each 1-unit increase in serum endocan level, the odds ratio (OR) for ALI development decreased (OR=0.69, 95% confidence interval (CI): CI: 0.49, 0.97, p=0.03). Lower endocan levels remained significantly associated with a higher incidence of ALI after adjusting for severity of illness and RBC transfusion as a dichotomous variable (Table 2). Although adjustment for number of units of packed red blood cells transfused did not alter the odds ratio significantly, the association between lower serum endocan levels and the development of ALI was no longer significant with adjustment for units of PRBCs transfused (p=0.052).

3.4 Stratified Analyses

As shown in Figure 3, we found a significant association between lower serum endocan levels and the development of ALI in blunt trauma (N=23, mean 3.0 ± 1.2 ng/mL in 10 ALI cases vs. 6.0 ± 2.6 ng/mL in 13 non-ALI controls, p=0.003). There was no significant association between serum endocan levels and incident ALI in penetrating trauma (N=25, mean 3.8 ± 1.4 ng/mL in ALI cases vs. 3.6 ± 2.0 ng/mL in non-ALI controls, p=0.74). When we limited our analysis to the 22 patients who did not receive blood in the ED, lower serum endocan levels were found to be significantly associated with the development of ALI (p=0.049).

3.5 Association between Endocan Levels, ALI, and Mortality

In-hospital mortality was 21% (10/48) for the entire cohort; 7 of the 24 cases (29%) died, compared to 3 of the 24 controls (12%, OR=2.88, 95% CI: 0.65, 12.87, p=0.16). The development of ALI was not associated with in-hospital mortality (OR=2.88, 95% CI: 0.64,

12.87, p=0.16), nor were serum endocan levels associated with in-hospital mortality (OR=1.26 for each 1-unit increase in serum endocan, 95% CI: 0.93, 1.70, p=0.14).

4. Discussion

In this small study, we found that lower serum endocan levels were associated with the subsequent development of ALI in critically ill trauma patients. The association between serum endocan levels and incident ALI appeared to be limited to blunt-injured trauma patients. Future, larger studies are necessary to validate whether lower serum endocan levels are associated with the development of ALI independently and, if confirmed, to better understand the role of serum endocan in the development of ALI.

The association between lower serum endocan levels and ALI development was observed in trauma patients who sustained a blunt injury. Serum endocan may reflect an active role in the pathogenesis of trauma-associated ALI and blunt trauma-associated ALI more specifically. In the study by Bechard et al (8), it was demonstrated that endocan binds to the integrin leukocyte function-associated antigen-1 (LFA-1) on the surface of leukocytes to directly inhibit binding to intercellular adhesion molecule-1 (ICAM-1). As such, endocan appears to inhibit leukocyte recruitment and higher levels may serve as a marker of protection against the development of ALI. Further, there is recent evidence that endocan can be cleaved by neutrophil-derived cathepsin G to generate a peptide fragment named p14 (14 kDa) (25). In vitro, p14, which was not measured in the present study, competitively inhibits endocan function. Given the established role of leukocyte migration and activation in the lung in the development of ALI (9-10), we hypothesize that the increased incidence of ALI in blunt-injured trauma patients with lower serum endocan levels reflects endothelial dysregulation as activated neutrophils inhibit endocan function which leads to unregulated leukocyte recruitment and activation. Future studies are necessary to understand how endothelial cell function is affected by different traumatic mechanisms and how serum endocan levels change during the hospitalization in patients who do and do not develop ALI. Further, markers of endothelial function and neutrophil recruitment (e.g., soluble intercellular adhesion molecule-1 (26)) and neutrophil activation (e.g., myeloperoxidase, elastase) should be measured concomitantly in future studies to better understand the relationship between endothelial function and neutrophil activation.

Although our sample size limited our ability to adjust for potential confounders, our analyses suggest that the association between lower serum endocan levels and the development of ALI may be independent of established risk factors for ALI development, such as age and severity of illness. Further, the association between lower serum endocan levels and the subsequent development of ALI was preserved in patients who did not receive a transfusion in the ED and the association appeared to be independent of whether or not a patient received RBC transfusion during the resuscitation period. However, when we adjusted for RBC transfusion as a continuous variable, the association between lower serum endocan levels and the development of ALI became marginally insignificant. One potential explanation for this finding is that RBC transfusions induce leukocyte-mediated endothelial injury, either through the effects of antileukocyte antibodies, soluble CD40 ligand, biologically active lipids, or some combination thereof (24). A plausible alternative explanation is that loss of significance was due to variance inflation, as the point estimate of the OR did not appreciably change.

In septic patients, a recent study demonstrated a relationship between serum endocan levels and severity of illness and outcomes (14). Endocan levels were significantly higher in septic shock patients (median 6.11 ng/mL), compared to patients with sepsis (1.95 ng/mL) or severe sepsis (1.97 ng/mL), and were significantly higher in non-survivors (6.98 ng/mL),

compared to survivors (2.45 ng/mL). In the present study, which excluded less severely ill trauma patients, we did not find an association between serum endocan levels, which were elevated in the entire cohort (3.8 ng/mL), and severity of illness, as measured by ISS or APACHE III score. Further, we did not find an association between higher serum endocan levels and in-hospital mortality. It is important to note that the relationship between serum endocan levels and the development of ALI was not tested in the study of septic patients conducted by Scherpereel et al (14). Nevertheless, our study highlights that trauma and sepsis differ clinically and biologically, as reported in the recent study by Calfee et al (27).

There are several limitations to our study. First, we acknowledge that our sample size was a major limitation to our study. Specifically, our sample size limited our ability to adjust for multiple potential confounders simultaneously. Importantly, when we adjusted for each potential confounder one covariate at-a-time, only one potential confounder (Injury Severity Score) altered the odds ratio estimate by greater than 10% to warrant being maintained in a multivariable model (28) and none of the potential confounders significantly altered the odds ratio towards the null. Nevertheless, we acknowledge the potential for uncontrolled confounding and are unable to conclude that lower serum endocan levels are associated independently with the development of ALI without confirmation in a larger sample.

Second, selection bias is a potential limitation given our case-control study design; however, this potential bias was minimized by our use of a nested design by selecting cases and controls at random from within a prospective cohort study (11). Third, ALI misclassification is a potential limitation of our study. To minimize this potential bias, we relied on the interpretation of two independent physician reviewers, used the Consensus Conference definition of ALI (3) and, if necessary, had a third physician adjudicate equivocal cases. Further, we only used definite cases of ALI in the present study to further minimize the potential for misclassification bias. Fourth, although we considered and tested each measured covariate as a potential confounder, we acknowledge the potential for residual confounding based on unmeasured covariates. For example, the time from initial injury to hospital presentation or the tidal volumes employed (29) were not available in patient records. These variables may have biased our results in unforeseen ways and future studies should measure and adjust for these potential confounders. Fifth, to address the primary research question, we limited our assessment to a single endothelial cell marker; future studies should incorporate additional markers of endothelial activation and injury, such as von Willebrand factor (30). Further, it is unknown whether lower serum endocan levels are due to a response to other milieu (e.g., inflammatory cytokines (5)), which were not measured in the present study, and this possibility warrants further investigation. Finally, as a small, single-center study limited to a single endocan measure at the time of initial presentation to the hospital, our findings warrant external validation which include serial measures of endocan levels to better understand the potential relationship between serum endocan levels and the development of ALI.

5. Conclusions

We found that lower serum endocan levels were associated with the subsequent development of ALI in patients after major trauma. The relationship between serum endocan levels and ALI development appears to occur in patients suffering from blunt trauma. We hypothesize that the association between lower serum endocan levels and the development of ALI in patients after major blunt trauma reflects dysregulation in leukocyte recruitment. Future studies are needed to validate our findings, to understand how serum endocan levels change over time in these patients, and to identify the potential mechanism(s) by which lower serum endocan levels may be associated with increased risk of ALI development.

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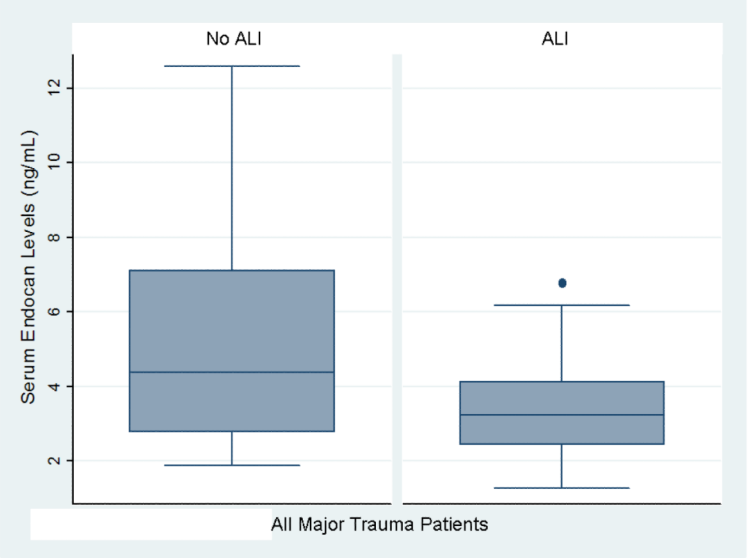

Figure 1.

Box-plot of serum endocan levels, by whether ALI developed, in 48 major trauma patients. Box plot shows the median (horizontal line) and interquartile range (25^{th} to 75^{th} percentile) (box). The whiskers show the lowest data within 1.5 IQR of the lower quartile and highest data within 1.5 IQR of the upper quartile; data outside 1.5 IQR of the upper quartile are depicted with a dot.

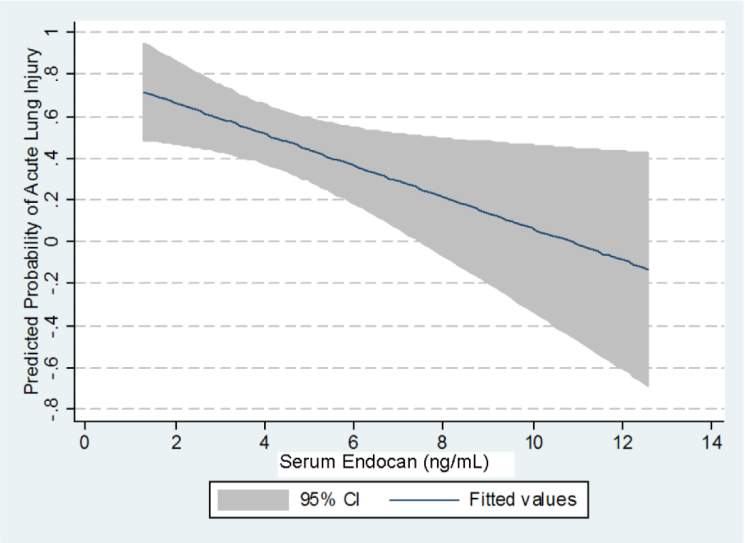

Figure 2.
Fitted relationship between serum endocan levels and development of ALI, using a linear regression model. None of the 7 patients with a serum endocan level ≥ 7 ng/mL developed ALI.

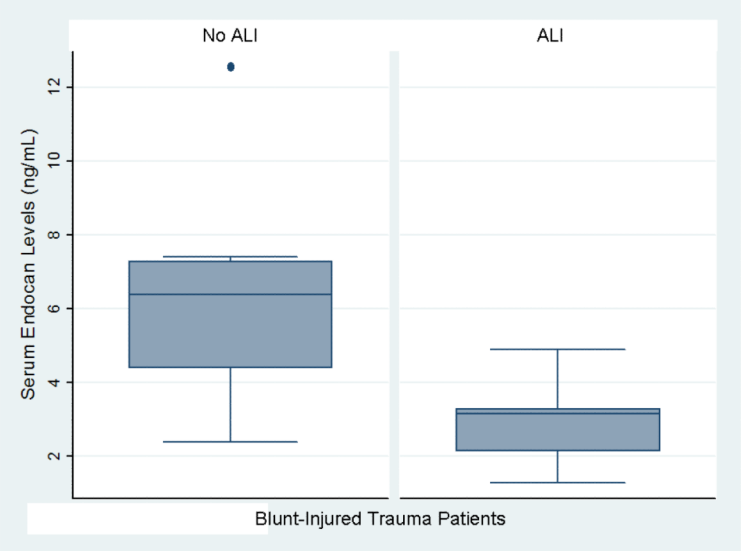

Figure 3.

Box-plot of serum endocan levels, by whether ALI developed, in 23 blunt-injured trauma patients. Box plot shows the median (horizontal line) and interquartile range (25^{th} to 75^{th} percentile) (box). The whiskers show the lowest data within 1.5 IQR of the lower quartile and highest data within 1.5 IQR of the upper quartile; data outside 1.5 IQR of the upper quartile are depicted with a dot.

Table 1

Univariate comparisons of patient-specific factors and the subsequent development of ALI.

Clinical Risk Factors	Non-ALI Group (n=24)	ALI Group (n=24)	p-value
Demographics			
Age (years)	33 ± 19	38 ± 20	0.41
Gender (male)	20, 83%	22, 92%	0.67
Severity of illness			
ISS	22 ± 6	27 ± 10	0.04
APACHE III	43 ± 19	62 ± 19	0.001
Vital Signs *			
Temperature, Fahrenheit	100.5 ± 1.2	100.9 ± 1.5	0.29
Heart rate	122 ± 24	135 ± 24	0.07
Respiratory rate	24 ± 8	22 ± 6	0.32
Mean arterial pressure, mm Hg	71 ± 13	66 ± 14	0.16
Laboratory Values *			
White Blood Cell count	13.5 ± 4.3	9.7 ± 4.6	0.01
Hematocrit	29 ± 5	27 ± 6	0.43
Platelet count	130 ± 59	90 ± 51	0.02
Ethanol level	39 ± 84	53 ± 104	0.64
Serum glucose (mg/dL)	150 ± 38	172 ± 52	0.10
Serum bicarbonate (mg/dL)	21 ± 3	20 ± 3	0.42
Serum creatinine (mg/dL)	0.9 ± 0.2	1.1 ± 0.3	0.01
Serum endocan (ng/mL)	4.9 ± 2.6	3.5 ± 1.4	0.02
Comorbid Conditions			
Chronic ethanol use	0, 0%	1, 4%	1.00
Cirrhosis	0, 0%	0, 0%	--
Diabetes mellitus	1, 4%	1, 4%	1.00
Hypertension	3, 12%	3, 12%	1.00
End-stage renal disease	0, 0%	0, 0%	--
Immunosuppressed	0, 0%	0, 0%	--
Oncology	0, 0%	0, 0%	-
Etiology of Traumatic Injury and Injuries Sustained			
Blunt	13, 54%	10, 42%	0.39
Penetrating	11, 46%	14, 58%	
Long-bone fractures †	8, 35%	7, 29%	0.68
Pelvic fractures	3, 12%	3, 12%	1.00
Pulmonary contusion	4, 17%	9, 37%	0.10
Interventions			
Intravenous fluids (cc) ‡	8395 ± 3775	9700 ± 7690	0.51
PRBC transfusion received ‡	15, 62%	20, 83%	0.10

Clinical Risk Factors	Non-ALI Group (n=24)	ALI Group (n=24)	p-value
PRBC transfusion, units ‡	3 ± 3	9 ± 9	0.004

Definition of abbreviation: APACHE=acute physiology and chronic health evaluation III score; ISS=Injury Severity Score; PRBC=packed red blood cells.

Continuous data presented as means and standard deviations.

Categorical data presented as counts and percentiles.

*Worst value in first 24 hours of admission.

†Long bone fracture defined as fracture to femur, fibula, forearm, humerus, or tibia.

‡Blood and crystalloid defined as blood transfused or crystalloid administered in emergency room and/or operating room during initial resuscitation period.

Table 2

Multivariable logistic regression models demonstrating adjusted odds ratio for development of ALI in 48 patients after major trauma.

Full Model (N=48)	Odds Ratio (95% CI)	p-value
Serum Endocan (base model) *	0.69 (0.49 – 0.97)	0.033
Adjusted for:		
Age	0.69 (0.49 – 0.96)	0.031
Gender	0.70 (0.50 – 0.98)	0.038
Diabetes mellitus	0.69 (0.49 – 0.97)	0.033
Pulmonary contusion	0.66 (0.46 – 0.96)	0.029
Packed RBC Transfused (dichotomous) †	0.71 (0.50 – 1.00)	0.048
Packed RBC Transfused, per unit †	0.66 (0.44 – 1.00)	0.052
APACHE III	0.66 (0.47 – 0.94)	0.021
Injury Severity Score	0.61 (0.40 – 0.92)	0.019

Definition of abbreviation: APACHE=Acute physiology and chronic health evaluation score; CI=confidence interval; RBC=red blood cells.

An odds ratio of less than 1 indicates that the factor is associated with lesser odds of developing ALI.

Potential confounders were added one covariate at-a-time.

*Odds ratio for ALI development decreased for each 1-unit increase in serum endocan level.

†Packed RBC transfused in emergency room and/or operating room during initial resuscitation period. RBC transfusion was evaluated as both a dichotomous variable (any transfusion during the initial resuscitation) and a linear variable (total number of units).