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Soluble intercellular adhesion molecule-1 and clinical outcomes in patients with acute lung injury

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Abstract Objective: To determine if levels of soluble intercellular adhesion molecule-1 (sICAM-1), a marker of alveolar epithelial and endothelial injury, differ in patients with hydrostatic pulmonary edema and acute lung injury (ALI) and are associated with clinical outcomes in patients with ALI. **Design, setting, and participants:** Measurement of sICAM-1 levels in (1) plasma and edema fluid from 67 patients with either hydrostatic pulmonary edema or ALI enrolled in an observational, prospective single center study, and (2) in plasma from 778 patients with ALI enrolled in a large multi-center randomized controlled trial of ventilator strategy. **Results:** In the single-center study, levels of sICAM-1 were significantly higher in both edema fluid and plasma (median 938 and 545 ng/ml, respectively) from ALI

patients compared to hydrostatic edema patients (median 384 and 177 ng/ml, $P < 0.03$ for both comparisons). In the multi-center study, higher plasma sICAM-1 levels were associated with poor clinical outcomes in both unadjusted and multivariable models. Subjects with ALI whose plasma sICAM-1 levels increased over the first 3 days of the study had a higher risk of death, after adjusting for other important predictors of outcome (odds ratio 1.48; 95% CI 1.03–2.12, $P = 0.03$). **Conclusions:** Both plasma and edema fluid levels of sICAM-1 are higher in patients with ALI than in patients with hydrostatic pulmonary edema. Higher plasma sICAM-1 levels and increasing sICAM-1 levels over time are associated with poor clinical outcomes in ALI. Measurement of sICAM-1 levels may be useful for identifying patients at highest risk of poor outcomes from ALI.

Keywords Acute respiratory distress syndrome · Acute lung injury · Intracellular adhesion molecule-1 · Pulmonary edema

Introduction

Previous studies on biomarkers in the plasma [1–3], edema fluid, [4] and urine [5] of patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) have demonstrated that specific markers may provide insight into both the pathogenesis and prognosis of this frequently fatal syndrome. For instance, biomarker studies that demonstrated elevation of markers of endothelial activation and dysregulated coagulation [6] led to recognition of this mechanism of injury as a key component of ALI [7, 8], and subsequently to the development of novel therapeutic approaches focused on pulmonary vascular microthrombi [9, 10]. Similarly, ancillary studies of plasma biomarkers in patients enrolled in the NHLBI ARDS Network's trial of low tidal volume ventilation have provided important insights into the mechanism of benefit of this effective supportive therapy [1–3].

Soluble intercellular adhesion molecule-1 (sICAM-1) is an adhesion molecule expressed on both alveolar epithelial cells and vascular endothelium [11, 12] and is thought to play an important role in neutrophil recruitment and trafficking into the lung [13]. Experimental animal studies have demonstrated increased sICAM-1 expression in the setting of acute lung injury [14, 15], and elevated plasma levels of sICAM-1 were associated with poor outcomes in a small cohort of adults with acute lung injury [16] and in pediatric lung injury [17]. Since injury to the alveolar epithelium and vascular endothelium is of central importance in the pathogenesis of ALI and ARDS [7], we hypothesized that release of sICAM-1 into the airspaces would be an important prognostic indicator in adult patients with ALI/ARDS. To test this hypothesis, we first determined whether sICAM-1 could be detected in the airspaces of patients with ALI in a small, single-center study, with the plan to validate and further explore the prognostic and pathogenic significance of sICAM-1 in a larger cohort if the single-center results were promising [3, 4, 18]. Because high levels of sICAM-1 were measured in both the plasma and pulmonary edema fluid of these subjects and were associated with poor clinical outcomes, we then determined the prognostic value of plasma sICAM-1 in a large multi-center study of patients with ALI/ARDS. We also tested the prognostic value of changes in sICAM-1 levels over time (in both edema fluid and plasma in the single-center study, and plasma alone in the multi-center trial). Some of the findings of this study have been previously reported in abstract form [19–21].

Materials and methods

Single-center study

The study was approved by the Committee on Human Research at the University of California, San Francisco.

Sixteen patients with hydrostatic pulmonary edema and 51 patients with ALI/ARDS were selected, based on availability of adequate sample volume, from a database of over 300 patients who were previously enrolled in a prospective study to collect pulmonary edema fluid and plasma from patients with acute pulmonary edema. Hydrostatic pulmonary edema [22] and ALI/ARDS [23] were defined based on previously published definitions. At the time of entry into the prospective database, all patients had pulmonary edema fluid and plasma collected within the first 4 h after endotracheal intubation. Pulmonary edema fluid was aspirated with a 14Fr suction catheter as previously described [23]. A subset of patients with ALI/ARDS ($n = 31$) had serial samples of pulmonary fluid obtained over the subsequent 8 h. All samples were immediately centrifuged at $3,000\times g$ for 10 min, and supernatants were aliquoted and frozen until assayed for sICAM-1.

Multi-center study

Clinical data and biological samples for the multi-center study were obtained from patients enrolled in a randomized controlled trial of lower tidal volume, plateau-pressure limited ventilation conducted by the National Heart, Lung, and Blood Institute's ARDS Network [24]. This trial enrolled 861 patients to test the hypothesis that ventilation with a lower tidal volume, plateau pressure-limited strategy would reduce mortality in patients with ALI [24]. The details and results of the clinical trial have been published earlier [24]. 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 factorialized trial of lisofylline versus placebo [25] and these patients are also included in the current analysis. All patients were followed until death, 180 days or until discharge to home with unassisted breathing. The trial demonstrated a significant reduction in 180-day mortality in the lower tidal volume treatment group (31 vs. 40%, $P = 0.007$). In a factorial design, ketoconazole [26] and lisofylline [25] were also administered to subsets of patients ($n = 117$ and $n = 116$, respectively) as investigational therapies for ALI, neither of which affected mortality. Inclusion and exclusion criteria are described in the original publication, and the institutional review boards of all involved hospitals approved the trial [24]. Plasma samples were obtained from all the patients at enrollment prior to randomization, day 1 and day 3 of the clinical trial. Plasma samples were centrifuged at $3,000\times g$, and the supernatants were aliquoted and frozen for later use.

Measurement of sICAM-1 in plasma and pulmonary edema fluid

sICAM-1 levels were measured in duplicate in plasma and pulmonary edema fluid samples by commercially available ELISA (Biosource International, Camarillo CA) against a standard curve of recombinant human sICAM-1 provided by the manufacturer. The lower limit of detection was 1.6 ng/ml; the intra-assay coefficient of variation was 9.5%, while the inter-assay coefficient of variation was 7.8%. Diluent was provided by the manufacturer.

Statistical analysis

Statistical analysis was performed with STATA/SE 9.2 (College Station, TX) and SPSS 13.0 for Macintosh (Chicago, IL). For comparison of clinical and demographic characteristics and clinical outcomes between the two groups, Student's *T*-tests were used to compare normally distributed data, and the Mann Whitney *U* test was used for non-normally distributed data; Chi-square or Fisher's Exact Test was used for categorical variables. For multiple group comparisons, the Kruskal–Wallis test was used. In the single center pilot study, ventilator-free days were dichotomized at 5 based on the results of exploratory analyses. To analyze serial levels of sICAM-1 in the pulmonary edema fluid in patients with ALI/ARDS, patients in the single-center study were categorized into two groups: those with an increase in sICAM-1 in the edema fluid during the first 8 h after enrollment and those with no change or a fall in sICAM-1 in the edema fluid during the first 8 h after enrollment.

In the multi-center study, multivariable linear and logistic regression models were used to control for potential confounding variables. Because sICAM-1 levels were not normally distributed, we applied natural log-transformation to the plasma sICAM-1 levels in order to fit linear models. We first tested the impact of sICAM-1 on mortality in an unadjusted logistic regression, and then created a multivariable logistic model to control for baseline clinical features that may have affected outcomes, including age, sepsis or trauma as etiology of lung injury, PaO₂/FiO₂, and severity of illness, as reflected by APACHE III score [27]. These covariates were selected on the basis of the bivariate analysis results and prior clinical research about predictors of outcomes in ALI [28]. We performed similar analyses using linear regression models for the outcomes of ventilator-free days and organ failure-free days. Logistic models were checked using the Hosmer–Lemeshow test and the linktest [29]; linear models were evaluated using residual-based diagnostics. The Wilcoxon signed-rank test was used to evaluate changes in sICAM-1 levels between Day 0 and Day 3, and analysis of covariance was used to test the impact of lower tidal volume ventilation on the change in sICAM-1 levels from Day 0 to Day 3.

Results

Single-center study

Clinical Characteristics of Subjects

Sixteen patients with hydrostatic pulmonary edema and 51 patients with ALI/ARDS were enrolled in the

Table 1 Clinical characteristics of patients enrolled in the single center study (*n* = 67) and the multicenter study (*n* = 778)

Patient characteristic	Hydrostatic pulmonary edema <i>n</i> = 16	Single-center ALI/ARDS <i>n</i> = 51	Multi-center ALI/ARDS <i>n</i> = 778
Male gender	88%*	51%	59%
Caucasian	69%	60%	73%
Current smoker	21%*	36%	N/A
Age (years)	59 ± 21	48 ± 17	51 ± 17
A – a O ₂ difference	467 ± 175	466 ± 146	N/A
PaO ₂ /FiO ₂	N/A	N/A	132 ± 62
Lung injury score	2.8 ± 0.6	2.7 ± 0.7	2.7 ± 0.6
Tidal volume, cc/kg PBW	N/A	N/A	10.7 ± 2.6**
Plateau pressure, cm H ₂ O	N/A	N/A	30 ± 7.7**
SAPSII Score	40 ± 6*	49 ± 15	N/A
APACHE III score	N/A	N/A	83 ± 28
Alveolar fluid clearance (%/h)	9.4 (3.2, 26.1)	3.0 (0, 8.3)	N/A
Ventilator free days	22 (2, 26)*	0 (0, 23)	10 (0, 22)
Hospital survival	75%	49%	65%
Plasma sICAM-1, ng/ml	177 (137, 703)*	545 (232, 1330)	604 (328, 1022)
Edema fluid sICAM-1, ng/ml	384 (217, 801)*	938 (675, 1743)	N/A

SAPSII Simplified Acute Physiology Score II, APACHE III acute physiology and chronic health evaluation III, LIS lung injury score [46]

* *P*-value for comparison with single center ALI patients <0.05

** Pre-randomization data

Data as percent, mean ± SD or median (interquartile range), as appropriate

single-center study. Patient characteristics are summarized in Table 1. Causes of hydrostatic pulmonary edema included acute myocardial infarction/ischemia ($n = 9$), congestive heart failure ($n = 4$) and acute volume overload ($n = 3$). Causes of ALI/ARDS included pneumonia ($n = 16$), nonpulmonary sepsis ($n = 12$), aspiration of gastric contents ($n = 6$), reperfusion injury after lung transplantation ($n = 6$), multiple transfusions ($n = 4$), drug overdose ($n = 3$) and other causes ($n = 4$). Compared with the hydrostatic edema group, significantly more patients with ALI/ARDS were female and smokers. Severity of illness was higher in patients with ALI/ARDS, and clinical outcomes were worse in this group, including significantly fewer days alive and free of mechanical ventilation (ventilator-free days) (Table 1).

sICAM-1 levels and etiology of pulmonary edema

Baseline levels of sICAM-1 were significantly higher in both the pulmonary edema fluid (Fig. 1a) and plasma (Fig. 1b) from patients with ALI/ARDS compared to patients with hydrostatic pulmonary edema. In both the patient groups, baseline edema fluid levels were higher than simultaneous plasma levels, although this difference did not reach statistical significance in the hydrostatic group (data not shown).

sICAM-1 Levels and clinical characteristics

Among patients with ALI/ARDS, several clinical characteristics were associated with higher levels of sICAM-1 (Table 2). Smokers had higher levels of sICAM-1 in the plasma [median 1191 (IQR 465–1480) ng/ml] and edema fluid [1,361(920–2,716) ng/ml] compared to non-smokers [plasma 354(194–974) ng/ml, $P = 0.03$; edema fluid 886 (390–1845) ng/ml, $P = 0.04$]. Patients with liver failure, as defined by serum bilirubin ≥ 4 g/dl, had higher levels of sICAM-1 in the plasma [1,191 (629–2229) ng/ml] compared to patients without liver failure [387 (233–1345) ng/ml, $P = 0.023$]. Gender, race-ethnicity, renal failure, and presence or absence of sepsis were not significantly associated with sICAM-1 levels.

sICAM-1 Levels and clinical outcomes of patients with ALI/ARDS

There was a trend towards higher edema fluid and plasma levels of sICAM-1 in patients who eventually died, but these differences did not reach statistical significance (Table 3). Patients with fewer days alive and free of mechanical ventilation (<5 ventilator free days) had significantly higher levels of both plasma and edema fluid sICAM-1 (Table 3).

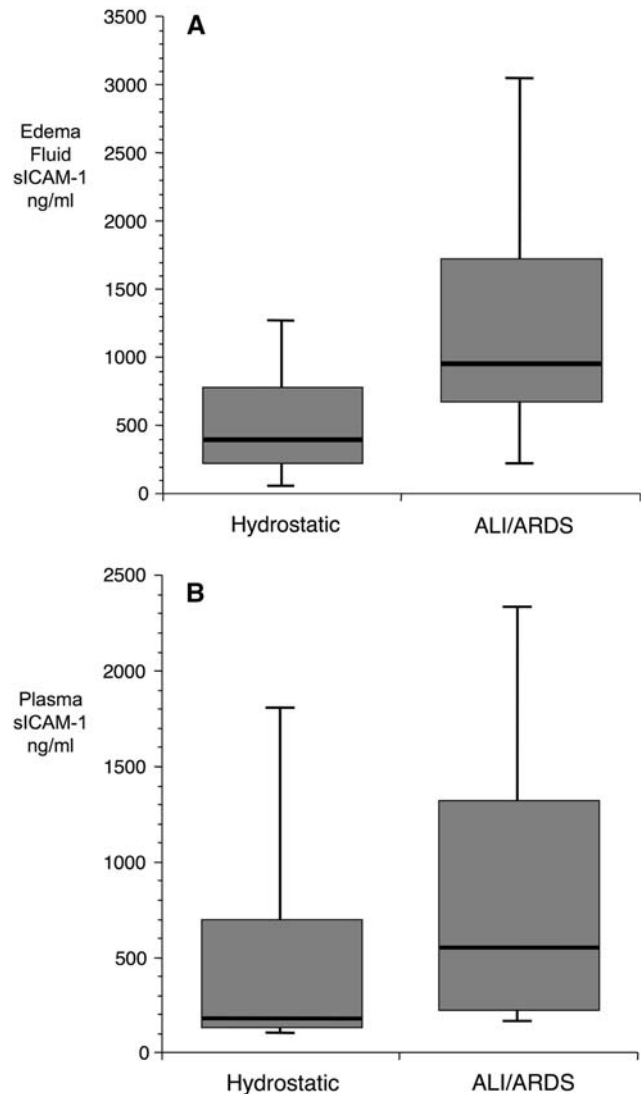


Fig. 1 Boxplot summary of edema fluid (a) and plasma (b) levels in patients with hydrostatic pulmonary edema ($n = 16$) and ALI/ARDS ($n = 51$) from the single-center study. Edema fluid sICAM-1 levels were significantly higher in subjects with ALI (median 938 ng/ml, IQR 675–1743) compared to subjects with hydrostatic pulmonary edema (median 384 ng/ml, IQR 217–801) (a; P value for comparison 0.004). Plasma sICAM-1 levels demonstrated a similar pattern (b; median in ALI/ARDS (545 ng/ml, IQR 232–1330) vs. median in hydrostatic (177 ng/ml, IQR 137–703; $P = 0.021$)

In a subset of patients with ALI/ARDS ($n = 31$), serial samples of pulmonary edema fluid and plasma were obtained over the 8 h after collection of the first sample. Hospital survival was threefold higher in patients with stable or decreasing levels of sICAM-1 in the edema fluid compared to patients with increasing levels (63% survival vs. 20% survival, $P = 0.029$). In contrast, changes in plasma ICAM-1 had no association with survival ($P = 1.0$).

Table 2 Clinical characteristics significantly associated with plasma sICAM-1 Levels in patients with ALI, single center and multi-center studies

Dichotomous variables				
Study	Characteristic	Plasma sICAM, ng/ml (median [IQR])	P value	
Single center ^a	Active smoker	1,191 (465, 1,480)	0.04	
	Not active smoker	354 (390, 1,845)		
	Liver failure (serum bilirubin >4 g/dL)	1,191 (629, 2,229)		
Multi-center ^b	No liver failure	387 (233, 1,345)	<0.0001	
	Sepsis	724 (436, 1,341)		
	No sepsis	555 (310, 956)		
	Trauma	346 (237, 605)		
	No trauma	639 (351, 1,044)		
	AIDS	596 (321, 993)		0.002
	No history of AIDS	842 (522, 1,512)		
	Hepatic encephalopathy	1,526 (996, 1,586)		0.02
	No hepatic encephalopathy	603 (325, 1021)		
	Cirrhosis	1,330 (965, 1,968)		<0.0001
	No cirrhosis	595 (322, 986)		
	Caucasian	562 (310, 959)		0.0008
	Non-Caucasian	713 (414, 1,192)		
Continuous variables				
Study	Characteristic	Spearman rank coefficient, with sICAM-1	P value	
Multi-center	APACHE III	0.16	<0.0001	
	Age	-0.11		
	PaO ₂ :FiO ₂	-0.07		
	Creatinine	0.14		
	Plateau pressure	0.15		
	Respiratory compliance	-0.11		

APACHE III Acute physiology and chronic health evaluation III, AIDS acquired immune deficiency syndrome

^a Not associated with sICAM-1 levels: gender, race-ethnicity, sepsis

^b Not associated with sICAM-1 levels: gender

Table 3 Clinical outcomes and sICAM-1 levels among patients with ALI/ARDS in the single center study ($n = 51$)

Outcome	Value	Plasma sICAM-1 (ng/ml)	P	Edema fluid sICAM-1 (ng/ml)	P
Ventilator-free days	<5 days	745 (336, 1,345)	0.036	1327 (880, 2,501)	0.037
	≥5 days	295 (175, 999)		820 (286, 1,394)	
Hospital survival	Died	737 (316, 1,344)	0.14	1221 (845, 1,959)	0.14
	Lived	338 (182, 1,033)		847 (353, 1,534)	

Data as median (interquartile range)

Multi-center study

Baseline clinical characteristics of subjects

Baseline plasma samples were available for study from 778 of the patients enrolled in the clinical trial. Clinical characteristics of these patients are summarized in Table 1 and are similar to clinical characteristics of the 124 patients who were not included in the study because plasma was not available (data not shown). The patients were equally distributed between the two treatment groups (6 and 12 ml/kg tidal volume). Several clinical characteristics were significantly associated with higher baseline sICAM-1 levels in this cohort (Table 2), including sepsis

as a risk factor for ALI, higher APACHE III score, lower PaO₂/FiO₂ ratio, non-Caucasian race-ethnicity, history of AIDS, history of hepatic encephalopathy or cirrhosis, higher baseline creatinine, higher plateau pressure, and lower compliance. Trauma as a risk factor for ALI and increasing age were both associated with lower sICAM-1 levels.

sICAM-1 levels and clinical outcomes

In analyses, adjusting solely for ventilator strategy, higher baseline plasma sICAM-1 levels were associated with poor clinical outcomes. Specifically, in a logistic

Table 4 Baseline plasma sICAM-1 levels and clinical outcomes in a multicenter study of 778 patients with ALI/ARDS

Measurement	Risk of death		Ventilator-free days		Organ failure-free days	
	OR (95% CI)	<i>P</i> value	Mean difference (days)	<i>P</i> value	Mean difference (days)	<i>P</i> value
Baseline plasma ICAM-1, per one-log increase, adjusted for ventilator strategy	1.22 (1.02, 1.46)	0.03	-1.87 (-2.76, -0.97)	<0.001	-2.32 (-3.24, -1.40)	<0.001
Baseline plasma ICAM-1, per one-log increase, multivariable model ^a	1.22 (0.99, 1.49)	0.06	-1.57 (-2.45, -0.69)	0.001	-1.67 (-2.56, -0.78)	<0.001

^a Controlling for ventilator strategy, APACHE III score, PaO₂/FiO₂ ratio, sepsis or trauma as risk factors for ALI, and age

regression model controlling for ventilator strategy, increasing baseline plasma sICAM-1 was associated with an increased odds of death [odds ratio (OR) 1.22 per one-log increase in sICAM-1 (95% CI 1.02–1.46); *P* = 0.03] (Table 4). Likewise, higher baseline plasma sICAM-1 levels were strongly associated with fewer ventilator-free days and fewer organ failure-free days in analyses controlling for ventilator strategy alone (Table 4). In multivariable models controlling for other important clinical covariates including sepsis, trauma, APACHE III score, PaO₂:FiO₂ ratio, and age, the association between sICAM-1 and each outcome remained strong, although the confidence interval was slightly wider and did not exclude unity in the case of mortality (Table 4). There was no evidence of a significant interaction between ventilator strategy and baseline plasma sICAM-1 level. As a sensitivity analysis, we evaluated the effect of treatment with ketoconazole or lisofylline on the multivariable model for mortality and found that they had no impact on the results.

Changes in plasma sICAM-1 levels over time

Paired plasma samples from Days 0 and 3 were available for 686 subjects. At baseline, the median plasma sICAM-1 level was 604 ng/ml (IQR 327–1022), similar to plasma levels in the ALI/ARDS patients in the single-center study. On Day 3 after randomization, the median plasma sICAM-1 level was slightly higher, 653 ng/ml (IQR 390–1153; *P* < 0.0001 for comparison with day 0). Subjects whose plasma sICAM-1 level increased over these 3 days had a trend towards an increased risk of death compared with those whose plasma level decreased over time (mortality 36.0 vs. 29.5%, *P* = 0.07; Table 5). After adjusting for other important predictors of outcome (age, APACHE III score, P:F ratio, presence of sepsis or trauma, and low tidal volume ventilation), the association between increasing sICAM-1 and death was statistically significant [odds ratio 1.48 (95% CI 1.03–2.12); Table 5]. The change in sICAM-1 levels over time was not affected by ventilator strategy.

Table 5 Change over time in plasma sICAM-1 levels and mortality in ALI

Predictor	Odds ratio for death at 180 days (95% CI) ^a	<i>P</i> value
Increase in plasma sICAM-1 over first 3 days, adjusted for ventilator strategy	1.33 (0.96, 1.84)	0.09
Increase in plasma sICAM-1 over first 3 days, multivariable model ^b	1.48 (1.03, 2.12)	0.03

^a Referent group: subjects whose sICAM-1 decreased over first 3 days

^b Controlling for ventilator strategy, APACHE III score, PaO₂/FiO₂ ratio, sepsis or trauma as risk factors for ALI, and age

Discussion

This study demonstrates that elevations in sICAM-1, a marker of lung epithelial and endothelial injury, were associated with poor clinical outcomes in two separate cohorts of patients with ALI. In addition, both edema fluid and plasma sICAM-1 levels were higher in subjects with ALI than in a control group of subjects with acute hydrostatic pulmonary edema. These results suggest that sICAM-1 may be a useful biomarker of lung injury in patients with ALI/ARDS. sICAM-1 has been associated with adverse clinical outcomes in patients at risk for ALI/ARDS from trauma or other critical illness [30, 31], pediatric patients with ALI/ARDS [17] and other critical illness [32], and in patients with acute lung injury due to primary graft dysfunction (reperfusion edema) after lung transplantation [33]. Higher levels of plasma sICAM-1 were also associated with adverse clinical outcomes in a small study of adults with ALI/ARDS [16]. However, the current study is the first to show that sICAM-1 is independently associated with adverse clinical outcomes in a large cohort of adults with ALI.

While baseline plasma sICAM-1 levels had prognostic value, increasing plasma sICAM-1 levels over the first 3 days of ALI were also associated with poor outcomes in the larger multi-center cohort. In the single-center study, increasing edema fluid sICAM-1 levels over the first 8 h

were associated with poor outcomes, while changes in plasma sICAM-1 over that same time period were not. There may be several explanations for the difference in the prognostic value of the plasma sICAM-1 levels between the single-center and multi-center cohorts. First, the difference in time elapsed between measurements in the two cohorts (8 h in single-center study vs. 3 days in multi-center study) may be responsible, particularly if plasma sICAM-1 levels change more slowly than edema fluid levels. Second, the single-center study was likely underpowered to detect an association between change in plasma sICAM-1 levels over time and clinical outcomes, given its small sample size. Finally, the differences in the underlying patient populations of the two cohorts may be responsible for these differing results.

In addition to its potential prognostic value, measurement of sICAM-1 in patients with acute lung injury may provide insight into the pathogenesis of this complex syndrome. ICAM-1 is a counter receptor for the $\beta 2$ integrins CD11a/CD18 and CD11b/CD18 and plays an important role in leukocyte migration and localization. ICAM-1 is widely expressed in human tissues, including the vascular endothelium and inflammatory cells, and can be induced by pro-inflammatory stimuli [11]. In the lung, ICAM-1 is highly constitutively expressed by the alveolar epithelium [34] where it is localized predominantly to the apical surface of alveolar epithelial type I cells under baseline conditions [12, 35]. In cell culture, exposure of lung epithelial cells to pro-inflammatory and infectious stimuli leads to increased ICAM-1 expression [36–39]. Similarly, in experimental models, pneumonia and acute lung injury up-regulate expression of ICAM-1 by alveolar epithelial type II cells [34, 40] and lead to shedding of a soluble form of ICAM-1 (sICAM-1) into the airspaces [14, 15]. Although the biologic function of sICAM-1 in the alveolar compartment remains unclear, sICAM-1 has been reported to bind alveolar macrophages and enhance inflammatory cytokine production by alveolar macrophages in response to injurious stimuli [41]. Thus, elevated sICAM-1 levels may be not only a marker of poor prognosis but also an important mediator involved in the pathogenesis of lung epithelial injury. Alternatively, endothelial sources of sICAM-1 may be an important contributor to elevated plasma and/or edema fluid levels, as pulmonary vascular endothelium has also been shown to up-regulate ICAM-1 expression in response to inflammatory stimuli [42].

The specific origin of the sICAM-1 measured in plasma in these study subjects cannot be definitively identified. In the single-center study, the finding that pulmonary edema fluid levels of sICAM-1 were consistently higher than simultaneous plasma levels suggests that the alveolar epithelium is the primary source of plasma sICAM-1. In contrast, the lack of either an interaction between plasma sICAM-1 levels and ventilator strategy or an impact of ventilator

strategy on the change in plasma sICAM-1 levels over time in the multi-center study argues against the alveolar epithelium as the sole source of sICAM-1 levels in these subjects. Since both alveolar epithelial and endothelial injury are hallmarks of ALI/ARDS [7], both sources probably contribute to elevated plasma levels in these subjects. Of note, the association between elevated sICAM-1 levels and liver disease observed in both the single-center and multi-center cohorts has been previously demonstrated in patients with diverse types of chronic liver disease. Elevated serum ICAM-1 levels have been previously observed in patients with chronic liver diseases including Hepatitis C [43], non-alcoholic steatohepatitis [44], and hepatocellular carcinoma [45], though the mechanism of these associations remains unclear.

This study has some limitations. First, because plasma was not available on all 902 subjects enrolled in the original multi-center trial, sICAM-1 levels were measured on a subset of the larger study sample. Plasma availability was the sole factor determining inclusion in this study, and important clinical characteristics of the included patients were similar to those of the patients for whom plasma was unavailable, suggesting that the 778 included patients are representative of the larger study population. However, we cannot definitively exclude selection bias. Second, the source of sICAM-1 levels in these patients cannot be definitively identified; however, a biological marker that reflects injury to more than one source may still be valuable in ALI because the pathogenesis of this syndrome involves injury to both the endothelium and epithelium. Finally, participants in randomized controlled trials of novel clinical therapies may not be similar to the broader population of patients with ALI/ARDS. However, the similarity of the results obtained in the single-center study, which was by nature less selective than a randomized controlled trial, suggests that these findings are generalizable to other populations of ALI patients, as do the results of prior analyses of sICAM-1 levels in pediatric ALI [17] and ALI after lung transplantation [33].

In conclusion, elevations in both plasma and pulmonary edema fluid levels of sICAM-1 are associated with poor outcomes in patients with ALI. Measurement of plasma sICAM-1, particularly in combination with other biologic markers, may be useful for identifying patients at highest risk of poor clinical outcomes. In addition, serial measurements of plasma sICAM-1 levels may have value in assessing prognosis and clinical response to new therapies.

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