Pulmonary vs Nonpulmonary Sepsis and Mortality in Acute Lung Injury

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Abstract

Background—Acute lung injury (ALI) is a frequent complication of sepsis. It is unclear if a pulmonary vs nonpulmonary source of sepsis affects mortality in patients with sepsis-induced ALI.

Methods—Two hundred eighty-eight consecutive patients with sepsis-induced ALI from 14 ICUs at four hospitals in Baltimore, MD were prospectively classified as having a pulmonary vs nonpulmonary source of sepsis. Multiple logistic regression was conducted to evaluate the independent association of a pulmonary vs nonpulmonary source of sepsis with inpatient mortality.

Results—In an unadjusted analysis, in-hospital mortality was lower for pulmonary vs nonpulmonary source of sepsis (42% vs 66%, $p < 0.0001$). Patients with pulmonary sepsis had lower acute physiology and chronic health evaluation (APACHE) II and sequential organ failure assessment (SOFA) scores, shorter ICU stays prior to the development of ALI, and higher lung injury scores. In the adjusted analysis, several factors were predictive of mortality: age (odds ratio [OR], 1.03; 95% confidence interval [CI], 1.01 to 1.06), Charlson comorbidity index (OR, 1.15; 95% CI, 1.02 to 1.30), ICU length of stay prior to ALI diagnosis (OR, 1.19; 95% CI, 1.01 to 1.39), APACHE II score (OR, 1.07; 95% CI, 1.03 to 1.12), lung injury score (OR, 1.64; 95% CI, 1.11 to 2.43), SOFA score (OR, 1.15; 95% CI, 1.06 to 1.26), and cumulative fluid balance in the first 7 days after ALI diagnosis (OR, 1.06; 95% CI, 1.03 to 1.10). A pulmonary vs nonpulmonary source of sepsis was not independently associated with mortality (OR, 0.72; 95% CI, 0.38 to 1.35).

Conclusions—Although lower mortality was observed for ALI patients with a pulmonary vs nonpulmonary source of sepsis, this finding is likely due to a lower severity of illness in those with pulmonary sepsis. Pulmonary vs nonpulmonary source of sepsis was not independently predictive of mortality for patients with ALI.

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Keywords

ARDS; critical illness; mortality; sepsis

Acute lung injury (ALI) is a frequent complication of sepsis, resulting in high short-term mortality.[1–3] Pulmonary vs nonpulmonary sepsis may differ in the mechanisms leading to ALI with pulmonary infections causing lung injury directly via the pathogen and host response vs nonpulmonary infections causing lung injury indirectly via systemic inflammation.[4]

It is unclear if patients with direct vs indirect lung injury have different clinical outcomes. Gattinoni and colleagues[5] reported different physiologic responses in respiratory system elastance and lung recruitment with positive end-expiratory pressure in patients with direct vs indirect etiologies for ARDS. These differences have contributed to the hypothesis that direct vs indirect lung injury may represent different syndromes.[5,6]

Studies examining the effect of ALI risk factors on patient outcomes have shown conflicting results. A study and metaanalysis[7–9] suggest that ALI risk factors are not independently associated with in-hospital mortality. Moreover, the beneficial effects of mechanical ventilation with a volume- and pressure-limited strategy were similar in patients with different ALI risk factors.[9] However, a large countywide epidemiologic study[2] suggests that ALI risk factors may influence outcomes. Specifically, patients with sepsis-induced ALI have a higher case fatality rate than those with trauma- and aspiration-induced ALI.[1,2,10]

To minimize the possibility that differences in mortality in ALI patients may be caused by differences in clinical risk factors,[1] we focused on examining patients with a single common risk factor, sepsis. Within this context, we sought to understand the role of direct vs indirect lung injury through classifying these patients as having a pulmonary vs nonpulmonary source of sepsis and comparing their demographic and clinical characteristics, ICU management, and inpatient mortality.

MATERIALS AND METHODS

Study Population

As part of an ongoing, multisite cohort study,[11] we evaluated consecutive ALI patients from November 2004 to April 2007 who had sepsis prospectively identified as the primary ALI risk factor. In this study, 12 ICUs at four teaching hospitals enrolled consecutive patients receiving mechanical ventilation who met the American-European consensus criteria for ALI.[12] Relevant exclusion criteria included the following: (1) preexisting illness with a life expectancy < 6 months, (2) transfer to a study site ICU with preexisting ALI of > 24 h in duration, (3) >5 days of mechanical ventilation prior to ALI diagnosis, and (4) limitations in ICU care (*eg*, no vasopressors) at eligibility.

Primary Outcome and Exposure Variables

The primary outcome was in-hospital mortality. The primary exposure variable was pulmonary vs nonpulmonary source of sepsis, with this classification prospectively obtained based on ICU physician documentation in the medical record. Patients with aspiration (without accompanying signs of pulmonary sepsis) as their primary ALI risk factor were not included in this cohort because chemical pneumonitis, without infection, can cause ALI,[13] and this cohort exclusively focused on sepsis-induced ALI. Any uncertainty in classification of the primary exposure variable was addressed by an ICU investigator at each study site based on review of the medical record and discussion with the treating ICU physicians.

Patient Demographic and Clinical Exposure Variables

Patient-related exposures of interest (independent variables) included the following: (1) patients demographics, (2) comorbid conditions (Charlson comorbidity index14), and (3) several measures of severity of illness: acute physiology and chronic health evaluation (APACHE) II15 at ICU admission, lung injury severity at onset of ALI (lung injury score, 16,17 calculated as an aggregate score from the number of affected quadrants on the chest radiograph, positive end-expiratory pressure, and Pao_2/fraction of inspired oxygen ratio), and organ failure score at onset of ALI (sequential organ failure assessment [SOFA]18).

ICU Management Exposure Variables

Data were collected on the following variables relevant to the ICU management of ALI patients: (1) tidal volume, (2) plateau pressure, and (3) fluid balance during the first 7 days after ALI diagnosis.[16,19] Tidal volume and plateau pressure were abstracted from medical records using settings/measurements for 6:00 AM on the day after ALI onset, with tidal volume reported in milliliters per kilogram of predicted body weight (PBW) as per the ARDS Network calculations.[16] Cumulative fluid balance was calculated during the first 7 days after ALI diagnosis that patients were alive and in the ICU based on the total IV and oral intake less the total urinary, GI, dialysis, and other fluid losses as applicable.

Statistical Analysis

Continuous variables were reported as medians with interquartile ranges and categorical variables as proportions. Continuous data were analyzed using Student *t* test for variables that appeared normally distributed and the Kruskal-Wallis test for variables that did not appear normally distributed based on visual inspection of histograms. Categorical data were analyzed using χ^2 test.

Univariable analyses of exposures potentially associated with mortality were conducted using simple logistic regression. Those exposures with a univariable p value < 0.10 were then included in a multiple logistic regression model evaluating the independent association of pulmonary vs nonpulmonary sepsis on inpatient mortality. We examined the final regression model using both forwards and backwards stepwise modeling techniques retaining variables if the p value was < 0.2. We checked for collinearity of variables using variance inflation factors. The final multivariable model was checked using both Pearson's χ^2 and Hosmer-Lemeshow goodness-of-fit tests. Potentially important statistical interactions of pulmonary vs nonpulmonary sepsis with selected exposure variables were determined on an *a priori* basis and evaluated by including individual multiplicative terms in logistic regression models.

All analyses were performed using statistical software (Stata 10.0; Stata Corporation; College Station, TX). A two-sided p value < 0.05 was used to determine statistical significance. The institutional review boards of Johns Hopkins University and all participating sites approved this study.

RESULTS

Of the 394 ALI patients enrolled in the ongoing parent study, we included in this analysis all 288 patients who had sepsis-induced ALI, with 163 patients (57%) having pulmonary sepsis and 125 patients (43%) having nonpulmonary sepsis. Patients with pulmonary sepsis had lower APACHE II scores (25 vs 29, p = 0.0002), SOFA scores (8 vs 11, p < 0.0001), and higher lung injury scores (2.7 vs 2.3, p = 0.02) [Table 1]. There were no significant differences between patients with pulmonary vs nonpulmonary sepsis regarding age, gender, race, or Charlson comorbidity index score (Table 1).

ALI patients with pulmonary vs nonpulmonary sepsis received similar tidal volumes and had similar plateau pressures (Table 2). There was no difference between these groups in the proportion of patients who received lung protective ventilation according to the ARDSNet protocol (plateau pressure < 30 cm H_2O and tidal volume < 6.5 mL/kg; data not shown). ALI patients with pulmonary vs nonpulmonary sepsis had a trend toward a lower cumulative fluid balance during the first 7 days after ALI diagnosis (10 L vs 11 L, p = 0.06; Table 2).

In univariable analysis, ALI patients with pulmonary vs nonpulmonary sepsis had significantly lower in-hospital mortality (42% vs 66%, p < 0.0001). Multivariable logistic regression analysis (Table 3) demonstrated an independent association for in-hospital mortality with the following exposure variables: age (odds ratio [OR], 1.03; 95% confidence interval [CI], 1.01 to 1.06), Charlson comorbidity Index (OR, 1.15; 95% CI, 1.02 to 1.30), ICU length of stay (LOS) prior to ALI diagnosis (OR, 1.19; 95% CI, 1.01 to 1.39), APACHE II score at ICU admission (OR, 1.07; 95% CI, 1.03 to 1.12), lung injury score at ALI diagnosis (OR, 1.64; 95% CI, 1.11 to 2.43), SOFA score at ALI diagnosis (OR, 1.15; 95% CI, 1.06 to 1.26), and cumulative fluid balance in first 7 days after ALI diagnosis (OR, 1.06; 95% CI, 1.03 to 1.10). After adjustment for these variables, pulmonary vs nonpulmonary sepsis was not associated with mortality (OR, 0.72; 95% CI, 0.38 to 1.35) [Table 3]. The area under the receiver operating characteristic curve of the final model was 0.84.

DISCUSSION

In this multisite study of 288 patients with sepsis-induced ALI, a pulmonary vs nonpulmonary source of sepsis was associated with substantially lower crude in-hospital mortality (42% vs 66%). However, the source of sepsis was not independently associated with mortality after adjusting for differences in demographic, clinical, and ICU-management factors of patients with pulmonary vs nonpulmonary sepsis. Specifically, patients with pulmonary sepsis had a lower severity of illness that contributed to their decreased inpatient mortality.

There are few studies examining the independent effect of the source of sepsis on mortality in patients with sepsis-induced ALI. Zilberberg and Epstein[20] studied 107 consecutive ALI patients admitted to a single medical ICU and reported that both sepsis and pneumonia were univariable predictors of inhospital mortality; however, in their adjusted analysis, sepsis but not pneumonia was a significant predictor. These authors,[20] however, used a different classification system for their primary exposure, with some pneumonia patients classified as sepsis if they meet three for four systemic inflammatory response syndrome criteria, thus making comparison with our results difficult. In contrast, Agarwal and colleagues[7] did not find a difference in mortality between pulmonary vs extrapulmonary causes of ALI in their study of 180 patients in a single respiratory ICU in India and in their related metaanalysis.[8] In each publication, Agarwal and colleagues included both infectious and noninfectious causes of ALI in their analysis. In our study, we solely examined patients with ALI caused by infection in order to minimize the known effects of different ALI risk factors on patient mortality. Our findings that a pulmonary vs nonpulmonary site of sepsis was not independently associated with in-hospital mortality reinforce those of Agarwal and colleagues.[7,8]

Patients with pulmonary vs nonpulmonary sepsis-induced ALI received similar tidal volumes and had similar plateau pressures on the first day after ALI onset. The mean tidal volumes were higher than the recommended 6 mL/kg PBW, but are lower than reported in prior studies.[21, 22] Patients with pulmonary sepsis had a trend toward a lower positive fluid balance in the first 7 days after ALI diagnosis. This may be noteworthy in the context of a randomized trial[19] that demonstrated that a conservative fluid strategy was associated with increased ventilator-free days but no difference in short-term mortality. However, the 7-day fluid balances in our patients

(data primarily collected from prior to publication of the trial) are even greater than the liberal fluid-strategy arm of this trial.

Our study has several potential limitations. First, as an observational study, we cannot prove causality of the effects found. We have, however, adjusted for known risk factors that have been demonstrated in other studies to be associated with in-hospital mortality for ICU patients, and have checked the multivariable model for goodness of fit. In addition, we limited our study population to patients with sepsis-induced ALI, reducing potential confounding from other causes of ALI. Second, since participants were recruited exclusively from teaching hospitals in a single city, the results may not be generalizable. However, the population did include patients from a total of 12 ICUs, including medical, surgical, and trauma units, to provide a broad spectrum of patients.

In addition, we cannot rule out the possibility of misclassification bias in the diagnosis of ALI and in our primary exposure variable of pulmonary vs nonpulmonary sepsis because both ALI and sepsis are syndromes diagnosed by consensus criteria.[12,23] However, clinicians and investigators at all study sites have experience with treating and enrolling patients in clinical trials for sepsis and ALI. Nonetheless, misclassification bias may remain.[24] If true, this bias may be nondifferential and attenuate our results toward the null hypothesis, potentially obscuring a true difference in mortality between the pulmonary and nonpulmonary sepsis groups. Given that our results are consistent with prior research,[7,8] there is additional external evidence supporting the validity of our results.

Finally, if effective treatment(s) was specifically tailored, or preferentially provided (intentionally or unintentionally) to patients with either pulmonary or nonpulmonary sepsis, this could obscure a potential difference in in-hospital mortality. However, we evaluated tidal volume and fluid balance, two important ICU therapies for ALI patients, and found little statistically or clinically significant differences between these two groups, hence minimizing this concern.

In conclusion, our study demonstrates that ALI patients with pulmonary vs nonpulmonary sepsis have lower crude mortality rates, but after adjustment for measures of severity of illness, pulmonary vs nonpulmonary source of sepsis is not associated with in-hospital mortality. Our findings, in conjunction with a prior study,[9] suggest that treatment of sepsis-induced ALI should be tailored to the overall syndrome (*ie*, sepsis), rather than the site of infection. Future trials of ALI and sepsis should ensure balance between treatment groups with regard to severity of illness or perform analyses to adjust the findings for such potential imbalances. Further research is necessary to determine whether specific treatment strategies directed at the site of infection may lead to clinical benefit in patients with sepsis-induced ALI.

Acknowledgments

Abbreviations

ALI	acute lung injury
APACHE	acute physiology and chronic health evaluation
CI	confidence interval
LOS	length of stay

OR	odds ratio
PBW	predicted body weight
SOFA	sequential organ failure assessment

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Table 1

Patient Demographics, Clinical Characteristics, and In-Hospital Mortality[*]

Variables	Pulmonary Sepsis (n = 163)	Nonpulmonary Sepsis (n = 125)	P Value[†]
Age, yr	51 (41, 61)	55 (46, 64)	0.06
Female gender	47	46	0.78
Race			
Black	44	39	0.12
White	55	56	
Other	1	5	
Charlson comorbidity index	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	0.61
APACHE II score at ICU admission	25 (19, 33)	29 (24, 36)	0.0002
Lung injury score at ALI diagnosis	2.7 (2.0, 3.3)	2.3 (2.0, 3.0)	0.02
ICU LOS prior to ALI diagnosis	0 (0, 2)	1 (0, 2)	0.02
Hospital LOS prior to ALI diagnosis	2 (1, 5)	2 (1, 5)	0.20
SOFA score at ALI diagnosis	8.0 (5, 11)	11 (9, 15)	< 0.0001
In-hospital mortality	42	66	< 0.0001

[*] Data are presented as median (interquartile range) or %.

[†] Calculated using Student t test for continuous data that appeared normally distributed, the Kruskal-Wallis test for variables that did not appear normally distributed, and the χ^2 test for categorical data.

Table 2

Ventilation and Fluid Parameters in IC[*]

Parameters	Pulmonary Sepsis	Nonpulmonary Sepsis	p Value[†]
Tidal volume, mL/kg PBW[‡]	6.7 (5.9, 8.0); n = 155	7.3 (6.1, 8.2); n = 106	0.16
Plateau pressure, cm H_2O[§]	24 (21, 31); n = 89	26 (21, 30); n = 65	0.93
Cumulative fluid balance during first 7 d after ALI onset, L[∥]	10 (4.0, 16); n = 163	11 (4.3, 20); n = 125	0.06

[*] Continuous variables are presented as median (interquartile range).

[†] Calculated using Student *t* test for continuous data that appeared normally distributed, and the Kruskal-Wallis test for variables that did not appear normally distributed.

[‡] Measured at 6:00 AM on day 1 after ALI onset.[16] The smaller sample size reflects patients receiving high-frequency oscillatory ventilation airway pressure release ventilation, patients who died, or patients were extubated prior to this data point (n = 6, 12, 8, and 1, respectively).

[§] Recorded from value measured closest to 6:00 AM on day 1 after ALI onset. One participating hospital did not routinely document plateau pressures in the medical record, resulting in a smaller sample size for this parameter.

[∥] From the National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Networks.[19]

Table 3

Exposures Associated With In-Hospital Mortality in 288 Patients With Sepsis-Induced AL

Exposures	Univariable*		Multivariable*	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age, yr	1.03 (1.02–1.05)	< 0.0001	1.03 (1.01–1.06)	0.002
Charlson comorbidity index	1.13 (1.03–1.25)	0.01	1.15 (1.02–1.30)	0.02
ICU LOS prior to ALI diagnosis	1.11 (0.98–1.25)	0.08	1.19 (1.01–1.39)	0.04
APACHE II score at ICU admission	1.09 (1.06–1.13)	< 0.0001	1.07 (1.03–1.12)	0.001
Lung injury score at ALI diagnosis	1.37 (1.02–1.86)	0.037	1.64 (1.11–2.43)	0.01
SOFA score at ALI diagnosis	1.28 (1.19–1.37)	< 0.0001	1.15 (1.06–1.26)	0.001
Cumulative fluid balance in first 7 d after ALI diagnosis	1.06 (1.03–1.09)	< 0.0001	1.06 (1.03–1.10)	< 0.001
Pulmonary vs nonpulmonary sepsis	0.34 (0.23–0.61)	< 0.0001	0.72 (0.38–1.35)	0.31

*
Calculated using logistic regression analysis. The OR indicates the increased odds of in-hospital mortality for a 1-U increase in each continuous exposure variable or for pulmonary vs nonpulmonary sepsis for this binary exposure variable.