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Identification of Early Acute Lung Injury at Initial Evaluation in an Acute Care Setting Prior to the Onset of Respiratory Failure*

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Abstract

Background—Despite being a focus of intensive investigation, acute lung injury (ALI) remains a major cause of morbidity and mortality. However, the current consensus definition impedes identification of patients with ALI before they require mechanical ventilation. To establish a definition of early ALI (EALI), we carried out a prospective cohort study to identify clinical predictors of progression to ALI.

Methods—Potential cases of EALI were identified by daily screening of chest radiographs (CXRs) for all adult emergency department and new medicine service admissions at Stanford University Hospital.

Results—Of 1,935 screened patients with abnormal CXRs, we enrolled 100 patients admitted with bilateral opacities present < 7 days and not due exclusively to left atrial hypertension. A total of 33 of these 100 patients progressed to ALI requiring mechanical ventilation during their hospitalization. Progression to ALI was associated with immunosuppression, the modified Rapid Emergency Medicine Score, airspace opacities beyond the bases, systemic inflammatory response syndrome, and the initial oxygen requirement (> 2 L/min). On multivariate analysis, only an initial oxygen requirement > 2 L/min predicted progression to ALI (odds ratio, 8.1; 95% confidence interval, 2.7 to 24.5). A clinical diagnosis of EALI, defined by hospital admission with bilateral opacities on CXR not exclusively due to left atrial hypertension and an initial oxygen requirement of > 2 L/min, was 73% sensitive and 79% specific for progression to ALI.

Conclusions—A new clinical definition of EALI may have value in identifying patients with ALI early in their disease course.

Keywords

acute lung injury; ARDS; diagnosis; multivariate analysis; prognosis; sensitivity; specificity

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The American-European Consensus Conference (AECC) defines acute lung injury (ALI) as acute respiratory failure with bilateral pulmonary infiltrates and a P_{aO_2} /fraction of inspired oxygen (F_{iO_2}) ratio of < 300 in the absence of left atrial hypertension.¹ Accurate measurement of the P_{aO_2}/F_{iO_2} ratio requires a known fraction of inspired oxygen and thus, in clinical practice, usually occurs only in mechanically ventilated patients. Multicenter clinical trials^{2–15} in ALI have focused on intubated patients, and a recent study¹⁶ of the incidence and outcomes of ALI only included patients receiving mechanical ventilation via an endotracheal tube or face mask.

Despite extensive investigation over the past 15 years, a lung-protective strategy of mechanical ventilation remains the only disease-specific therapy shown to improve survival.² Numerous pharmacologic treatments have demonstrated promising results in early-phase clinical trials but have failed to improve survival in multicenter trials.^{17,18} Although limiting the diagnosis of ALI to patients receiving mechanical ventilation helps standardize patients for epidemiologic purposes, it limits insight into a potentially treatable phase of ALI prior to overt respiratory failure. Following the paradigm of early goal-directed therapy for severe sepsis,¹⁹ clinical benefit may derive from identifying patients and initiating treatment prior to the need for positive-pressure ventilation (and therefore prior to meeting current study entry criteria).

Therefore, we carried out a prospective cohort study to establish a clinical definition of early ALI (EALI) using clinical characteristics at initial assessment in an acute care setting.

MATERIALS AND METHODS

Study Population

Study physicians performed daily screening of all chest radiograph (CXR) reports for adult emergency department and medicine service admissions at Stanford University hospital. A qualifying CXR was defined as bilateral opacities (including interstitial opacities consistent with pulmonary edema, more equivocal findings of basilar opacities consistent with either atelectasis or consolidation, and/or effusions with possible adjacent consolidation) present for < 7 days. Patients admitted to the hospital with an abnormal CXR not meeting criteria (ie, unilateral abnormalities) were enrolled if they had a subsequent qualifying CRX within 72 h of the initial one. Other inclusion criteria were age ≥ 18 years and hospital admission.

Exclusion criteria were endotracheal intubation prior to leaving the emergency department, evidence of left atrial hypertension (pulmonary capillary wedge pressure > 18 or a right atrial pressure > 14 mm Hg, echocardiographic evidence of left ventricular dysfunction; N-terminal pro-B-type natriuretic peptide > 400 pg/mL; or criteria for acute coronary syndrome²⁰); severe chronic lung or neuromuscular disease with respiratory failure as defined by the National Heart, Lung, and Blood Institute ARDS Network;⁵ pregnancy; and patient/family refusal of invasive or noninvasive mechanical ventilation (do not intubate [DNI] status).

Because up to 30% of patients with ALI may have concomitant volume overload,⁵ patients with suspected left atrial hypertension (by the criteria just listed) were eligible if they had these admission diagnoses: pneumonia (defined by focal airspace opacities on CXR or purulent sputum and an abnormal temperature [$< 36^\circ\text{C}$ or $> 38^\circ\text{C}$] or WBC count $> 12,000$, $< 4,000$, or $> 10\%$ bands) or sepsis (defined by criteria for the systemic inflammatory response syndrome [SIRS]²¹ and a known infectious etiology. Additional details about our inclusion and exclusion criteria are available in the online supplement. The internal review board at Stanford University Medical Center approved the study with a waiver of consent for collection of the available clinical data analyzed in this study.

Data Collection

Demographic characteristics, comorbidities, admission diagnosis, physiologic data (defined in online supplement), and the modified Rapid Emergency Medicine Score (modified REMS = REMS – oxygen saturation component of score)²² were collected at time of enrollment. The REMS is an acute physiology score validated from variables available in the emergency department (online supplement). We excluded the room air saturation component of the score because it was often missing in hypoxemic patients and due to concern for collinearity with use of the full REMS score in addition to the initial oxygen requirement in our multivariable models. CXRs were classified descriptively by the primary author as: (1) bibasilar opacities only, (2) bilateral airspace opacities beyond the lung bases, or (3) predominantly interstitial opacities. Subjects were followed until hospital discharge for the primary outcome of progression to ALI (defined by AECC criteria while receiving mechanical ventilation through an endotracheal tube or face mask).

Statistical Analysis

Categorical variables were analyzed by χ^2 and Fisher exact tests. Continuous variables were analyzed by t tests for normally distributed data (mean $\pm$ SD) and Wilcoxon rank sum tests for nonnormally distributed data (median and interquartile range [IQR]). All variables significantly associated ($p < 0.05$) with progression to ALI on bivariate analysis were entered into a multivariate logistic regression model. Oxygen requirement (to maintain a saturation $\geq 90\%$) was analyzed as both a dichotomous (≤ 2 vs > 2 L/min nasal cannula) and multilevel categorical variable (no oxygen; ≤ 2 , > 2 to 6, and > 6 L/min nasal cannula or by face mask).

RESULTS

Baseline Characteristics

In 295 days of screening, we reviewed 11,213 CXRs. Of 1,935 patients with abnormal CXR findings, 100 were admitted to the hospital with bilateral opacities not due exclusively to left atrial hypertension. Of these, 33 progressed to ALI (Fig 1). Table 1 shows baseline characteristics. Pneumonia (including aspiration) and nonpulmonary infections were the predominant diagnoses. Baseline immunosuppression and direct admission from the emergency department to the ICUs were more common among patients progressing to ALI.

Table 2 shows baseline physiologic characteristics. Higher initial oxygen requirement, higher modified REMS score, SIRS, and a CXR with airspace opacities beyond the bases were associated with progression to ALI. Severe sepsis was uncommon, with a trend toward increased prevalence among patients progressing to ALI (25% vs 4%, respectively; $p = 0.06$). There were no differences in initial respiratory rate, rates of an abnormal temperature or WBC count, or concomitant volume overload.

Multivariate Predictors of Progression to ALI

In multivariate analysis (Table 3), an initial oxygen requirement > 2 L/min was an independent predictor of progression to ALI (odds ratio [OR], 8.1; 95% CI, 2.7 to 24.5; $p = 0.0002$). The sensitivity and specificity of an initial oxygen requirement > 2 L/min for identifying progression to ALI were 73% and 79%, respectively, with an area under the receiver operating characteristic curve (AUC) of 0.76. With an ALI prevalence of 33%, the positive and negative predictive values of this finding were 63% and 85%, respectively.

In addition, the modified REMS (OR, 1.2; 95% CI, 1.0 to 1.4; $p = 0.07$) and immunosuppression (OR, 2.6; 95% CI, 0.9 to 7.4; $p = 0.07$) were associated with progression to ALI with borderline statistical significance. The AUC of a model including these variables and an initial oxygen requirement > 2 L/min was 0.82.

Table 4 shows the AUC, sensitivity, specificity, and positive and negative predictive values for progression to ALI of different definitions of EALI. By increasing the initial oxygen requirement cutoff to > 6 L/min, specificity improved to 93%, but sensitivity was only 48%. Similarly, adding a modified REMS ≥ 8 or immunosuppression to an oxygen requirement > 2 L/min increased specificity but at substantial cost to sensitivity.

Outcomes

Table 5 shows the outcomes of patients' hospital admissions. Median time to progression to ALI was 22 h (IQR, 10 to 43 h). Nine patients (27%) progressed within 12 h, and 17 (52%) patients progressed within 24 h of their qualifying chest radiograph (Fig 2). Five patients (15%) progressed beyond 72 h. Of these, only two had evidence of a secondary precipitating event. The other three patients had a slow but steady decline toward respiratory failure. When we excluded these five patients in a sensitivity analysis, predictors of progression to ALI and the size of their effects were similar (data available from authors).

Patients progressing to ALI had significantly more organ dysfunction on day 2, as defined by Brussels criteria²³ (Table 5). All patients progressing to ALI required ICU admission, and 48% and 70% received mechanical ventilation through a face mask and/or endotracheal tube, respectively. Among nonprogressors, 16% required ICU admission, and 2 patients (3%) received face mask ventilation (none was intubated). The in-hospital mortality rate was 48% among patients who progressed to ALI compared with no deaths among nonprogressors ($p < 0.0001$); similarly, hospital length of stay was longer, and only 17% of progressors to ALI were discharged home compared with 88% of nonprogressors ($p < 0.0001$).

DISCUSSION

We conducted a prospective cohort study to test whether patients at risk for progressing to ALI could be identified on initial evaluation in an acute care setting. A clinical syndrome of EALI defined by the following: (1) hospital admission with bilateral opacities on CXR, (2) the absence of isolated left atrial hypertension, and (3) the need for > 2 L/min of supplemental oxygen identified patients progressing to ALI with a sensitivity of 73% and a specificity of 79%.

Other authors have identified risk factors for developing ALI or ARDS. Hudson et al²⁷ prospectively evaluated 695 ICU patients at risk for development of ARDS. The presence of one or more of seven clinical risk factors (sepsis, aspiration, trauma, etc.) was 79% sensitive and 26% specific for developing ARDS. Sepsis (43%), massive transfusion (40%) and multiple trauma (25%) carried the greatest risk of developing ARDS. Increasing age, acute physiology and chronic health evaluation (APACHE) II score, and Injury Severity Score were also associated with an increased incidence of ARDS. Previously, Fowler et al²⁸ found pneumonia (12%), aspiration (36%), and disseminated intravascular coagulation (22%) were the strongest predictors, but the overall incidence of ALI was only 6.8%.

Also, some studies of ALI have included nonmechanically ventilated patients. Ferguson et al prospectively followed 815 ward and ICU patients with at least one predefined risk factor for ALI.²⁴ Fifty-three patients (6.5%) developed ALI. Of 23 ALI patients initially admitted to a ward, 15 (of whom 4 died) were never admitted to an ICU. In a pediatric study of ALI, 85 of 328 children were not intubated at the time of diagnosis; 39 eventually required intubation and mechanical ventilation.²⁵ A second pediatric study²⁶ retrospectively identified emergency department patients with acute hypoxic respiratory failure defined as a Pao_2/Fio_2 ratio < 300 (using a Pao_2 calculated from recorded saturations and charted Fio_2). However, only 5% of these patients were intubated during the follow-up period. Although these studies established risk factors for developing ALI or included nonmechanically ventilated patients in their

definition of ALI, no studies have prospectively identified clinical criteria that define an early phase of lung injury and reliably predict progression to ALI and the need for mechanical ventilation.²⁹

In establishing a clinical definition of EALI, we attempted to preserve the principal components of the AECC criteria for ALI minus mechanical ventilation and the need to calculate a P_{aO_2}/F_{iO_2} ratio. We used an intentionally broader definition of a qualifying CXR (including minimal bibasilar opacities, effusions with associated consolidation, and interstitial opacities) to be as sensitive as possible and to maximize lead time to progression to ALI. Rice et al³⁰ established criteria for ALI based on an oxygen saturation to F_{iO_2} ratio, obviating the need for arterial blood gas sampling. However, accurate estimation of the F_{iO_2} remains problematic in patients breathing in a nonclosed system (ie, not via a tight-fitting face mask or endotracheal tube). We chose to avoid establishing a direct corollary to a P_{aO_2}/F_{iO_2} ratio < 300 and instead classified the degree of oxygenation impairment by the level of supplemental oxygen required to maintain an oxygen saturation > 90%. *A priori*, we selected oxygen flow rates of ≤ 2 , > 2 to 6, and > 6 L/min via nasal cannula (or face mask) because in clinical practice many patients with little or no oxygen requirement are treated with 2 L/min, and patients who require > 6 L/min are often transitioned to a face mask. Interpreting differences between 10 L by nonrebreather mask vs 50% by Venturi mask is not likely to be informative. Defined in this way, the initial oxygen requirement strongly predicted progression to ALI. Using a simple cutoff of > 2 L/min retained most of the predictive value (AUC, 0.76; all categories, 0.79). We suspect this level of oxygen requirement is particularly useful because it reflects a sufficient oxygenation impairment to exclude subjects with CXR abnormalities due to atelectasis or hypoventilation but retains sensitivity for mild early lung injury.

The ideal sensitivity and specificity of a definition of EALI for identifying prospective cases of ALI may change depending on the application. One might prefer a highly sensitive definition as entry criteria for a trial of a low-risk therapy such as aerosolized β agonists or statins. For a high-risk or expensive therapy such as the recently completed clinical trial of activated protein C,⁶ a more specific definition would be preferable. Increasing the initial oxygen requirement to > 6 L/min in our definition of EALI increased specificity to 93% and the positive predictive value to 76%. In Table 4 we present other potential definitions with varying sensitivity and specificity.

Although our sample size is modest, our model is not likely to be overfitted because only one variable was statistically significant. A type II error is possible. However, with > 30 patients progressing to ALI, we had sufficient power to detect significance of at least three independent variables. Because we aimed to develop the best predictive model or definition of early ALI (rather than test specific hypotheses about the predictive value of individual variables), some of our analyses were not planned in advance. Also, our study was conducted at a single university teaching hospital, potentially limiting its generalizability. However, tertiary referral center bias should be minimized by primarily enrolling patients through the emergency department. Nevertheless, prospective validation in an independent multicenter cohort is needed before we can advocate widespread adoption of this definition of EALI. Finally, despite designing our study to identify ALI on initial assessment, the median time of progression to ALI was < 24 h. Ferguson et al found a similarly rapid progression to ALI among patients with a pulmonary risk factor (median, 0 days; IQR, 0 to 2).²⁴ However, 73% and 48%, respectively, of patients in our study progressed beyond 12 and 24 h of their qualifying CXR, which may provide opportunity for treatment in many patients.

Our study is strengthened by our prospective design and the finding that a simple and readily available clinical definition of EALI identified patients at risk for progression to ALI with good accuracy (positive and negative predictive values of 63% and 85%, respectively). Furthermore,

this definition of EALI identified patients at high risk for poor clinical outcomes; 48% of patients progressing to ALI died, and only 18% were discharged directly to home. This mortality rate is higher than the overall mortality rate reported by Rubenfeld et al.¹⁶ However, a majority of our ALI cohort had pneumonia (including aspiration) and, given our small sample size, our mortality rate (48%; 95% CI, 33 to 66%) is similar to that reported by Rubenfeld et al.¹⁶ among patients with pneumonia (41%; 95% CI, 35 to 46%) and aspiration (44%; 95% CI, 32 to 55%). We believe that patients with EALI may be at sufficient risk to warrant enrollment in future clinical trials. Also, identifying patients at high risk for progression to ALI not identified by other physiologic variables may have important implications for triage. In our cohort, 70% of patients progressing to ALI were admitted to a ward service prior to transfer to an ICU. Finally, more accurate risk stratification for developing ALI may require addition of plasma biomarker profiles^{31–36} to a patient's clinical indexes. We have defined a cohort of patients in which to study the predictive value of plasma biomarkers.

CONCLUSIONS

In summary, we prospectively identified clinical criteria for EALI, including hospital admission with bilateral infiltrates on CXR and an initial oxygen requirement of > 2 L/min in the absence of isolated left atrial hypertension. In our cohort, these criteria identified patients progressing to ALI with 73% sensitivity and 79% specificity. To our knowledge, this is the first study to establish a definition of the early phase of ALI prior to progression to respiratory failure. Following further validation, application of this definition could identify a cohort of patients at sufficient risk for progression to ALI to warrant inclusion in future clinical trials of novel therapies.

Abbreviations

AECC, American-European Consensus Conference
 ALI, acute lung injury
 APACHE, acute physiology and chronic health evaluation
 AUC, area under receiver operator characteristic curve
 CI, confidence interval
 CXR, chest radiograph
 DNI, do not intubate
 EALI, early acute lung injury
 F_{iO_2} , fraction of inspired oxygen
 IQR, interquartile range
 OR, odds ratio
 REMS, Rapid Emergency Medicine Score
 SIRS, systemic inflammatory response syndrome

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Figure 1.
Flow diagram of patient selection and progression to ALI. ER = emergency department.

Figure 2.
Time of progression from qualifying CXR to ALI.

Table 1

Baseline Characteristics*

Characteristics	No ALI (n = 67)	ALI (n = 33)	p Value
Age, yr	61 ± 18	63 ± 18	0.83
Male gender	37 (55)	16 (48)	0.53
Hispanic	9 (13)	3 (9)	0.75
Race			0.22
White	57 (85)	25 (76)	
African American	3 (4)	3 (9)	
Asian	4 (6)	5 (15)	
Hawaiian/PI	3 (4)	0	
Comorbidities			
Cardiac	13 (19)	8 (24)	0.58
COPD	5 (7)	2 (6)	1.0
Diabetes	13 (19)	7 (21)	0.83
CRI	5 (7)	5 (15)	0.23
Immunosuppression	21 (31)	18 (55)	0.03
DNI	5 (7)	5 (15)	0.23
Diagnosis			0.84
Pneumonia	37 (55)	20 (61)	
Nonpulmonary infection	14 (21)	7 (21)	
Trauma	6 (9)	1 (3)	
Idiopathic	1 (1)	1 (3)	
Other	9 (13)	4 (12)	
Hospital admission source			
Direct admission	7 (10)	2 (6)	0.71
Outside hospital	5 (7)	4 (12)	0.47
ED	55 (82)	27 (82)	0.97
ED to ICU	6 (9)	10 (30)	0.006

* Values are given as the mean ± SD or No. (%) unless specified otherwise. Cardiac = history of nonsinus arrhythmia, coronary artery disease, or congestive heart failure; ED = emergency department; CRI = chronic renal insufficiency (baseline creatinine > 1.5); diabetes = therapy with insulin or oral hypoglycemic; ED to ICU = direct admission from emergency department to ICU; immunosuppression = as defined by APACHE II score; PI = Pacific Islander.

Table 2**Baseline Physiologic Characteristics***

Characteristics	No ALI (n = 67)	ALI (n = 33)	p Value
Initial oxygen requirement			< 0.001
Room air	31 (46)	6 (18)	
≤ 2 L/min O ₂	22 (33)	3 (9)	
> 2–6 L/min O ₂	9 (13)	8 (24)	
> 6 L/min O ₂	5 (7)	16 (48)	
SIRS	46 (69)	29 (88)	0.04
Severe sepsis	3 (4)	6 (18)	0.06
Modified REMS	6.6 ± 3.3	8.6 ± 3.8	0.008
Initial respiratory rate, breaths/min	22 ± 6	25 ± 7	0.10
Abnormal temperature [†]	21 (31)	9 (27)	0.68
Abnormal WBC count [‡]	30 (45)	18 (55)	0.36
Volume overload	3 (4)	3 (9)	0.39
CXR appearance			
Bibasilar only	25 (37)	6 (18)	
Airspace opacities beyond bases	30 (45)	22 (67)	0.04 [§]
Interstitial	12 (18)	5 (15)	
Positive cultures			
Blood	12 (18)	7 (21)	0.69
Sputum	4 (6)	5 (15)	0.13
Urine	7 (10)	4 (12)	0.72
Any	20 (30)	13 (39)	0.34

* Values are given as No. (%) or mean ± SD, unless specified otherwise.

[†] Temperature < 36°C or > 38°C.

[‡] WBC count < 4,000 or > 12,000.

[§] χ^2 for airspace opacities beyond bases vs other two categories.

Table 3
Multivariate Analysis of Risk Factors for Progression to ALI

Risk Factor	OR	95% CI	p Value
> 2 L/min supplemental O ₂	8.1	2.7–24.5	0.0002
Modified REMS (per 1 pt inc.)	1.2	1.0–1.4	0.07
Immunosuppression	2.6	0.9–7.4	0.07
Airspace opacity beyond bases	1.3	0.4–3.8	0.68
SIRS	0.9	0.2–4.0	0.88

Table 4
Predictive Value for Progression to ALI of Different Definitions of EALI*

EALI Definition	AUC	SENS	SPEC	PPV	NPV	Pos LR	Neg LR
> 2 L/min supplemental O ₂	0.759	73%	79%	63%	85%	3.5	0.34
> 6 L/min supplemental O ₂	0.705	48%	93%	76%	78%	7.4	0.56
> 2 L/min supplemental O ₂ and modified REMS ≥ 8	0.735	55%	93%	78%	81%	7.9	0.48
> 2 L/min supplemental O ₂ and immunosuppression	0.637	36%	91%	67%	74%	4.0	0.70

* EALI definition includes (1) hospital admission with bilateral opacities on CXR, (2) absence of clinical evidence of isolated left atrial hypertension, and (3) the above specified additional criteria. NPV = negative predictive value; Pos and Neg LR = positive and negative likelihood ratio; PPV = positive predictive value; SENS = sensitivity; SPEC = specificity.

Table 5**Outcomes of Hospital Admission***

Outcomes	No ALI (n = 67)	ALI (n = 33)	p Value
Time to ALI, h	NA	22 (10–43)	
ICU admission	11 (16)	33 (100)	< 0.0001
Mechanical ventilation [†]			
Mask	2 (3)	16 (48)	< 0.0001
Intubation	0	24 (73)	< 0.0001
Brussels Organ Failure (day 2)			
Cardiac	0	8 (24)	< 0.0001
Coagulation	10 (15)	11 (33)	0.03
Renal	8 (12)	8 (24)	0.11
Hepatic	7 (10)	5 (15)	0.52
Any	20 (30)	20 (60)	0.003
Length of stay, d	5 (3–10)	15 (6–26)	< 0.0001
Disposition			< 0.0001
Home	57 (85)	6 (18)	< 0.0001
Died	0	16 (48)	< 0.0001
Skilled nursing	10 (15)	8 (24)	
Other acute care	0	2 (6)	

* Values are given as median (IQR) or No. (%) unless specified otherwise. NA = not applicable.

[†] Categories not exclusive.