Determining the Etiology of Pulmonary Edema by the Edema Fluid-to-Plasma Protein Ratio

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Abstract

Question: We hypothesized that the edema fluid-to-plasma protein (EF/PL) ratio, a non-invasive measure of alveolar capillary membrane permeability, can accurately determine the etiology of acute pulmonary edema.

Methods: 390 mechanically ventilated patients with acute pulmonary edema were enrolled. A clinical diagnosis of acute lung injury (ALI), cardiogenic pulmonary edema, or a mixed etiology was based on expert medical record review at the end of hospitalization. The EF/PL ratio was measured from pulmonary edema fluid and plasma samples collected at intubation.

Results: 209 patients had a clinical diagnosis of ALI, 147 had a diagnosis of cardiogenic pulmonary edema and 34 had a mixed etiology. The EF/PL ratio had an area under the receiver-operating curve of 0.84 for differentiating ALI from cardiogenic pulmonary edema. Using a predefined cutoff of 0.65, the EF/PL ratio had a sensitivity of 81% and a specificity of 81% for the diagnosis of ALI. An EF/PL ratio ≥ 0.65 was also associated with significantly higher mortality and fewer ventilator free days.

Conclusions: Non-invasive measurement of the EF/PL ratio is a safe and reliable bedside method for rapidly determining the etiology of acute pulmonary edema that can be used at the bedside in both developed and developing countries.

Keywords
acute pulmonary edema, acute lung injury, acute respiratory distress syndrome, alveolar capillary membrane permeability, diagnosis
INTRODUCTION

Acute pulmonary edema may be due either to increased permeability of the alveolar capillary barrier, in the case of acute lung injury (ALI),(1-3) or to increased pulmonary microvascular hydrostatic pressure, (4) in the case of cardiogenic pulmonary edema (CPE). Accurate determination of the etiology of acute pulmonary edema is of major clinical importance because the treatments for ALI and CPE are fundamentally different.(4, 5) The shift in the practice of clinical medicine in both academic and non-academic medical centers away from invasive measures such as the pulmonary artery catheter emphasizes the need for other approaches to determine the clinical cause of pulmonary edema.

Accurate and rapid determination of the cause of acute pulmonary edema at the bedside can be challenging. Although history, physical examination and laboratory testing are useful, the etiology of pulmonary edema remains unclear in a significant number of patients even after initial diagnostic testing is completed, (4) and clinical definitions are imperfect.(6) Echocardiography can provide information about left ventricular performance and filling pressures but is not rapidly available in many centers. The gold standard for determining the etiology of acute pulmonary edema is measurement of the pulmonary arterial occlusion pressure by pulmonary artery catheterization.(7, 8) However, pulmonary artery catheterization is invasive and has become much less common in the United States (9) with the publication of a number of studies suggesting that routine use of pulmonary artery catheterization for management of critically ill patients is associated with increased complications compared to central venous catheterization and does not improve patient outcomes.(10-12) Furthermore, a
recent large multicenter trial of pulmonary arterial catheterization found that close to one third of patients with acute lung injury had elevated pulmonary arterial wedge pressures.(12)

The pulmonary edema fluid-to-plasma protein (EF/PL) ratio is a rapid, safe, and non-invasive measure of alveolar capillary membrane permeability.(13) The EF/PL ratio can be measured inexpensively at the bedside, and thus, could be easily implemented as a diagnostic tool in both developing and developed countries. In addition, the EF/PL ratio can be measured at the onset of respiratory failure, immediately after intubation, providing critical diagnostic information long before other diagnostic test results are available. The EF/PL ratio was first proposed as a tool to determine the etiology of acute pulmonary edema in a study of 24 patients by Fein and colleagues in 1979.(14) The EF/PL ratio has subsequently been used by our research group (15-18) and other investigators (13, 19-24) as a supplement to clinical data for determination of the etiology of acute pulmonary edema. Based on both clinical and experimental evidence, we have proposed that an EF/PL ratio ≥ 0.65 is characteristic of patients with ALI whereas an EF/PL ratio < 0.65 is characteristic of patients with CPE.(17, 18, 25) However, other than the original 24 patient study by Fein and colleagues (14), the clinical utility of the EF/PL ratio for determination of the cause of acute pulmonary edema has never been validated. Validation in a larger group of patients is needed to assess the performance of this diagnostic test in a larger, more heterogeneous group of critically ill patients.

The primary goal of this study was to test the hypothesis that the EF/PL ratio, a non-invasive measure of the degree of alveolar capillary membrane permeability, can reliably differentiate the etiology of acute pulmonary edema in critically ill patients. To
further assess the clinical utility of measuring the EF/PL ratio, we also tested the
association between the EF/PL ratio and important clinical outcomes, including mortality.
METHODS

Patients. Institutional review boards at University of California San Francisco and Vanderbilt University approved the study with a waiver of informed consent. We studied 390 consecutively enrolled patients who were intubated and ventilated with positive pressure. These patients were included in a pulmonary edema fluid databank at UCSF Moffitt-Long Hospital, San Francisco General Hospital and Vanderbilt University Medical Center between 1981 and 2007. Criteria for enrollment in the databank included the acute onset of pulmonary edema and mechanical ventilation. All patients in the database who had simultaneous samples of pulmonary edema fluid and plasma were included in the current study. Some patients were included in prior reports.(16-18, 25-27)

Clinical diagnosis of the cause of pulmonary edema. The clinical etiology of acute pulmonary edema was determined by expert review of the medical record by the authors at the end of the hospitalization and was based on clinical data available at discharge including history, physical findings, laboratory testing, findings on chest radiograph, fluid balance, echocardiography, other tests of cardiac function, pulmonary artery catheterization, culture results, response to therapy, autopsy findings and impression of the treating physician. The clinical diagnosis was determined to be ALI when the standard American European Consensus Definition (28) of ALI or ARDS was met in the setting of clinical findings consistent with sepsis, pneumonia, aspiration of gastric contents, severe trauma, multiple transfusions, reperfusion injury after lung transplantation, drug overdose, drug reaction or acute pancreatitis. The clinical diagnosis was determined to be CPE when the clinical findings were consistent with acute systolic
or diastolic heart failure, acute myocardial infarction or acute volume overload. In a small subgroup of patients, the clinical findings were consistent with both ALI and CPE; this group was given a diagnosis of a mixed etiology of pulmonary edema. The expert reviewers were blinded to the EF/PL ratio.

Sample Collection for the EF/PL Ratio. Undiluted pulmonary edema fluid and simultaneous plasma samples were obtained by previously described methods.(15) In brief, pulmonary edema fluid was obtained by inserting a standard bedside suction catheter (usually 14-gauge) into the endotracheal tube and advancing the catheter into the distal airways. Gentle suction was then applied to remove 0.5 to 2.0 ml of free flowing pulmonary edema fluid that was suctioned directly into a standard suction trap. Next, a 3 ml blood sample was collected into a heparinized or EDTA-treated collection tube, usually from an existing arterial line or central venous line. Samples were centrifuged (3000 x g for 10 min), and the supernatant was stored at -70C. The total protein was measured in both the edema fluid and plasma by the Biuret method,(15) and the EF/PL ratio was calculated as the edema fluid protein concentration divided by the plasma protein concentration. The time from endotracheal intubation to aspiration of edema fluid was recorded.

Statistical Analysis. Statistical analysis was performed using statistical software (Stata/SE 9.2, College Station, TX) and means ± standard deviations or medians with interquartile ranges (IQR) are reported as appropriate. Analysis of variance with the post-hoc Tukey test was used to compare normally distributed continuous variables. For continuous variables that were not normally distributed, the Kruskall Wallis test was used with a post-hoc Bonferroni correction. Chi square analysis was used to compare
categorical variables. Receiver-operator curves were generated using the EF/PL ratio as
the predictor and the expert clinical diagnosis as the outcome. Cox proportional hazards
regression was used to evaluate the impact of the EF/PL ratio on the percent of patients
alive and free of mechanical ventilation over the first 28 days. A p value < 0.05 was
considered statistically significant.

RESULTS

Patients. There were 390 patients with simultaneous samples of pulmonary edema fluid
and plasma entered into the database over the study period. Baseline characteristics of
the patients are listed in Table 1. Among the 209 patients with a clinical diagnosis of
ALI, the most common underlying etiology was pneumonia (28%), followed by non-
pulmonary sepsis (26%), aspiration of gastric contents (17%), drug reaction or overdose
(6%), multiple transfusions (6%), or other causes (17%) including reperfusion injury after
lung transplantation, acute pancreatitis and severe trauma. Among the 147 patients with
a clinical diagnosis of CPE, the most common underlying etiology was acute myocardial
infarction/ischemia (33%), followed by volume overload/diastolic dysfunction (27%),
congestive heart failure (16%), and other causes (24%) including valvular disease,
arrhythmia, post-obstructive pulmonary edema and neurogenic pulmonary edema. The
median time from ICU admission to endotracheal intubation was 0.0 hours (IQR 0.0 –
4.25 h) in the group with a clinical diagnosis of CPE and 0.0 hours (IQR 0.0 – 11.0h) in
the group with a clinical diagnosis of ALI. There were 34 patients in whom the clinical
diagnosis determined at the end of the hospitalization was consistent with a mixed
etiology of pulmonary edema. These patients were excluded from the initial analysis of
the diagnostic performance of the EF/PL ratio to discriminate between ALI and CPE.
Comparison of EF/PL ratio to clinical diagnosis of ALI versus CPE. The diagnostic performance of the EF/PL ratio was compared to the clinical diagnosis determined at the end of the hospitalization using receiver-operator curve analysis. Compared to the clinical diagnosis based on all information available at the end of the hospitalization, the EF/PL ratio determined early in the hospital course had excellent diagnostic discrimination with an area under the curve (AUC) of 0.84 (95% CI 0.79 to 0.88) (Figure 1A). By contrast, neither the edema fluid protein level alone (AUC 0.73, 95% CI 0.67 – 0.78) or the plasma protein level alone (AUC 0.33, 95% CI 0.27 – 0.39 ) provided the same degree of diagnostic discrimination. Because the edema fluid protein level can rise over time if alveolar fluid clearance mechanisms are intact,(15, 17) we repeated the analysis restricting inclusion to the 183 patients who had pulmonary edema fluid sampled within 3 hours of endotracheal intubation. In this group, the diagnostic performance of the EF/PL ratio was similar with an AUC of 0.85 (95% CI 0.79 to 0.91) (Figure 1B).

As a sensitivity analysis, the receiver-operator curve analysis was repeated including the patients who had been classified as having a mixed etiology of pulmonary edema. Because all patients in this mixed etiology group had clinical evidence of lung injury as well as hydrostatic causes of pulmonary edema, the mixed edema patients were classified as ALI for this analysis. In the entire patient cohort (n = 390), the EF/PL ratio determined early in the hospital course continued to perform well as a diagnostic test with an AUC of 0.81 (95% CI 0.77 to 0.86) (Figure 1C). This analysis was also repeated with the sample restricted to those patients who had edema fluid sampled within 3 hours of endotracheal intubation. In this group (n = 200), the AUC was 0.81 (95% CI 0.74 to 0.87) (Figure 1D).
Using a predefined cutoff of 0.65, the sensitivity and specificity of the EF/PL ratio for diagnosing ALI among patients with acute pulmonary edema was evaluated first with exclusion of the patients with a mixed etiology of pulmonary edema. The sensitivity of the cutoff of $\text{EF/PL} \geq 0.65$ was 81% and the specificity was 81%. When only patients with EF sampled less than 3 hours after endotracheal intubation were included, the sensitivity was 85% and the specificity was 83%. We then repeated these analyses including the patients with a clinical diagnosis of a mixed etiology of acute pulmonary edema. In the entire cohort, the sensitivity was 75% and the specificity was 81%. Restricting the analysis to patients with EF sampled within 3 hours of intubation, the sensitivity was 75% and the specificity was 83%.

**Association of EF/PL ratio with clinical outcomes.** To test the clinical relevance of using the EF/PL ratio to classify the etiology of pulmonary edema, we compared outcomes in patients with EF/PL above and below the cutoff of 0.65. Major outcomes in the two groups are shown in Table 3 and Figure 2. Patients with EF/PL $\geq 0.65$ had worse clinical outcomes including mortality and number of ventilator-free days, particularly when the analysis was limited to patients in whom edema fluid was sampled less than 3 hours after intubation (Table 3).

**DISCUSSION**

The EF/PL ratio, a non-invasive measure of the degree of alveolar capillary membrane permeability, was first proposed as a clinical tool to differentiate the etiology of acute pulmonary edema by Fein and colleagues in 1979.(14) In that study, edema
fluid and plasma protein concentrations were measured in 24 patients with acute pulmonary edema. In the 20 patients with a clinical diagnosis of ALI, the EF/PL ratio was ≥ 0.65 in all but three patients. By contrast, in the 4 patients with CPE, the EF/PL ratio was < 0.65 in all patients. Although the protein level in edema fluid has subsequently been measured experimentally in animal models of both ALI and CPE and has been used to differentiate the etiology of acute pulmonary edema in a number of clinical studies, it has never been validated in a large group of patients. Validation in a larger group of patients is needed to assess the performance of this diagnostic test in a larger more heterogeneous group of critically ill patients. In the current study of 390 critically ill patients, the EF/PL ratio had excellent diagnostic discrimination between ALI and CPE and was strongly associated with different clinical outcomes, confirming that the diagnostic classification of ALI versus CPE was clinically meaningful. These findings confirm the clinical relevance of the measurement of the EF/PL ratio in a large, heterogenous group of patients with acute pulmonary edema.

Differentiation of the etiology of acute pulmonary edema is of major clinical importance since the therapeutic approaches to the two most common etiologies of acute pulmonary edema, CPE and ALI are fundamentally different. Patients with CPE require therapy to optimize cardiac function that includes therapies targeted at reduction of cardiac preload and/or afterload and optimization of myocardial performance. The underlying cause of CPE (myocardial infarction, congestive heart failure, diastolic dysfunction, acute volume overload) may have additional implications for treatment. Treatment of ALI should focus first and foremost on the search for underlying cause. A source of infection should be sought in all patients since pulmonary and non-
pulmonary sepsis are by far the most common causes of ALI. Lung protective ventilation is lifesaving and should be instituted promptly in all patients with ALI. In addition, patients who have severe sepsis as the underlying cause of lung injury may be candidates for treatment with recombinant activated protein C (drotecogin-alfa activated). In the absence of shock and tissue hypoperfusion, patients with ALI should be treated with a conservative fluid strategy.

Pulmonary edema fluid is an underutilized diagnostic specimen that is readily and safely available and requires no special equipment for collection. Although the plasma and edema fluid concentrations of protein in the current study were determined using a laboratory assay, the concentrations of protein can also be measured at the bedside after centrifugation using a handheld refractometer. Lien and colleagues reported excellent correlation ($r = 0.991$) between protein concentrations measured by refractometry and standard laboratory assay in pulmonary edema fluid and plasma. As a safe, non-invasive, bedside test for the etiology of pulmonary edema, widespread use of the EF/PL would be tremendously beneficial in facilitating rapid institution of appropriate therapy directed at the underlying cause of acute pulmonary edema, particularly in developing countries where other diagnostic tools such as pulmonary artery catheterization and echocardiography may have limited availability. The ease with which the EF/PL ratio can be measured compares favorably to the comparison of pleural fluid and plasma protein concentrations, one of the primary tools for diagnostic classification of the etiology of pleural effusion. Of note, pleural fluid protein concentrations have also been measured at the bedside using refractometry.
The primary limitation of this study is the retrospective nature of the review of the medical record for the clinical classification of the etiology of pulmonary edema, although the study analysis plan was designed prospectively before medical charts were reviewed. Medical records were reviewed at the end of the hospitalization to allow all available clinical information, including autopsy findings, to be considered in the clinical diagnosis. To avoid being biased by the EF/PL ratio, the investigators were not aware of the EF/PL ratios while doing the chart review. A second limitation is that pulmonary edema fluid was not sampled immediately after endotracheal intubation in every patient. The median time between endotracheal intubation and sampling of pulmonary edema fluid was 2.5 hours. Delays in collection of edema fluid can lead to elevated EF/PL ratios in patients who have intact alveolar fluid clearance mechanisms. Over time, water and solute is absorbed faster than protein, thereby concentrating the protein within the alveolar space. Thus, delays in sampling of pulmonary edema fluid could lead to misclassification of patients. For example, a patient with pure hydrostatic pulmonary edema could be classified erroneously as a mixed etiology. This is the likely explanation for the slightly better diagnostic performance of the EF/PL ratio when the analysis was restricted to the group of patients with edema fluid sampled within 3 hours of endotracheal intubation. A third potential limitation is that patients were not protocolized to different diagnostic strategies in a way that would assess the relative value of the EF/PL ratio compared to other diagnostic modalities. Although some prior reports have assessed the contribution of individual diagnostic tests such as the chest radiograph or plasma N-terminal BNP, no prior studies have systematically assessed the specific contribution of all the available diagnostic tests in a time-dependent analysis in patients.
with acute pulmonary edema. We believe that the current study has face validity and practical value because the results demonstrate the value of a non-invasive test that can be done rapidly, similar to the widely accepted diagnostic classification of pleural effusions as transudates or exudates based on pleural fluid and plasma protein concentrations, a classification that is used to guide further diagnostic tests and therapy for pleural effusions.

Although exact estimates of the global incidence of acute pulmonary edema are not available, data from the World Health Organization’s Global Burden of Disease Study consistently place ischemic heart disease, a common cause of CPE, and lower respiratory infections, a common cause of ALI, in the top five causes of death worldwide both in the original study (38) and in projections out to the year 2030.(39) In this study and others, both ALI and acute CPE are associated with high rates of morbidity and mortality, highlighting the need for prompt recognition and institution of appropriate therapy. Our findings indicate that the EF/PL ratio can be used to determine the etiology of acute pulmonary edema. The rapid, safe, non-invasive nature of this diagnostic test renders it highly appealing for routine use in both developed and developing countries. Since the accepted treatment strategies for cardiogenic and noncardiogenic pulmonary edema are different,(4, 5) rapid non-invasive determination of the cause of pulmonary edema can direct the clinician to the correct therapies, an especially important objective in critically ill, ventilated patients with acute pulmonary edema. Because the EF/PL ratio can be measured at the onset of respiratory failure, immediately after intubation, it can provide this critical diagnostic information, long before other diagnostic test results are available. Future studies could test the contributions of the different diagnostic tests for
distinguishing cardiogenic and non-cardiogenic pulmonary edema, including the electrocardiogram, the portable chest radiograph, the plasma levels of troponin and BNP, and the EF/PL ratio in ventilated patients with acute pulmonary edema.

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34. Light RW. Falsely high refractometric readings for the specific gravity of pleural fluid. *Chest* 1979;76(3):300-1.


Table 1. Clinical characteristics of 390 patients with acute pulmonary edema classified by clinical diagnosis based on expert review of the medical record at the end of the hospitalization

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>Acute Lung Injury</th>
<th>Cardiogenic Pulmonary Edema</th>
<th>Mixed Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>209</td>
<td>147</td>
<td>34</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47 (18)*</td>
<td>55 (20)</td>
<td>50 (19)</td>
</tr>
<tr>
<td>Male</td>
<td>58%</td>
<td>54%</td>
<td>53%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>67%</td>
<td>67%</td>
<td>50%</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>73%</td>
<td>73%</td>
<td>71%</td>
</tr>
<tr>
<td>LIS</td>
<td>3.0 (0.7)*</td>
<td>2.6 (0.7)</td>
<td>2.7 (0.7)</td>
</tr>
<tr>
<td>SAPS II</td>
<td>52 (20) *</td>
<td>43 (14)</td>
<td>49 (16)</td>
</tr>
<tr>
<td>A-a Oxygen Difference (mmHg)</td>
<td>511 (128)</td>
<td>487 (135)</td>
<td>510 (126)</td>
</tr>
<tr>
<td>EF/PL Protein Ratio</td>
<td>0.89 (0.36)**</td>
<td>0.53 (0.21)</td>
<td>0.62 (0.19)</td>
</tr>
</tbody>
</table>

Data as mean (SD) or %; LIS: Lung injury score\(^{34}\); SAPS II, simplified acute physiology score II\(^{35}\); A-a Oxygen Difference, highest alveolar-arterial oxygen difference on the day of edema fluid sampling; EF/PL, edema fluid-to-plasma protein ratio

* p < 0.001 vs. Cardiogenic Pulmonary Edema group
** p < 0.001 vs. Cardiogenic Pulmonary Edema Group and Mixed Etiology group
Table 2. Clinical outcomes of 390 patients with acute pulmonary edema classified by clinical diagnosis based on expert review of the medical record at the end of the hospitalization

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>Acute Lung Injury</th>
<th>Cardiogenic Pulmonary Edema</th>
<th>Mixed Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>209</td>
<td>147</td>
<td>34</td>
</tr>
<tr>
<td>Ventilator Free Days</td>
<td>0 (0 - 17)*</td>
<td>22 (0 - 26)</td>
<td>11 (0 - 23)</td>
</tr>
<tr>
<td>ICU Free Days</td>
<td>0 (0 - 16)*</td>
<td>17 (0 - 24)</td>
<td>2 (0 - 21)</td>
</tr>
<tr>
<td>Hospital Mortality</td>
<td>59%*</td>
<td>32%</td>
<td>47%</td>
</tr>
</tbody>
</table>

Data as Median (Interquartile Range) or % of patients

1 Comparison of Acute Lung Injury, Cardiogenic Pulmonary Edema and Mixed Etiology groups by Chi-Square for hospital mortality. Ventilator free days and ICU free days compared across groups by Kruskal Wallis Test.
* p < 0.001 vs. Cardiogenic Pulmonary Edema group
Table 3. Clinical outcomes of patients with acute pulmonary edema classified by edema fluid to plasma protein ratio.

<table>
<thead>
<tr>
<th>Edema Fluid to Plasma Protein Ratio (EF/PL)</th>
<th>EF/PL &lt; 0.65</th>
<th>EF/PL ≥ 0.65</th>
<th>P Value $^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>n = 175</td>
<td>n = 215</td>
<td></td>
</tr>
<tr>
<td>Ventilator Free Days</td>
<td>10 (0 - 26)</td>
<td>0 (0 - 22)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hospital Mortality</td>
<td>50%</td>
<td>61%</td>
<td>0.022</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subgroup with interval from intubation to edema fluid sampling &lt; 3 hours</th>
<th>n = 103</th>
<th>n = 97</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator Free Days</td>
<td>22 (0 – 26)</td>
<td>4 (0 – 23)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hospital Mortality</td>
<td>41%</td>
<td>65%</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Data as Median (Interquartile Range) or % of patients

$^1$ Comparison of EF/PL groups by Chi-Square for hospital mortality. Ventilator free days compared by Mann-Whitney U test.
Figure Legends

Figure 1. Receiver operator curve (ROC) analyses of the utility of the Edema Fluid to Plasma Protein Ratio (EF/PL) for differentiating the etiology of acute pulmonary edema.
A. Comparison of the EF/PL ratio to the clinical diagnosis based on all information available at the end of the hospitalization, excluding patients with a clinical diagnosis of a mixed etiology of acute pulmonary edema (n = 356). The EF/PL ratio determined early in the hospital course had excellent diagnostic discrimination for ALI vs. CPE with an area under the curve (AUC) of 0.84 (95% CI 0.79 to 0.88). B. The same analysis was restricted to the subgroup of patients who had pulmonary edema fluid sampled within 3 hours of endotracheal intubation (n = 183). In this group, the diagnostic performance of the EF/PL ratio was similar with an AUC of 0.85 (95% CI 0.79 to 0.91). C and D. For these analyses, the patients with a clinical diagnosis of a mixed etiology of acute pulmonary edema were classified as having ALI, and the entire cohort (n = 390, panel C) and the subgroup with pulmonary edema fluid sample within 3 hours of endotracheal intubation (n = 200, panel D) were analyzed. For the entire cohort, the AUC was 0.81 (95% CI 0.77 to 0.86). For the subgroup with edema fluid sampled within 3 hours of endotracheal intubation the AUC was 0.81 (95% CI 0.74 to 0.87).
Figure 1.

A

B

N = 356

N = 183
Figure 2. Percent of patients alive and breathing without assistance during the first 28 days after enrollment. Panel A shows the entire cohort (n = 390). P = 0.058 for group with EF/PL < 0.65 compared to group with EF/PL ≥ 0.65 by Cox proportional hazards regression analysis. Panel B is restricted to the subgroup (n = 200) in whom the edema fluid was sampled within 3 hours of endotracheal intubation. P = 0.005 for group with EF/PL < 0.65 compared to group with EF/PL ≥ 0.65 by Cox proportional hazards regression analysis.
Figure 2

A

Percent alive and free of mechanical ventilation

Days after enrollment

B

Percent alive and free of mechanical ventilation

Days after enrollment