

TITLE:

One-year mortality and predictors of death among hospital survivors of acute respiratory distress syndrome

ABSTRACT:

**PURPOSE:** Advances in supportive care and ventilator management for acute respiratory distress syndrome (ARDS) have resulted in declines in short-term mortality, but risks of death after survival to hospital discharge have not been well described. Our objective was to quantify the difference between short-term and long-term mortality in ARDS and to identify risk factors for death and causes of death at 1 year among hospital survivors. **METHODS:** This multi-intensive care unit, prospective cohort included patients with ARDS enrolled between January 2006 and February 2010. We determined the clinical characteristics associated with in-hospital and 1-year mortality among hospital survivors and utilized death certificate data to identify causes of death. **RESULTS:** Of 646 patients hospitalized with ARDS, mortality at 1 year was substantially higher (41 %, 95 % CI 37–45 %) than in-hospital mortality (24 %, 95 % CI 21–27 %),  $P < 0.0001$ . Among 493 patients who survived to hospital discharge, the 110 (22 %) who died in the subsequent year were older ( $P < 0.001$ ) and more likely to have been discharged to a nursing home, other hospital, or hospice compared to patients alive at 1 year ( $P < 0.001$ ). Important predictors of death among hospital survivors were comorbidities present at the time of ARDS, and not living at home prior to admission. ARDS-related measures of severity of illness did not emerge as independent predictors of mortality in hospital survivors. **CONCLUSIONS:** Despite improvements in short-term ARDS outcomes, 1-year mortality is high, mostly because of the large burden of comorbidities, which are prevalent in patients with ARDS. **ELECTRONIC SUPPLEMENTARY MATERIAL:** The online version of this article (doi:10.1007/s00134-013-3186-3) contains supplementary material, which is available to authorized users.

Introduction:

The last decade has seen many advancements in care for patients with acute respiratory distress syndrome (ARDS) including improvements in ventilator management [1, 2], noninvasive mechanical ventilation strategies [3–5], sepsis management [6], and intensive care unit system changes [7, 8]. More patients with ARDS are now surviving to hospital discharge, a phenomenon that has been reported in both observational studies and randomized trials [9–11]. For example, 60-day mortality decreased from 40 % in the traditional tidal volume arm of the ARDS network ARMA study published in 2000 to 21 % in the most recent ARDS network trial published in 2011, in spite of increased severity of illness and more comorbidities in the more recent trial [1, 12]. However, less is known about the epidemiology of long-term survival in ARDS, particularly in the context of increasing severity of illness and comorbidities among ICU patients today [13]. Initial studies of long-term outcomes in ARDS found that in-hospital survival from ARDS provided a good estimate of long-term survival [14–17]; however, these populations are not reflective of ARDS patients in modern practice. In-hospital mortality in these studies was higher at 37–40 %, as these cohorts predated widespread implementation of low tidal volume ventilation. Furthermore, patients who survived to hospital discharge and were selected for these studies were young (mean age mid-40 s), had few coexisting conditions, and lower severity of illness on presentation. More recent data demonstrate a widening difference between ARDS survival at discharge and long-term follow-up [11, 18, 19]. This “survival gap” suggests that while modern ICU interventions have resulted in short-term improvements in ARDS survival, the overall survival after ARDS may not have improved. Temporal changes in ICU patient characteristics including increased severity of illness and more comorbid illnesses may explain some of the changes in trajectory of illness following discharge [13]. Although factors that predict short-term mortality have been well described [20–29], a better understanding of predictors of long-term mortality in ARDS is required for improved prognostication and a better understanding of the effects of ICU interventions on long-term outcomes [19]. A small study predating low tidal volume ventilation found that comorbidities, ARDS risk factor, and age were most highly associated with mortality 6 months following ARDS diagnosis [30], but the influence of increased severity of illness over time has not been assessed. A more recent study found that the survival benefits of adherence to low tidal volume ventilation persisted at 2 years follow-up, suggesting that modern changes in clinical practice may provide long-standing improvements in survival [19]. However, this study excluded sicker patients with

cancer or life-limiting disease—diagnoses that are frequent in patients presenting with ARDS. The predictors and causes of death in a broad sample of patients surviving to hospital discharge with ARDS are not known.

The purpose of the current study was to (1) quantify the gap between in-hospital and 1-year ARDS mortality in modern practice, (2) identify the most influential risk factors for death at 1 year among hospital survivors in a large, multi-ICU prospective cohort study of patients with ARDS, and (3) examine causes of death among patients dying in the year after diagnosis of ARDS. Some of these data have previously been presented in the form of an abstract [31].

#### Subjects ::: Materials and methods:

The study subjects were drawn from the validation of biomarkers in acute lung injury diagnosis (VALID) study, an ongoing prospective, multi-ICU cohort study of critically ill patients at Vanderbilt University Medical Center, a tertiary medical center in Nashville, TN. The inclusion criteria and exclusion criteria of VALID have been reported previously and are described in the supplemental appendix [32]. Specifically, patients with severe chronic lung disease were excluded, but patients with other underlying comorbidities including advanced cancer and HIV were not excluded. The study was approved by the Vanderbilt University Institutional Review Board.

For this analysis, we included patients enrolled between January 2006 and February 2010 who had or developed acute lung injury (ALI)/ARDS during the first 4 days after admission to the ICU. During the study period, there were a total of 2,181 total patients enrolled in VALID of whom, 1,894 had at least one risk factor for ARDS. Of these, the current study focused on the 646 who met the American European consensus conference (AECC) criteria for ALI/ARDS [33].

#### Data collection ::: Materials and methods:

Data collection and definitions have been described previously [32]. Diagnosis of ALI/ARDS was defined by the AECC definition ( $\text{PaO}_2/\text{FiO}_2 \leq 300$  mmHg for ALI and  $\text{PaO}_2/\text{FiO}_2 \leq 200$  mmHg for ARDS) [33], and could be established at any time during the first 4 days in the ICU. Both mechanically ventilated (defined as invasive mechanical ventilation within 4 days of AECC ALI/ARDS diagnosis) and not mechanically ventilated patients meeting AECC criteria were included in our primary analysis. In a sensitivity analysis, we also considered the Berlin definition for ARDS [34, 35]. Berlin severity levels were defined as mild ( $200 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 300$  mmHg with PEEP or CPAP  $\geq 5$  cmH<sub>2</sub>O), moderate ( $100 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 200$  mmHg with PEEP  $\geq 5$  cmH<sub>2</sub>O), and severe ( $\text{PaO}_2/\text{FiO}_2 \leq 100$  mmHg with PEEP  $\geq 5$  cmH<sub>2</sub>O). For both AECC and Berlin definitions, the ratio of pulse oximetric saturation to fraction of inspired oxygen ( $\text{SpO}_2/\text{FiO}_2$ ) was used as a validated surrogate for  $\text{PaO}_2/\text{FiO}_2$  among patients without an arterial blood gas measurement at the time of ALI/ARDS diagnosis:  $\text{SpO}_2/\text{FiO}_2 = 64 + 0.84 \times (\text{PaO}_2/\text{FiO}_2)$  [36]. The discharge location for patients who survived hospitalization was categorized as home, rehabilitation hospital, nursing home, hospice, or other acute care hospital. The lung injury score [37], Brussels organ failure [38], and definitions for sepsis, pneumonia, aspiration, and trauma are included in the supplemental appendix.

#### Outcome measures ::: Materials and methods:

All patients were followed until death or for at least 1 year after study enrollment. Short-term mortality was defined as all-cause mortality during hospitalization. Long-term mortality was defined as all-cause mortality 1 year following enrollment in VALID in patients who survived to hospital discharge. Patient deaths were identified by medical record review and query of the social security death index (SSDI) [39]. Causes of death were determined by review of death certificate data obtained from the Tennessee Vital Records Office of the Tennessee Department of Health. Underlying causes of death were categorized as infection, malignancy (primary, metastatic, or hematologic), cardiovascular, respiratory, gastrointestinal/hepatic, trauma, or other causes (listed in supplemental appendix) based on ICD-9 coding of the primary cause of death on the death certificate.

#### Statistical analysis ::: Materials and methods:

We used t tests, chi-squared tests, and Fisher's exact tests as appropriate to compare baseline demographics and clinical risk factors across groups. Descriptive statistics and McNemar's were used to compare in-hospital and 1-year mortality. Since all events were accounted for over the year of follow-up, logistic regression was used to analyze associations between candidate risk factors and mortality. Kaplan–Meier survival plots demonstrate the time from discharge to death in hospital survivors and the log-rank test was used to estimate differences according to discharge

location. Clinical characteristics associated with 1-year mortality with  $P < 0.10$  on bivariable analysis were entered into a stepwise elimination model to retain potential risk factors if they remained associated at a  $P$  value of less than 0.05. Because of the modest number of outcomes, the forward stepwise elimination was used to maintain model parsimony. In a sensitivity analysis, we analyzed only patients meeting the Berlin definition of ARDS [34]. Analyses were performed using STATA version 10 (STATA Corp, College Station, TX). Statistical significance was defined as a two-tailed  $P < 0.05$  for all analyses.

#### Clinical characteristics and outcomes ::: Results:

Among 646 patients with ALI/ARDS, the proportion of patients who died increased from 24 % ( $n = 153$ , 95 % CI 21–27 %) during hospitalization to 41 % ( $n = 263$ , 95 % CI 37–45 %) during the year after discharge ( $P < 0.0001$ ). One-year mortality was higher than in-hospital mortality regardless of ALI/ARDS etiology (Supplemental Fig. 1). In the subset of patients with 2-year outcomes available ( $n = 527$ , 82 %), the 2-year cumulative incidence of death was 54 % ( $n = 282$ , 95 % CI 49–59 %,  $P = 0.0004$ ).

In a sensitivity analysis of 551 patients meeting the Berlin definition of ARDS [34] (excluded 95 patients: 87 non-mechanically ventilated in first 4 days of enrollment; two patients with missing PEEP; two patients with PEEP  $< 5$  cmH<sub>2</sub>O; and four patients not meeting hypoxemia criteria on day otherwise meeting all Berlin criteria) we found similar rates of hospital and 1-year mortality (Supplemental Table 1). Severity of ARDS defined by Berlin levels (mild, moderate, severe) was associated with in-hospital mortality but not with mortality at 1-year among hospital survivors.

#### Comparison of baseline characteristics by hospital and 1-year outcomes ::: Results:

Demographics, comorbidities, and initial clinical characteristics did not differ substantially between those who died early (in hospital) and those who died over the subsequent year (Table 1). Patients who died in the hospital ( $n = 153$ ) were more likely to have a hematologic malignancy and less likely to have COPD or metastatic cancer than patients who died after surviving hospitalization but were otherwise demographically similar. In addition, there was no difference in underlying cause of ALI/ARDS although patients who died during hospitalization had a lower P/F ratio and a higher incidence of hepatic failure compared to those dying after hospitalization. By contrast, compared to patients who died in the year following hospital discharge ( $n = 110$ ), survivors at 1 year ( $n = 383$ ) were younger, were more likely to have been admitted through the emergency department and had substantially fewer comorbidities such as COPD, HIV, diabetes, chronic heart failure, chronic kidney disease, or malignancy (Table 1). In addition, patients who were alive at 1 year were more likely to have trauma and less likely to have sepsis as the cause of ALI/ARDS. Increased severity of illness on presentation was associated with higher 1-year mortality among patients who survived hospitalization: respiratory rate, APACHE II score, presence of coagulation failure, renal failure, and circulatory failure were all significantly associated with death after discharge (Table 1).

#### Comparison of hospital course between hospital survivors who were dead or alive at 1 year :::

##### Results:

Among patients with ALI/ARDS who survived hospitalization, those who survived to 1 year had significantly shorter time from hospital admission to ICU admission, lower creatinine at discharge, and were more likely to be discharged home or to a rehabilitation facility and less likely to be discharged to a nursing home or hospice facility (Table 2). Specifically, discharge destination among hospital survivors was strongly associated with long-term mortality (Fig. 1) ( $P < 0.001$ ). There were no differences in ICU length of stay ( $P = 0.76$ ) or duration of mechanical ventilation ( $P = 0.62$ ) between hospital survivors that died and survived at 1-year follow-up.

#### Independent predictors of 1-year mortality after discharge ::: Results:

Stepwise elimination identified several baseline characteristics as independent predictors of mortality among hospital survivors. These included age and severe comorbidities: HIV, metastatic cancer, hematologic malignancy, non-metastatic cancer, and chronic renal disease (Table 3). Trauma as a cause of ARDS and living at home prior to hospitalization were strong independent

predictors of decreased odds of mortality at 1 year. Increased length of hospital stay was the only characteristic of hospitalization that was independently associated with increased odds of death at 1 year among hospital survivors. Severity of illness measures including LIS, APACHE II, organ failure, and PaO<sub>2</sub>/FiO<sub>2</sub> did not emerge as independent predictors of mortality in survivors. The C-statistic for the final adjusted model was 0.81. Predictors of 1-year mortality among survivors were similar after excluding 23 patients discharged to hospice, and characteristics associated with 1-year mortality among those surviving the hospitalization were similar to those associated with overall 1-year mortality (data not shown).

#### Causes of death ::: Results:

Death certificate data was available for 244 (93 %) of the 263 patients who died within 1 year of enrollment. Overall, the most common underlying cause of death both in the hospital and among hospital survivors was malignancy (Fig. 2). Seventy-two percent of patients with known malignancy at the time of ARDS were found to have malignancy as the underlying cause of death at 1 year. There were no significant differences in underlying cause of death between patients who died in the hospital and patients who died after discharge.

#### Discussion:

Short-term mortality in ARDS has declined over the last decade owing to improvements in supportive care and of the use of protective ventilator strategies [9, 10]. We sought to quantify the survival gap between short- and long-term ARDS mortality and identify risk factors for death and causes of death at 1 year for hospital survivors. In this study of a broad, heterogeneous cohort of critically ill patients with ALI/ARDS, overall hospital mortality was 24 %, concordant with short-term mortality rates of ALI/ARDS mortality reported in the era of low tidal volume ventilation [10, 11], and 1-year mortality was substantially higher at 41 %, consistent with other recent studies [11, 18, 19]. This finding did not vary according to etiology of ARDS or in the presence of sepsis. Furthermore, in a large subgroup of patients followed for 2 years, we found that more than half of the patients with ALI/ARDS had died. Disposition after hospitalization was highly associated with 1-year mortality, suggesting that functional status after discharge may be an important contributing factor to long-term mortality after ARDS. The independent predictors of death at 1 year were age, living somewhere other than home prior to admission, and serious comorbidities. Although several measures of severity of illness and characteristics of hospital course were associated with long-term mortality among hospital survivors, only length of hospital stay remained an independent predictor of long-term mortality in a stepwise elimination model. Restriction of the analysis to patients meeting the Berlin definition for ARDS did not change the findings, and Berlin level of severity of ARDS did not predict long-term mortality in hospital survivors.

This study provides several insights into recent reports of declines in ARDS mortality. Although short-term mortality in ARDS has decreased in the last decade, our findings expand upon other recent studies demonstrating a widening survival gap between ARDS survival at discharge and long-term follow-up [11, 18, 19]. This gap suggests that while modern ICU interventions have improved short-term outcomes in ARDS, other factors contribute to a persistently high long-term mortality in ARDS. One possible explanation is the temporal changes in characteristics of ICU patients over the last several decades. Large studies have demonstrated that older age, the number of comorbidities, and the severity of illness have increased both in the general ICU population and in ARDS patients specifically [10, 13]. ICU treatment cannot address the underlying comorbidities and increasing age that ultimately contribute to high long-term mortality in ICU patients today. Although a recent study found that adherence to low tidal volume ventilation in ARDS was associated with a survival benefit up to 2 years following hospitalization, these conclusions may only be generalizable to the most healthy of ARDS patients because those with significant comorbidities, poor social status, and life-limiting illnesses were excluded from enrollment in the observational study [19].

Our findings are consistent with prior studies focusing on long-term mortality in general critically ill patients, a finding that supports the hypothesis that long-term outcomes in ARDS are more related to the medical conditions and age of patients requiring ICU care in general rather than the development of ARDS specifically [30]. In a recent study of Medicare patients, ICU survivors had higher 3-year mortality than non-ICU hospital survivors or non-hospitalized controls, and a separate study showed that critically ill patients have decreased survival for up to 15 years

compared to age- and sex-matched population controls [40, 41]. Furthermore, predictors of long-term outcomes for critically ill patients are similar to those we observed in ARDS, with comorbidities as top predictors for subsequent re-hospitalization and death [41]. One possible explanation for the persistently high risk of death in patients with critical illness includes a persistent pro-inflammatory state that may exacerbate or trigger other underlying inflammatory disorders including cardiovascular disease, recurrent infection, cancer, and renal failure—all common causes of death among patients in our study who survived to hospital discharge. This study has several strengths including the large sample size, broad patient population with few exclusion criteria, and the careful prospective phenotyping for ALI/ARDS, sepsis, and other important clinical variables. Because there were very few exclusion criteria for enrollment in VALID, the findings are likely to be generalizable. The study also has some limitations. First, it is a single-center study. However, this is counterbalanced by the broad spectrum of heterogeneous critically ill patients from four different intensive care units included. Second, it is possible that we underestimated the 1-year mortality rate of ARDS survivors; although the SSDI has been shown to be a valuable tool for determining long-term outcomes [39], some patients without social security numbers may not be included. Third, mortality does not capture the full burden of disease. Long-term sequelae of ARDS, including impaired pulmonary function, neuromuscular weakness, and neuropsychiatric are well described [15, 42–45]. However, these limitations would have led us to underestimate rather than overestimate long-term effects of ARDS and do not weaken the findings. Finally, we were unable to test the effect of specific ICU interventions such as low-tidal volume ventilation on long-term outcomes.

#### Conclusions:

Long-term mortality is substantially higher than short-term mortality in a broad sample of patients with ARDS. In spite of improvements in supportive care and significantly improved short-term outcomes, long-term outcomes remain poor. The top predictors of 1-year mortality in hospital survivors include non-modifiable factors including age and comorbidities, and the most common causes of death are malignancy and infection. These results underscore the importance of considering the interaction between comorbid illness and ARDS on the trajectory of long-term outcomes in hospital survivors of ARDS for testing new interventions and providing prognoses. Researchers must measure whether effects of interventions can influence the overall trajectory of survival in ARDS patients who do and do not have major comorbidities. Possible clinical applications of such research include improved guidance of initial discussions of prognosis and the benefits of full resuscitation for high-risk patients. For clinical trials, it is perhaps more realistic to target shorter-term endpoints such as 30- to 90-day mortality, since 1-year mortality will be driven primarily by comorbidities that cannot be reversed or influenced by treatments for increasing survival from ARDS such as lung protective or prone ventilation. This study, along with others, demonstrates that premorbid illnesses are the top predictors of long-term outcomes after ARDS in critically ill patients today.