

# Effect of ARDS Severity and Etiology on Short-Term Outcomes

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**BACKGROUND:** We evaluated the outcome of subjects with ARDS in relation to etiology and severity in a retrospective cohort study of the ARDS Network randomized controlled trials. The primary outcome was 28-d mortality. The secondary outcomes were 60-d mortality and ventilator- and ICU-free days. For severity of ARDS, subjects were stratified according to  $P_{aO_2}/F_{IO_2}$ . The etiology of ARDS was classified into sepsis, pneumonia, aspiration, trauma, and others. **RESULTS:** A total of 2,914 subjects were included in these trials. Outcomes were modeled with multivariable regressions adjusted for baseline covariates, age, sex, race, Acute Physiology and Chronic Health Evaluation III (APACHE III), vasopressor use, modified lung injury score, diabetes mellitus, cancer status, body mass index, pre-ICU location, ICU location, and study. There was no statistically significant difference in 28-d mortality in relation to ARDS severity. Subjects with trauma, compared with other etiologies of ARDS, had significantly lower mortality at 28 d (odds ratio [OR] = 0.47, 95% CI 0.26–0.83,  $P = .01$ ). Sixty-day mortality was significantly lower for trauma subjects and those with severe ARDS group (OR = 0.5, 95% CI 0.3–0.85,  $P = .01$  and OR = 0.71, 95% CI 0.52–0.98,  $P = .034$ , respectively). There were statistically significantly more ICU-free days and ventilator-free days for the aspiration group (OR = 1.09, 95% CI 1.02–1.17,  $P = .01$  and OR = 1.09, 95% CI 1.02–1.16,  $P = .01$ , respectively). There was no statistically significant difference in ICU-free days or ventilator-free days in relation to severity of ARDS. **CONCLUSIONS:** Severity of ARDS based on  $P_{aO_2}/F_{IO_2}$  did not impact 28-d mortality, ventilator-free days, or ICU-free days. Among the etiologies of ARDS, trauma subjects had the lowest 28- and 60-d mortality, whereas subjects with aspiration had more ICU-free days and ventilator-free days. *Key words:* ARDS; outcome; etiology; severity. [Respir Care 2017;62(9):1178–1185. © 2017 Daedalus Enterprises]

## Introduction

ARDS is a constellation of pathophysiologic changes associated with an early acute lung injury that results in increased capillary leak and pulmonary edema. Clinically, patients manifest with hypoxemia, diffuse radiographic pulmonary infiltrates, and decreased lung compliance. In the

United States, it is estimated that there are 150,000 cases of ARDS annually with a mortality of 40–50%.<sup>1</sup>

There are conflicting results in the literature about the predictors of outcome in patients with ARDS. Factors such as age and the diagnosis of cancer are associated with poor outcome, but not sex, body mass index, diagnosis of diabetes mellitus, or location of the patient.<sup>2-4</sup> There are few data on the role of etiology and severity of ARDS upon presentation on different outcomes of patients, and these also show variable results.<sup>5-7</sup> The purpose of this study is to analyze the ARDS Network randomized controlled trials database to determine whether etiology and severity of ARDS affected the short-term outcomes of these subjects.

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The authors have disclosed no conflicts of interest.

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## Methods

The ARDS Network has conducted several randomized controlled trials to evaluate therapeutic interventions in the management of ARDS. These trials have

been previously published.<sup>8-13</sup> Table 1 summarizes the relevant features of these trials. Briefly, all subjects fulfilled diagnostic criteria for ARDS and were mechanically ventilated. Similar inclusion and exclusion criteria were used in all of the trials. The National Institutes of Health and the local institutional review boards of each of the sites approved all studies.

We had authorized access to the original data for each of these studies. This paper was prepared using the KARMA (ketoconazole and respiratory management in acute lung injury (ALI)/ARDS), LaSRS (late steroid rescue study), LARMA (lisofylline and respiratory management in ALI/ARDS), ALVEOLI (assessment of low tidal volume and elevated end-expiratory volume to obviate lung injury), FACTT (fluids and catheters treatment trial), and ALTA (albuterol for the treatment of acute lung injury) research materials obtained from the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center. The primary objective of the KARMA trial was to investigate the efficacy and safety of ketoconazole and respiratory management in the treatment of ALI and ARDS. The ketoconazole arm of the study was later stopped due to an inability to show efficacy. Subjects continued to be randomized to the respiratory management arms of the study (ARMA), which compared 2 ventilator strategies: a tidal volume of 6 mL/kg versus 12 mL/kg (<https://biolincc.nhlbi.nih.gov/studies/ardsnet/>, Accessed February 27, 2017). The subjects reported in ARMA ( $N = 861$ ) were a combination of those from KARMA ( $N = 667$ ) and LARMA ( $N = 194$ )<sup>8</sup> (<https://biolincc.nhlbi.nih.gov/studies/ardsnet/>, Accessed February 27, 2017). The findings of the current study do not necessarily reflect the opinions or views of the KARMA, LASRS, LARMA, ALVEOLI, FACTT, and ALTA investigators or the National Heart, Lung, and Blood Institute. For the purpose of this analysis, we included only subjects who had  $P_{aO_2}/F_{IO_2} \leq 300$  to fulfill the Berlin definition of ARDS.<sup>14</sup>

The 2 variables that we are studying are the severity as well as the etiology of ARDS. The severity was stratified according to  $P_{aO_2}/F_{IO_2}$  into mild ( $P_{aO_2}/F_{IO_2} = 200-300$ ), moderate ( $P_{aO_2}/F_{IO_2} = 100$  to  $< 200$ ), and severe ( $P_{aO_2}/F_{IO_2} < 100$ ) as per the Berlin definition of ARDS. The etiology was classified based on the original ARDS Network trials' determination into pneumonia, aspiration, trauma, sepsis, and others.

### Statistical Analysis

Descriptive statistics for subject baseline characteristics were summarized within each of the 6 studies. The authors made every effort to ensure that each subject was unique and that there were no overlaps between the different studies. Medians with ranges were reported for continuous data, whereas frequencies and percentages were reported

## QUICK LOOK

### Current knowledge

ARDS remains a major problem in critically ill patients with high mortality. There are conflicting data in the literature about predictors of outcome in subjects with ARDS.

### What this paper contributes to our knowledge

Analysis of the ARDS Network robust database shows that severity of ARDS based on  $P_{aO_2}/F_{IO_2}$  did not predict short-term outcome of these subjects and that trauma was associated with better outcome compared with other causes of ARDS.

for categorical data. The primary objective for our study was mortality at 28 d after enrollment in the study in relation to severity and etiology of ARDS. Covariates in the multivariable regressions included age ( $< 60$  and  $\geq 60$ ), sex, ethnicity (white, black, and other), pre-ICU location, type of ICU, Acute Physiology and Chronic Health Evaluation III (APACHE III), vasopressor use, cause of lung injury (pneumonia, sepsis, aspiration, trauma, and others), modified lung injury score, cancer status, body mass index, diabetes mellitus, and study. These variables were specified a priori to be clinically sound or based on our previous publications.<sup>2-4</sup> The commonly used measure of acute lung injury score was proposed in 1988 by Murray et al.<sup>15</sup> The score is composed of 4 components: (1) chest radiograph; (2)  $P_{aO_2}/F_{IO_2}$ ; (3) PEEP; and (4) lung compliance. We proposed the modified lung injury score in this study by excluding the  $P_{aO_2}/F_{IO_2}$  component. We added individual scores for each category and then divided by the number of components used. Hence, the  $P_{aO_2}/F_{IO_2}$  was reported independently in our study because it is one of the variables of interest for this work. The secondary clinical outcomes evaluated were 60-d mortality, ventilator-free days, and ICU-free days. The ventilator-free days were defined as the number of days of at least 48-h unassisted breathing during the first 28 d after enrollment.

The univariate analysis of association between our variable of interest, namely severity and etiology of ARDS, and clinical outcomes, including 28-d mortality, 60-d mortality, categorized ventilation-free days in weeks, and categorized ICU-free days in weeks, were performed for statistical significance using a chi-square test or Fisher exact test where appropriate. In-hospital mortality curves for the 3 subgroups of severity of hypoxemia were constructed with the cumulative incidence function method using discharge as competing events.

A multivariable logistic regression model and multivariable zero-inflated negative binomial regression

Table 1. Summary of the ARDS Network Trials

Characteristics	KARMA	LASRS	LARMA	ALVEOLI	FACTT	ALTA
Years	1996–1998	1997–2003	1998–1999	1999–2002	2000–2005	2007–2008
No. of Subjects	667	180	235	550	1,000	282
Intervention	Low-tidal volume ventilation/ketoconazole use in ARDS	Use of steroids in ARDS	Low-tidal volume ventilation/Lisofylline use early in ALI/ARDS	High-PEEP/low- $F_{IO_2}$ vs low-PEEP/high- $F_{IO_2}$ ventilation strategy	PA catheter vs central venous catheter; conservative vs liberal fluid strategy in management of subjects with ALI/ARDS	Aerosolized albuterol vs saline placebo in subjects with ALI/ARDS
Outcome	No effect of ketoconazole on mortality; improved mortality with low-tidal volume ventilation	No change in mortality	No effect of lisofylline on mortality; improved mortality with low-tidal volume ventilation	No change in mortality	No change in mortality	No change in mortality

KARMA (low-tidal volume trial)<sup>8</sup> included subjects initially enrolled in KARMA and continued enrollment with LARMA.

ALI = acute lung injury

PA = pulmonary artery

model were then used to evaluate the effect of severity and etiology of ARDS on clinical outcomes, including 28-d mortality or 60-d mortality and ventilation-free days or ICU-free days, respectively. All *P* values are 2-sided with a significance level of .05. The results of these analyses should be regarded only as exploratory findings, and raw *P* values were reported without adjustment for multiple testing. All calculations were performed with R 3.2.2.

## Results

A total of 2,914 subjects were included in these trials. Five subjects with  $P_{aO_2}/F_{IO_2} > 300$  and 2 with missing data were excluded from analysis. Table 2 describes the baseline characteristics of these subjects.

Based on univariate analysis, there were significant differences in 28-d mortality between the different etiologies of ARDS (Fig. 1A). The highest mortality was with sepsis (32.29%), followed by pneumonia (24.91%), other causes (24.14%), aspiration (23.06%), and trauma (8.81%). The differences between these groups were significant ( $P < .001$ , chi-square test). Similar associations were observed with 60-d mortality (Fig. 1A). For the severity of ARDS based on  $P_{aO_2}/F_{IO_2}$ , there were significant differences in 28-d mortality, with the highest mortality in severe ARDS (28.61%), followed by moderate ARDS (22.75%) and mild ARDS (22.17%) ( $P = .001$ , chi-square test). Similar associations were observed with 60-d mortality (Fig. 1B). Higher mortality acceleration was observed in the severely hypoxemic group within 28 d (Fig. 2). The early phase of accelerated mortality leveled off between 28 and 60 d. Then the hospital mortality rate plateaued after 60 d.

Univariate analysis of other secondary outcomes also revealed that ventilator-free days and ICU-free days were most frequent in the case of aspiration and lowest with sepsis (Figs. 3A and 4A) and did not follow a specific pattern in relation to  $P_{aO_2}/F_{IO_2}$  (Figs. 3B and 4B).

On multivariable analysis of outcomes to assess the role of etiology and severity, the following variables were included as covariates: age, sex, race, APACHE III, modified acute lung injury score, vasopressor use, diabetes mellitus, cancer status, body mass index, pre-ICU location, ICU location, and study. With sepsis as the reference variable, trauma had significantly lower 28- and 60-d mortality (odds ratio [OR] = 0.47, 95% CI 0.26–0.83,  $P = .01$  and OR = 0.5, 95% CI 0.3–0.85,  $P = .01$ , respectively) (Table 3). As for the severity of ARDS, with mild serving as reference, there were no significant differences in 28-d mortality; however, subjects with severe ARDS had significantly lower 60-d mortality (OR = 0.71, 95% CI 0.53–0.98,  $P = .034$ ).

EFFECT OF ARDS SEVERITY AND ETIOLOGY ON OUTCOMES

Table 2. Baseline Subject Characteristics by Study

Variable	KARMA (N = 667)	LASRS (N = 180)	LARMA (N = 235)	ALVEOLI (N = 550)	FACTT (N = 1,000)	ALTA (N = 282)
Age, median (range) y	51 (18–89)	47 (16–89)	49 (18–86)	50 (16–88)	49 (17–89)	52 (17–89)
Sex, n (%)						
Male	392 (59)	89 (49)	145 (62)	302 (55)	534 (53)	156 (55)
Female	275 (41)	91 (51)	90 (38)	248 (45)	466 (47)	126 (45)
Race, n (%)						
White	482 (72)	131 (73)	179 (76)	413 (75)	641 (64)	217 (77)
Black	118 (18)	28 (16)	37 (16)	77 (14)	217 (22)	46 (16)
Others	67 (10)	21 (12)	19 (8)	60 (11)	142 (14)	19 (7)
Vasopressor use, n (%)						
Yes	269 (40)	56 (31)	78 (33)	156 (28)	330 (33)	141 (50)
Missing	3 (0.45)	2 (1.11)	2 (0.85)	18 (3.27)	1 (0.1)	0 (0)
Cause of lung injury, n (%)						
Sepsis	178 (27)	36 (20)	58 (25)	120 (22)	233 (23)	77 (27)
Pneumonia	205 (31)	63 (35)	84 (36)	221 (40)	471 (47)	107 (38)
Aspiration	96 (14)	30 (17)	38 (16)	85 (15)	149 (15)	54 (19)
Trauma	74 (11)	23 (13)	22 (9)	45 (8)	74 (7)	23 (8)
Others	114 (17)	28 (16)	33 (14)	79 (14)	73 (7)	21 (7)
P <sub>aO<sub>2</sub></sub> /F <sub>IO<sub>2</sub></sub> , n (%)						
Mild	100 (15)	0 (0)	26 (11)	72 (13)	157 (16)	51 (18)
Moderate	320 (48)	118 (66)	125 (53)	270 (49)	459 (46)	129 (46)
Severe	247 (37)	61 (34)	82 (35)	208 (38)	381 (38)	101 (36)
>300*	0 (0)	0 (0)	1 (0)	0 (0)	3 (0)	1 (0)
Missing	0 (0)	1 (1)	1 (0)	0 (0)	0 (0)	0 (0)
Modified LIS, median (range)	2.5 (0.67–4)	3.33 (2–4)	2.5 (0–4)	2.67 (0.67–4)	2.67 (0–4)	2.5 (0–4)
APACHE III, median (range)	81 (22–178)	85.5 (16–155)	86 (30–195)	91 (0–191)	91 (17–205)	90.5 (32–185)

\* Five subjects with P<sub>aO<sub>2</sub></sub>/F<sub>IO<sub>2</sub></sub> > 300 were removed from further analyses.  
LIS = lung injury score

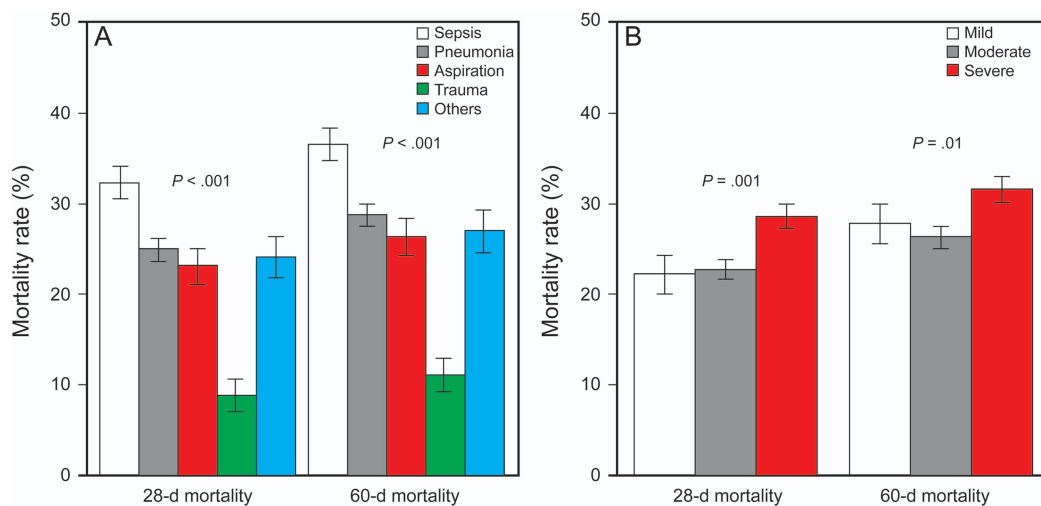


Fig. 1. Mortality rate by cause of lung injury (A), and P<sub>aO<sub>2</sub></sub>/F<sub>IO<sub>2</sub></sub> (B). Chi-squared test was used to calculate P values. Bars show mortality rate ± SD from subgroups defined by each variable. Chi-squared test was used to test the association between the mortalities (alive or dead) and cause of lung injury (sepsis, pneumonia, aspiration, trauma, and other) for A and association between mortalities and P<sub>aO<sub>2</sub></sub>/F<sub>IO<sub>2</sub></sub> (mild, moderate, and severe) for B.

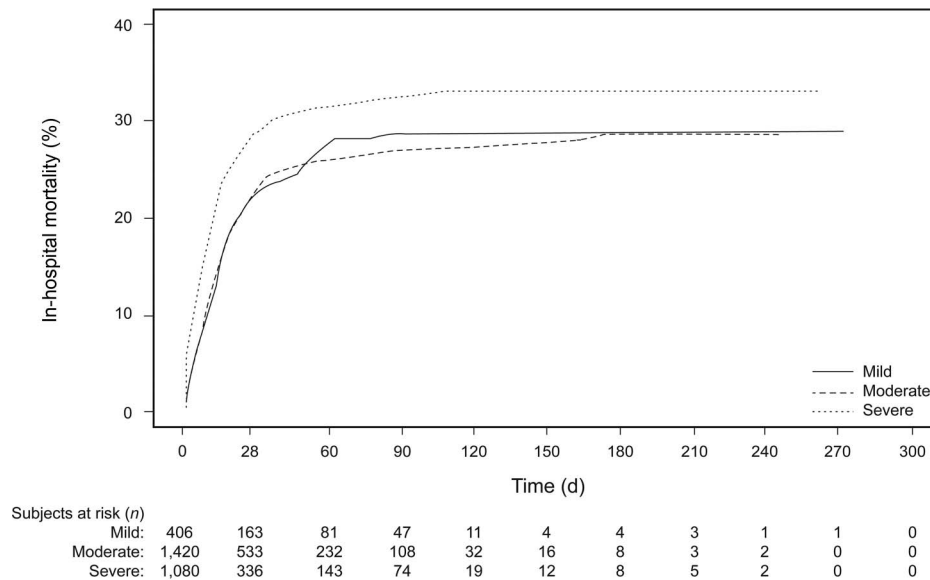


Fig. 2. Cumulative incidence of in-hospital mortality by  $P_{aO_2}/F_{IO_2}$  category.

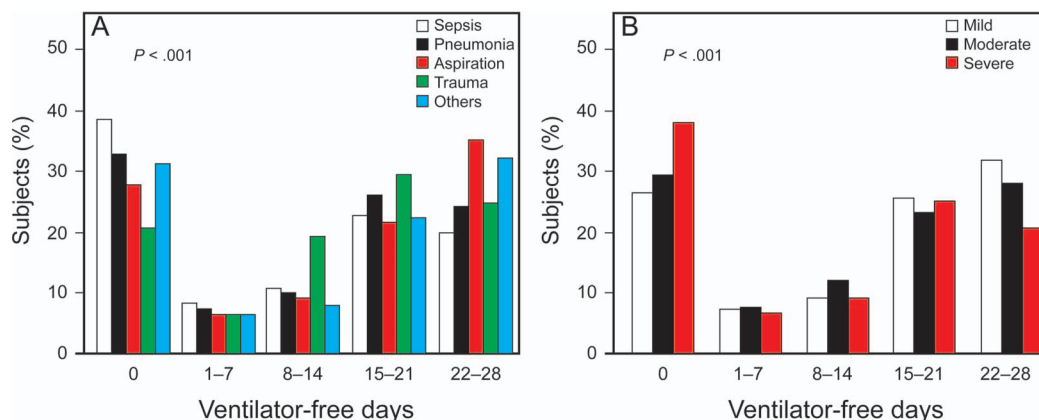


Fig. 3. Percentage of subjects with 0, 1–7, 8–14, 15–21, and 22–28 categorized ventilator-free days during the first 28 d after enrollment by cause of lung injury (A), and  $P_{aO_2}/F_{IO_2}$  ratio (B); chi-squared test was used to test the association between the categorized ventilator-free days and cause of lung injury (sepsis, pneumonia, aspiration, trauma, and other) for A and association between categorized ventilator-free days and  $P_{aO_2}/F_{IO_2}$  (mild, moderate, and severe) for B.

Also, trauma was associated with the lowest ICU-free days (OR = 0.9, 95% CI 0.83–0.99,  $P = .02$ ). Aspiration had higher ICU- and ventilator-free days (OR = 1.09, 95% CI 1.02–1.17,  $P = .01$  and OR = 1.09, 95% CI 1.02–1.16  $P = .01$ , respectively) (Table 3). There were no significant differences between the severity of ARDS in relation to ventilator- and ICU-free days (Table 3).

## Discussion

The current analysis of the ARDS Network trials was conducted to determine the effect of etiology and severity of ARDS on short-term patient outcomes. It shows that

trauma had the lowest 28- and 60-d mortality; it was also associated with the lowest ICU-free days. Aspiration was associated with higher ventilator- and ICU-free days. There were no significant differences between other etiologies of ARDS. Using  $P_{aO_2}/F_{IO_2}$  as a surrogate for severity of ARDS, there were no differences in 28-d mortality or ventilator- or ICU-free days. Subjects with severe ARDS had lower 60-d mortality.

The impact of etiology of ARDS on outcome has been previously studied with variable and sometimes contradictory results.<sup>5,6</sup> The current study shows that there is no difference in mortality between the different etiologies of ARDS except for trauma, which was associated with better prognosis. This finding is consistent with other studies.<sup>5</sup> A meta-analysis of



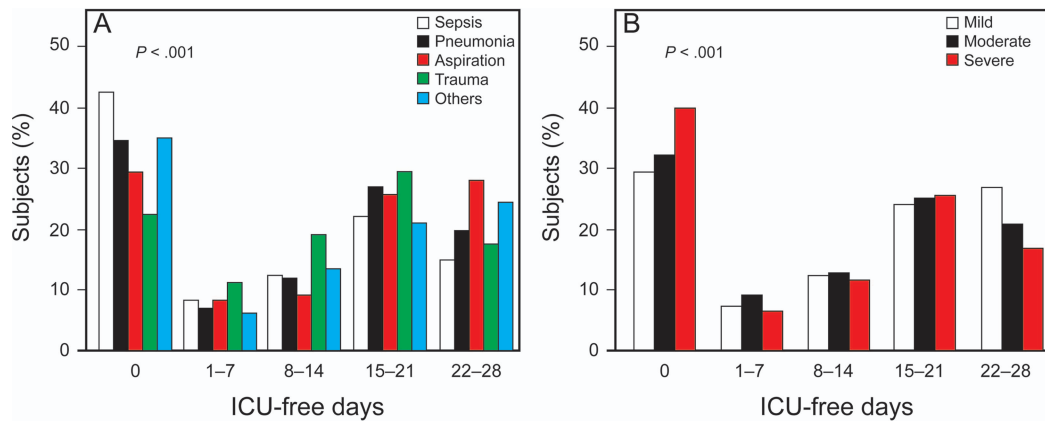


Fig. 4. Percentage of subjects with 0, 1–7, 8–14, 15–21, and 22–28 categorized ICU-free days during the first 28 d after enrollment by cause of lung injury (A) and  $P_{aO_2}/F_{IO_2}$  (B); chi-squared test was used to test the association between the categorized ICU-free days and cause of lung injury (sepsis, pneumonia, aspiration, trauma, and other) for A and association between categorized ICU-free days and  $P_{aO_2}/F_{IO_2}$  (mild, moderate, and severe) for B.

Table 3. Results of Multivariable Regression Models

Characteristics	28-d Mortality*		60-d mortality*		ICU-Free Days†		Ventilator-Free Days†	
	OR (95% CI)	P	OR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
Cause of lung injury								
Sepsis	Reference		Reference		Reference		Reference	
Pneumonia	0.98 (0.76–1.27)	.88	0.99 (0.77–1.26)	.91	1.02 (0.96–1.07)	.60	1.01 (0.96–1.06)	.73
Aspiration	0.84 (0.61–1.17)	.31	0.8 (0.58–1.1)	.17	1.09 (1.02–1.17)	.01	1.09 (1.02–1.16)	.01
Trauma	0.47 (0.26–0.83)	.01	0.5 (0.3–0.85)	.01	0.9 (0.83–0.99)	.03	0.93 (0.86–1.02)	.12
Others	1.09 (0.77–1.54)	.62	1.03 (0.74–1.44)	.86	1.07 (0.99–1.15)	.08	1.06 (0.99–1.13)	.12
$P_{aO_2}/F_{IO_2}$								
Mild	Reference		Reference		Reference		Reference	
Moderate	0.86 (0.63–1.19)	.36	0.75 (0.55–1.01)	.055	0.94 (0.89–1)	.058	0.95 (0.9–1.01)	.11
Severe	0.87 (0.63–1.22)	.42	0.71 (0.52–0.98)	.034	0.98 (0.92–1.05)	.54	0.98 (0.92–1.04)	.47

Each model was adjusted for baseline covariates, age, sex, race, APACHE III, vasopressor use, modified lung injury score, diabetes mellitus, cancer status, body mass index, pre-ICU location, patient location, and study.

\* Multivariable logistic regression.

† Multivariable zero-inflated negative binomial regression.

OR = (adjusted) odds ratio

RR = only (adjusted) rate ratio for count component is shown here

34 studies was performed to determine the difference in outcome (mortality) between subjects with pulmonary and extrapulmonary causes of ARDS. There was no difference in mortality between the 2 groups (OR of mortality in pulmonary ARDS group compared with the extrapulmonary ARDS group was 1.11 (95% CI 0.88–1.39)).<sup>6</sup> In the case ARDS in the setting of trauma, earlier studies suggested that it has worse prognosis; however, other reports show better outcomes.<sup>16,17</sup> The current study of a large and robust database confirms better mortality outcomes for trauma patients but lower ICU-free days.

The better outcome in subjects with ARDS and trauma compared with other groups may be related to multiple factors, including younger age, no co-morbid illnesses, improved ICU care, and the possibility that earlier studies

included subjects who had trauma and other complications, such as sepsis, which increased their risk of dying. Also, ARDS in patients with trauma may be in part related to fluid resuscitation and massive transfusions, which are usually associated with fewer inflammatory changes than sepsis or aspiration.<sup>18</sup> Furthermore, there is evidence that the severity of lung endothelial and alveolar epithelial injury in ARDS from major trauma appears to be less than that of other clinical disorders associated with acute lung injury.<sup>19,20</sup>

The implications of potential differences in outcome in relation to the etiology of ARDS are that different diseases may respond differently to therapeutic interventions. However, this theory was not demonstrated in previous studies, including the ARDS Network trials (Table 1). In a study

that specifically reviewed the efficacy of low tidal volume in different etiologies of ARDS, there was no difference in outcome.<sup>21</sup>

Another important finding of this analysis is that the primary outcome of ARDS is not affected by  $P_{aO_2}/F_{IO_2}$  at the time of enrollment. Also, there were no differences in ventilator- and ICU-free days but lower 60-d mortality in subjects with severe ARDS ( $P_{aO_2}/F_{IO_2} < 100$ ). Whereas some studies have suggested that initial  $P_{aO_2}/F_{IO_2}$  determined outcome and was lower in non-survivors,<sup>22</sup> others have shown that initial  $P_{aO_2}/F_{IO_2}$  did not independently predict outcome.<sup>7,23</sup> The current study provides further evidence, based on a more vigorous database and strict definition of ARDS, that the severity of ARDS, as measured by initial  $P_{aO_2}/F_{IO_2}$ , does not predict outcome, and patients should receive the same level of care and lung-protective measures regardless of how mild or severe the initial assessment of ARDS.  $P_{aO_2}/F_{IO_2}$  is useful in early identification of patients with ARDS, in fulfilling diagnostic criteria to enroll in clinical trials, and to initiate the appropriate therapies for ARDS; however, it should not be used as a predictor of outcome. A more important predictor of outcome may be the direction of  $P_{aO_2}/F_{IO_2}$  during the course of management of ARDS, as suggested by one study.<sup>24</sup>

The explanation of why there are no differences in outcome in relation to initial severity of ARDS could possibly be due to delay in diagnosis and/or management of ARDS in patients with milder disease, leading to worse outcome. Another explanation is that patients with severe ARDS (lower  $P_{aO_2}/F_{IO_2}$  at randomization) are more likely to receive protective lung strategies or other interventions that have been shown to improve outcome of ARDS, such as muscle relaxation or proning.

The study has several strengths, including the multicenter prospective database, the robust diagnosis of ARDS, strict definition of severity of ARDS at the time of randomization based on the Berlin criteria, heterogeneous patient population including surgical and trauma, and the therapeutic interventions in these trials. There are few limitations that warrant mention. These include the retrospective analysis of the prospective database and the fact that details about the different etiologies, including microbiology, antibiotic treatment, and type of trauma, are lacking. Also, this study does not provide long-term outcomes of the subjects. Further studies are needed to address these limitations.

### Conclusions

This study provides further insight about predictors of outcome in subjects with ARDS. Despite the importance of  $P_{aO_2}/F_{IO_2}$  in making the diagnosis of ARDS and strati-

fying its severity at the time of diagnosis, this study shows that  $P_{aO_2}/F_{IO_2}$  does not predict outcome of these subjects. Among the etiologies of ARDS; trauma was associated with best survival compared with other causes.

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