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Recent Trends in Acute Lung Injury Mortality: 1996-2005

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Abstract

Background: Studies from single centers have suggested that mortality from acute lung injury (ALI) has declined over time. However, recent trends in ALI mortality from centers across the U.S. are unknown. Whether recent advances in the treatment of ALI or related critical illnesses have resulted in decreased mortality from ALI is not clear.

Methods: In a study of 2451 mechanically ventilated patients with ALI enrolled in the Acute Respiratory Distress Syndrome (ARDS) Network randomized controlled trials between 1996-2005, we evaluated whether there was a temporal improvement in 60-day mortality. We also investigated whether there were temporal improvements in mortality specific to individual causes of lung injury (pneumonia, sepsis, trauma, aspiration, transfusion).

Results: Crude mortality was 35% in 1996-1997 and declined during each subsequent time period to a low of 26% in 2004-2005 (test for trend $p < 0.0005$). After adjusting for demographic and clinical covariates, including receipt of lower tidal volume ventilation and severity of illness, the temporal trend persisted (test for trend $p = 0.002$). When analyzed by individual causes of lung injury, there were not any statistically significant temporal trends in 60-day mortality for the most common causes of lung injury (pneumonia, sepsis, aspiration, trauma).

Conclusions: Over the past decade, there appears to be a clear temporal improvement in survival among patients with ALI treated at ARDS Network centers. Our findings strongly suggest that other advancements in critical care, aside from lower tidal volume ventilation, accounted for this improvement in mortality.

Keywords

acute respiratory distress syndrome; acute lung injury; mortality; temporal trend; epidemiology

Introduction

Acute lung injury (ALI) is a life-threatening form of acute respiratory failure that affects approximately 200,000 patients annually in the U.S. and accounts for 10-15% of intensive care unit (ICU) admissions.¹⁻³ When first described 40 years ago, mortality from ALI was approximately 60%.⁴ Using data from the 1980's and 1990's, several single-center studies showed that mortality from ALI declined to 30-35% during that time period.⁵⁻⁷ More recently, lower tidal volume ventilation has been shown to improve survival for patients with ALI⁸, but

whether other important advances in the treatment of sepsis and other critical illnesses have translated into decreased mortality from ALI over the past decade is not yet clear. The Acute Respiratory Distress Syndrome (ARDS) Network randomized controlled trials enrolled large numbers of patients with ALI using similar inclusion and exclusion criteria during a 10 year period from March 1996 to October 2005. We evaluated whether there was a temporal trend in 60-day mortality among patients with ALI.

Subjects and Methods

Subjects

The ARDS Network has conducted multiple randomized controlled trials to evaluate therapeutic interventions for the treatment of ALI. These trials have been described previously.⁸⁻¹³ Details of the three trials included in this study are shown in Table 1. Briefly, patients were eligible for trial participation if they met diagnostic criteria for ALI and required mechanical ventilation. Similar inclusion and exclusion criteria were used for all three trials; the most recent trial, the Fluid and Catheter Treatment Trial (FACTT), had an additional exclusion criterion for patients with renal failure requiring renal replacement therapy.^{12, 13} All studies were approved by the National Institutes of Health, the National Heart, Lung and Blood Institute and the institutional review boards at each participating study site.

Measurements

The year of enrollment was recorded for each patient participating in the trials. There were small numbers of patients (<150) enrolled in the years 1999 and 2003, therefore five 2-year increments were used (1996-1997, 1998-1999, etc.) to compare mortality. Demographic and clinical data were collected and included age, gender, body mass index, and comorbid conditions. For each patient, the clinical coordinator and physician investigator assessed the predominant clinical risk factor for ALI within 48 hours of onset. Based on careful review of the clinical and laboratory data, the predominant clinical risk factor was classified as pneumonia, sepsis, aspiration, trauma, multiple transfusion, other or unknown. Baseline measurements preceding randomization included APACHE (Acute Physiologic and Chronic Health Evaluation) III score, vasopressor administration, hemodynamic and respiratory measurements including ventilator parameters. To separate acute physiologic derangements from chronic comorbidities, an acute physiology score (APS) was calculated from the APACHE III score.

The primary outcome measure for this analysis was 60-day mortality after study enrollment. Patients who were discharged home and breathing without mechanical ventilation were presumed to be alive at day 60.

Statistical Methods

Demographic and baseline clinical characteristics of the patients enrolled during the five 2-year time periods were compared using a chi-square or Fisher's exact test for categorical variables and an analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables.

We used logistic regression to evaluate the temporal trends in ALI survival during the 10-year observation period. To create the regression models, we selected variables for inclusion if they were thought to be possible confounders in the relationship between time period of enrollment and mortality from ALI. We included variables if they were associated with time of enrollment in the bivariate analyses ($p < 0.20$) or if they were considered clinically relevant on an *a priori* basis. The initial model included age, gender, body mass index, cause of lung injury (pneumonia, sepsis, aspiration, trauma, transfusion, other or unknown) $\text{PaO}_2\text{:FiO}_2$ ratio,

comorbid conditions (diabetes, chronic dialysis, HIV/AIDS, cirrhosis, solid tumors, leukemia, lymphoma and immunosuppression), receipt of low tidal volume ventilation and acute physiology score (APS) calculated from the APACHE III score. Backwards selection was used and the likelihood ratio test compared nested models. We removed variables if their removal did not cause a statistically significant change in the overall model ($p > 0.05$). All models were adjusted for the clustering of patients at the hospital level through the use of generalized estimating equations with an exchangeable correlation structure, modeling hospital as a random factor. These results were nearly identical to those models that did not adjust for patient clustering, therefore only the original results are presented. To test for a significant temporal trend, we used linear contrasts in the coefficients corresponding to the variables representing time period of trial enrollment.¹⁴

To investigate whether there were temporal improvements in mortality specific to individual causes of lung injury (for example, perhaps mortality improved for patients with sepsis-associated ALI, but mortality did not improve for patients with trauma-associated ALI), we first assessed crude mortality by individual cause of lung injury, using the score test for trend of odds to determine if a temporal trend existed.¹⁴ We then performed multivariable analyses stratified by individual cause of lung injury, using linear contrasts to test for a significant temporal trend.¹⁴ In addition, we evaluated possible statistical interactions between time period of enrollment and each cause of lung injury. We used the likelihood ratio test to compare a model including cause of lung injury-time period of enrollment interaction terms with a nested model that included only the main effects and time period of enrollment and no interaction terms. A statistically significant interaction term would indicate that mortality for an individual cause of lung injury differed by enrollment period.

Patients with renal failure requiring renal replacement were excluded from the final clinical trial (FACTT) and not from the earlier trials (ARMA and ALVEOLI). To address the impact of renal failure on our results, we repeated all analyses after excluding any patient who needed renal replacement therapy prior to trial enrollment. An additional analysis excluding those patients from ARMA who received ventilation with 12 ml/kg was performed to address whether the results were significantly affected by the transition to lower tidal volume ventilation in the later trials.

Finally, we performed an exploratory multivariable analysis using one-year time increments to examine whether patients who received higher tidal volume ventilation during the ARMA trial (1996-1999) had a temporal improvement in mortality.

We used STATA, version 9.2 (College Station, Texas) for all analyses. Statistical significance was defined as a two-tailed $p < 0.05$.

Results

There were a total of 2451 patients who were enrolled in the ARDS Network clinical trials from 1996-2005 and were included in the cohort. Baseline characteristics by enrollment period are shown in Table 2. The age of patients was similar across all enrollment periods. More men than women were enrolled during every period. Patients enrolled in 1996-1997 had the lowest BMI compared with other periods. APACHE III scores and acute illness severity, as measured by APS, increased over time. Other temporal differences are shown in Table 2.

Crude mortality was 35% in 1996-1997 and declined during each subsequent time period to a low of 26% in 2004-2005 (Table 3, test for trend $p < 0.0005$). Crude mortality was higher for patients who received higher tidal volume ventilation compared to those who received lower tidal volume ventilation. Crude mortality declined for patients who received lower tidal volume ventilation, but this was not a statistically significant trend (test for trend $p = 0.19$, Figure 1).

The temporal trend toward decreased mortality persisted after adjustment for age, gender, receipt of low tidal volume ventilation, APS, comorbid conditions (HIV/AIDS, lymphoma), trauma as the cause of lung injury and PaO₂:FiO₂ (Figure 2).

When crude mortality was analyzed by cause of lung injury, the mortality trend over time was downward in all groups except the trauma group, which had an exceptionally low baseline mortality (Table 3). Because statistical power was lower in these subgroup analyses, p values did not always meet the conventional level of statistical significance, but were ≤ 0.10 in all cases except for trauma. The test for trend p value was highly significant for the overall cohort ($p < 0.0005$). Adjusted mortality appeared to improve for patients with all causes of lung injury except trauma during the 10-year study period (Figure 3). However, the only statistically significant temporal trend was among patients with other or unknown causes of lung injury. There were no significant interactions between the time period of enrollment and any of the causes of lung injury (pneumonia, sepsis, trauma or aspiration, transfusion, other/unknown) after adjusting for age, gender, receipt of low tidal volume ventilation, APS, comorbid conditions (HIV/AIDS, lymphoma) and PaO₂:FiO₂ ($p \geq 0.10$ for all interaction terms).

None of the point estimates or confidence intervals for any of the analyses was substantively changed after excluding patients who required renal replacement therapy prior to trial enrollment. Similarly, when the analysis was restricted to patients who received lower tidal volume ventilation, the downward temporal trend persisted, and none of the point estimates or confidence intervals were substantively altered.

The exploratory multivariable analysis using one-year time increments revealed that mortality declined for patients who received higher tidal volume ventilation ($n=429$) during the years 1996-1999 (OR for death in 1996=1.0 (reference) OR for death in 1997=0.69, OR for death in 1998=0.73, OR for death in 1999=0.59). However, this was not a statistically significant trend (test for trend $p=0.42$).

Discussion

In this study of patients with ALI who were enrolled in the ARDS Network clinical trials between 1996 and 2005, there was a strong, statistically significant temporal improvement in 60-day mortality when comparing enrollment periods. During the 10-year study period, adjusted mortality appeared to improve for patients with the most common causes of lung injury – sepsis, pneumonia and aspiration. However, these trends did not meet statistical significance, likely because of the smaller number of patients in these subgroups. In sum, it appears that general improvements in ICU care translated into decreased ALI mortality for patients treated at ARDS Network centers over the 10 year study period. These findings support previous studies that have shown that mortality from ALI is declining.⁵⁻⁷ However, these prior studies were limited in that they were performed at single centers, and the data supporting these investigations were primarily from years prior to 1994, predating both the American-European Consensus Conference definition of ALI and the introduction of lower tidal volume ventilation. A recent meta-analysis by Zambon and Vincent that included 72 studies and examined survival among patients with ALI from 1994 through 2006 showed that overall mortality decreased by approximately 1.1% per year during this period.¹⁵ This meta-analysis was limited by the heterogeneity of the study populations and the lack of individual-level data. The authors were not able to adjust for differences in study inclusion or exclusion criteria, severity of illness or other important clinical or demographic differences.

The present study uses current multi-center data with a uniform definition of ALI and clearly demonstrates that mortality from ALI has improved over the past decade for patients who were treated at ARDS Network centers. Additional strengths of this study include the large number

of patients and the detailed patient-level data including information about comorbid conditions and severity of illness. Importantly, prior studies did not perform multivariable analysis with adjustments for severity of illness or comorbid conditions.^{5-7 15}

Several recent studies have shown that there has been a decline in case fatality from sepsis over the past two decades.^{16, 17} In addition, Milberg and colleagues observed a significant decrease in mortality from 1983-1993 among patients with sepsis as their cause of lung injury.⁶ Given the recent advances in the treatment of severe sepsis, including early goal-directed therapy¹⁸ and activated protein C¹⁹, it is reasonable to hypothesize that mortality for patients with sepsis-related ALI has improved over the past decade. While there were not statistically significant temporal improvements in mortality among patients with sepsis-associated ALI enrolled in the ARDS Network trials, our study was underpowered to detect small to moderate differences in mortality among the subgroups of patients with different causes of lung injury. This overall temporal trend in improved mortality for patients with diverse causes of lung injury supports the hypothesis that advancements in the general care of critically ill patients may be responsible for these findings. While our study was not capable of determining what mechanisms accounted for the improvement in mortality, recent changes in critical care including, restrictive transfusion protocols, early antibiotic use and nutritional support and appropriate prophylaxis measures are likely contributing.²⁰ Although mortality varied by cause of lung injury, we do not believe that year-to-year variation in case mix accounted for the observed temporal improvement in mortality, as we adjusted for cause of lung injury in the multivariable analysis.

Our study has some limitations. Because this was a secondary analysis of data from randomized controlled trials, it is possible that enrollment targeted patients who were less severely ill in the later trials. Disputing this possibility is the finding that APACHE III scores and APS increased with each subsequent enrollment period. Exclusion of patients requiring renal replacement therapy from FACTT could also have influenced our temporal mortality estimates. However, when the analysis was restricted to patients who did not need renal replacement therapy, the downward temporal mortality trend persisted. Similarly, the transition to lower tidal volume ventilation in the later trials did not appear to be accounting for our findings, as the results were not substantively altered when the analysis was restricted to patients who received lower tidal volume ventilation. Although we had information about many comorbid conditions, we were not able to make comprehensive adjustments for all comorbid conditions. Also, we did not have information about the severity of patients' comorbid conditions like HIV/AIDS or diabetes. It is possible that patients had fewer and less severe comorbid conditions in the later enrollment periods, although there is no apparent reason why this should be so.

Our study may be limited in its generalizability. Over 90% of screened patients were excluded from the ARDS Network trials. We do not have mortality data about patients who were not enrolled in the trials because of issues related to the protection of privacy. Inclusion and exclusion criteria were similar across all trials, making temporal selection bias unlikely. Excluded patients were more likely to have comorbid conditions (transplant, chronic lung disease) and were more likely to be older - characteristics associated with higher mortality. Alternatively, excluded patients were more likely to have trauma as the cause of lung injury and a higher PaO₂:FiO₂ ratio.²¹ These characteristics are associated with lower mortality. Thus, it is difficult to speculate whether mortality was higher or lower among patients who were not enrolled. Further, we do not have information about patients who died before they could be screened or enrolled in the trials. If more severely ill patients died before they could be screened or enrolled during the later time periods, this would have biased our results towards finding a temporal improvement in mortality. Finally, because all patients were cared for at specialized ARDS Network centers, our findings may reflect an improvement of care only at these centers, rather than broad improvements in care throughout the U.S.

Our findings strongly suggest that other advancements in critical care, aside from lower tidal volume ventilation, resulted in improved mortality for patients with ALI treated at ARDS Network centers from 1996-2005. Although we are unable to identify what exactly is accounting for the improvement in mortality, one possible explanation is the bundling of care for patients with ALI restrictive transfusion protocols, early antibiotic administration and nutritional support and appropriate prophylaxis. Importantly, for clinical trials involving patients with ALI, the decreasing mortality rate poses significant challenges in trial design. Future clinical trials investigating new therapies for ALI will need to enroll larger numbers of patients in order to be adequately powered to detect differences in mortality. Alternatively, future trials may need to choose non-mortality outcomes or target higher risk groups in order to find meaningful differences in mortality.

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Figure 1. Crude 60-day Mortality Among ARDS Network Patients, 1996-2005

Test for trend p value= 0.19 for patients who received lower tidal volume ventilation.

Figure 2. Adjusted 60-day Mortality Among ARDS Network Patients, 1996-2005

Points represent adjusted 60-day mortality for the enrollment period, and error bars the 95% confidence intervals.

Adjusted for age, gender, receipt of low tidal volume ventilation, Acute Physiology Score (APS), comorbid conditions (HIV/AIDS, lymphoma), trauma as the cause of lung injury and $\text{PaO}_2:\text{FiO}_2$.

Reference period is 1996-1997 enrollment period (OR=1.0).

Figure 3. Adjusted 60-day Mortality by Cause of Lung Injury, 1996-2005

Points represent adjusted 60-day mortality for the enrollment period, and error bars the 95% confidence intervals.

Adjusted for age, gender, receipt of low tidal volume ventilation, Acute Physiology Score (APS), comorbid conditions (HIV/AIDS, lymphoma), trauma as the cause of lung injury and $\text{PaO}_2:\text{FiO}_2$.

Test for trend $p \geq 0.05$ for all causes of lung injury, except other/unknown $p=0.008$

Reference period is 1996-1997 enrollment period (OR=1.0).

Table 1

Description of ARDS Network Randomized Controlled Trials

Trial	ARMA ^a	ALVEOLI ^b	FACTT ^c
Years	1996-1999	1999-2002	2000-2005
Intervention	Low tidal volume ventilation (6 ml/kg vs. 12 ml/kg)	Higher PEEP ^d vs. lower PEEP ^d	Pulmonary artery catheter vs. central venous catheter + Conservative vs. liberal fluid management strategy
Number of patients enrolled (N)	902	549	1000
Did intervention(s) reduce mortality?	Yes	No	No

^a ARMA = Respiratory Management of Acute Lung Injury

^b ALVEOLI = Assessment of Low Tidal Volume and Elevated End-Expiratory Lung Volume to Obviate Lung Injury

^c FACTT = Fluid and Catheter Treatment Trial

^d PEEP = positive end-expiratory pressure

Table 2
Demographic and Clinical Characteristics by Years of Enrollment^{ab}

Characteristic	1996-1997 (n=558)	1998-1999 (n=372)	2000-2001 (n=738)	2002-2003 (n=243)	2004-2005 (n=540)	P value ^e
Age	52 ± 17	52 ± 17	51 ± 17	50 ± 16	51 ± 16	0.30
Male	327 (59)	227 (61)	396 (54)	131 (54)	292 (54)	0.08
BMI, kg/m ²	26.4 ± 6.3	28.0 ± 7.4	27.5 ± 7.0	29.0 ± 7.5	28.9 ± 7.4	<0.0005
APACHE III ^c	82 ± 27	86 ± 31	95 ± 32	95 ± 31	96 ± 33	<0.0005
Acute Physiology Score (calculated from APACHE III)	71 ± 25	75 ± 30	85 ± 31	85 ± 29	86 ± 32	<0.0005
Vasopressor use	237 (43)	43 (31)	204 (28)	74 (30)	186 (34)	<0.0005
Cause of lung injury						<0.0005
pneumonia	163 (29)	144 (39)	321 (44)	121 (50)	232 (43)	
sepsis	157 (28)	82 (22)	165 (22)	53 (22)	132 (24)	
aspiration	79 (14)	59 (16)	108 (15)	37 (15)	84 (16)	
trauma	62 (11)	35 (9)	59 (8)	12 (5)	47 (9)	
transfusion	14 (3)	14 (4)	24 (3)	5 (2)	5 (1)	
other or unknown	83 (15)	38 (10)	61 (8)	15 (6)	40 (7)	
Comorbid conditions						
Diabetes	66 (12)	64 (17)	118 (16)	38 (16)	96 (19)	0.05
Chronic Dialysis	15 (3)	8 (2)	15 (2)	0 (0)	1 (0.2)	0.03
HIV or AIDS	29 (5)	20 (5)	57 (8)	17 (7)	32 (6)	<0.0005
Cirrhosis	19 (3)	8 (2)	24 (3)	5 (2)	22 (4)	0.39
Solid tumors	13 (2)	4 (1)	12 (2)	3 (1)	7 (1)	0.64
Leukemia	14 (3)	5 (1)	15 (2)	4 (2)	11 (2)	0.81
Lymphoma	3 (1)	10 (3)	9 (1)	0 (0)	7 (1)	0.02
Immunosuppression	58 (11)	42 (11)	108 (15)	16 (7)	36 (7)	<0.0005
Baseline respiratory variables						
Tidal volume (ml)/kg PBW ^d	10.4 ± 1.8	10.2 ± 2.1	8.06 ± 2.4	7.5 ± 2.0	7.2 ± 1.5	<0.0005
Plateau pressure, cm H ₂ O	30 ± 8	30 ± 8	27 ± 7	26 ± 7	26 ± 7	0.01
Peak airway pressure, cm H ₂ O	37 ± 10	37 ± 9	33 ± 9	32 ± 8	32 ± 9	<0.0005
Mean airway pressure, cm H ₂ O	17 ± 12	17 ± 12	16 ± 5	15 ± 5	15 ± 5	0.30
PEEP, cm H ₂ O	8.3 ± 3.7	8.7 ± 4.0	9.6 ± 4.3	9.3 ± 3.9	9.4 ± 3.9	<0.0005

Characteristic	1996-1997 (n=558)	1998-1999 (n=372)	2000-2001 (n=738)	2002-2003 (n=243)	2004-2005 (n=540)	P value ^e
Arterial pH	7.40 ± 0.08	7.40 ± 0.08	7.38 ± 0.09	7.36 ± 0.10	7.35 ± 0.09	<0.0005
PaO ₂ , mm Hg	86 ± 32	86 ± 32	86 ± 37	92 ± 43	91 ± 40	0.20
PaCO ₂ , mm Hg	36 ± 8	37 ± 9	40 ± 10	40 ± 10	40 ± 9	<0.0005
PaO ₂ :FiO ₂	148 ± 71	148 ± 66	149 ± 69	152 ± 68	154 ± 70	0.71

^aValues are mean ± SD or n (%).

^bAll clinical variables were measured at the time of trial enrollment, prior to randomization.

^cAcute Physiology and Chronic Health Evaluation

^dPredicted body weight.

^eP values were calculated using the chi-squared or Fisher's exact test for categorical variables, and the analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables.

Table 3
Crude 60-day Mortality During Each Enrollment Period by Cause of Lung Injury

Cause of lung injury	1996-1997 ^a	1998-1999	2000-2001	2002-2003	2004-2005	Test for trend p value ^b
Pneumonia, No. (%)	59/163 (36) (OR=1.0)	48/144 (33) (OR=0.9)	89/321 (28) (OR=0.7)	33/121 (27) (OR=0.7)	66/232 (28) (OR=0.7)	0.07
Sepsis, No. (%)	64/157 (41) (OR=1.0)	37/82 (45) (OR=1.2)	54/165 (33) (OR=0.7)	19/53 (36) (OR=0.8)	44/132 (33) (OR=0.7)	0.10
Aspiration, No. (%)	31/79 (39) (OR=1.0)	12/59 (20) (OR=0.4)	31/108 (29) (OR=0.6)	7/37 (19) (OR=0.4)	17/84 (20) (OR=0.4)	0.01
Trauma, No. (%)	6/62 (10) (OR=1.0)	4/35 (11) (OR=1.2)	6/59 (10) (OR=1.1)	3/12 (25) (OR=3.1)	4/47 (9) (OR=0.9)	0.92
Transfusion, No. (%)	5/14 (36) (OR=1.0)	8/14 (57) (OR=2.4)	6/24 (25) (OR=0.6)	0/5 (0) (OR=0)	1/5 (20) (OR=0.5)	0.09
Other or unknown, No. (%)	28/83 (34) (OR=1.0)	11/38 (29) (OR=0.8)	17/61 (28) (OR=0.8)	4/15 (27) (OR=0.7)	7/40 (18) (OR=0.4)	0.09
All subjects, No. (%)	193/558 (35) (OR=1.0)	120/372 (32) (OR=0.9)	203/738 (27) (OR=0.7)	66/243 (27) (OR=0.7)	139/540 (26) (OR=0.7)	0.0004

^aReference period is 1996-1997 enrollment period (OR=1.0).

^bScore test for trend of odds was used to calculate p values.