Long-term Survival in Patients with Severe Acute Respiratory Distress Syndrome and Rescue Therapies for Refractory Hypoxemia

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Abstract

Objective: To assess survival up to 5 years in patients who develop severe acute respiratory distress syndrome (ARDS) and evaluate differences in characteristics and outcomes for patients selected for treatment with a rescue therapy (inhaled nitric oxide, inhaled epoprostenol or prone position ventilation) versus conventional treatment.

Design and Setting: Retrospective cohort study of patients admitted to the intensive care unit (ICU) at a 413-bed Level 1 trauma university hospital.

Patients: Patients diagnosed with severe ARDS, according to the Berlin definition, within 72 hours of ICU admission between 1/1/2008 and 12/31/2011.

Methods: Data were abstracted from the electronic medical record and included demographic and clinical variables, hospital and ICU length of stay, discharge disposition, and hospital costs. We compared patients placed on inhaled nitric oxide, inhaled epoprostenol or ventilated in the prone position with patients treated conventionally. To determine survival beyond hospital discharge, patient-level data were linked to the Washington State Death Registry. Kaplan-Meir survival analysis methods were used to assess survival. Cox's proportional hazards models were used to compare differences in outcomes between patients treated with a rescue therapy and those treated conventionally. Costs were analyzed using the Lin method to estimate mean total costs in the presence of censoring.

Main Results: 428 patients meeting the inclusion criteria were identified, of whom 62 (14%) were placed on a rescue therapy. Five-year survival for all patients was 54.9% (95% CI: 50.2%, 60.1%). For patients who were discharged from the hospital alive, 5-year survival was 84.5% (95% CI: 79.8%, 89.4%). Mean hospital cost was $701 K (95% CI: $97K, $846 K). Admission PaO_2/FIO_2 ratios were similar between patients treated with a rescue therapy and those treated

conventionally. However, prior to initiation of rescue therapy, patients treated with a rescue therapy had substantially lower PaO_2/FIO_2 ratios by 72 hours (54 mm Hg ± 17 versus 69 mm Hg ± 17; p=<.01). The hazard ratio of death up to 5 years following their ICU admission was not different between patients with and without rescue therapy (HR: 1.31, 95% CI: 0.89, 1.94; p = 0.17).

Conclusions: Severe ARDS patients surviving to hospital discharge have relatively good long-term survival. Patients with worsening hypoxemia are selected to receive a rescue therapy. Future prospective studies should investigate the impact of the timing of initiation of a rescue therapy prior to the development of life-threatening critical hypoxemia on long-term outcomes.

Introduction:

Each year, roughly 175,000 Americans will be diagnosed with acute respiratory distress syndrome (ARDS), a clinical diagnosis that carries 30-40% mortality.(1-6) Despite advances made in therapies such as the use of lung protective ventilation, ARDS continues to be associated with high morbidity and mortality. While long-term outcomes have been studied in patients with mild and moderate ARDS, patients who develop severe ARDS are typically under-represented in clinical trials, and to our knowledge, the long-term outcomes of these patients, including those treated with rescue therapies, have never been studied.(6-9)

Patients with severe ARDS may develop life-threatening refractory hypoxemia that persists despite use of conventional lung protective ventilation strategies.(3) In clinical practice, as an effort to improve oxygenation in these patients, several different "rescue therapies" are often used, including inhaled nitric oxide, inhaled epoprostenol and prone position ventilation.(3, 10-12) However, randomized control trials conducted to date utilized rescue therapies as an adjunctive modality to treat ARDS, not as a "last resort" intervention for treatment of critical hypoxemia in patients unlikely to survive.(13-19)

The main objective of this study was to assess the long-term survival up to 5 years in a cohort of patients meeting severe ARDS criteria according to the Berlin definition.(5) Our secondary objectives were to describe how patients placed on a rescue therapy differ in characteristics and outcomes from patients treated conventionally.

Materials and Methods

Ethics Approval and Setting

The University of Washington Institutional Review Board approved this study with a waiver of informed consent. The study setting was Harborview Medical Center (HMC), a 413-

bed Level 1 trauma hospital located in Seattle, Washington. HMC is affiliated with the University of Washington and is the only Level 1 trauma center for Washington, Alaska, Montana and Idaho. There are 88 intensive care unit (ICU) beds distributed among five ICUs (medical/cardiac, trauma/surgical, neurology/neurosurgical, burn and pediatric).

Population Selection and Study Eligibility Criteria

We used the ARDS Definition Task Force's Berlin definition for severe ARDS, defined by a PaO_2/FIO_2 ratio $\leq$ 100 mm Hg, to develop our cohort. (5) All medical records for patients ages 18 and older, admitted to a HMC ICU between 1/1/2008 and 12/31/2011, who were mechanically ventilated and met criteria for severe ARDS were screened. To reduce heterogeneity in the study population with regard to ARDS risk factors among early or late onset ARDS, criteria were further narrowed to development of a PaO_2/FIO_2 ratio $\leq$ 100 within 72 hours of ICU admission. Patients were excluded if their radiographic criteria were not consistent with a diagnosis of ARDS. The radiographic criteria used for diagnosis of ARDS were the presence of bilateral opacities that are not fully explained by effusions, fluid overload, cardiac failure, lung/lobar collapse or nodules.(5)

To verify radiographic criteria, screened patients meeting our inclusion criteria were linked to the HMC Acute Lung Injury Registry, a registry that is maintained by the on-site ARDS network study coordinator. Among patients who matched, we randomly reviewed 25% of the chest x-rays to ensure greater than 95% agreement. We reviewed chest x-rays of subjects identified via the electronic search who were not included in the ALI registry, starting with 8 hours prior and up to 24 hours after the study qualifying first PaO_2/FIO_2 ratio $\leq$ 100. When needed, manual record review of the patient's chart was used to verify the diagnosis of ARDS by ensuring radiographic findings were not a result of congestive heart failure, pulmonary edema or

chronic lung disease. Patients placed on inhaled nitric oxide, inhaled epoprostenol or ventilated in the prone position for the treatment of critical hypoxemia were identified within this cohort.

Data collection

Data were electronically and manually abstracted from the HMC electronic medical record (EMR). Demographic variables including age, gender, body mass index (BMI) and race/ethnicity were collected. Clinical admission variables collected included type of ICU admission (medical, trauma, non-trauma surgical) and primary admission diagnostic category based on ICD-9 codes. To capture disease severity at ICU admission, the simplified acute physiology score II (SAPS II) was calculated for each patient. Additionally, for trauma patients, injury severity score (ISS) and abbreviated injury severity (AIS-Head, AIS-Chest) were collected from the HMC Trauma Registry, a computerized database that contains comprehensive information for all patients evaluated for a traumatic injury at HMC.(20) Admission PaO_2/FIO_2 ratios and mechanical ventilation were also collected.

Clinical and physiologic variables during the ICU stay were collected and included the study qualifying PaO_2/FIO_2 ratio, defined as first ratio ≤ 100 within 72 hours of ICU admit, the time from ICU admit to the qualifying ratio, the lowest PaO_2/FIO_2 ratio within 24 hours and within 72 hours of ICU admit, days spent with $FIO_2 > 60\%$, and days of mechanical ventilation. Variables associated with exposure to a rescue therapy were collected and included the hours since ICU admission to initiation of therapy, PaO_2/FIO_2 ratio prior to initiation of therapy and duration of therapy. Use of vasopressors, neuromuscular blockade, mean sequential organ failure assessment (SOFA) and max SOFA were also recorded.

Costs were estimated from the institutional perspective. For each patient, hospital charges were obtained from hospital billing records. Charges were converted to costs by

applying the institutional charge-to-cost ratio (0.668). Dollar values for cost have been adjusted for inflation and are reported in 2012 U.S. dollars.

Washington State death data from the WA State Department of Health Center for Health Statistics were obtained for all deaths occurring between 1/1/2008 and 12/31/2012. Data from 2013 were not available at the time. Patient identifying information obtained from the HMC electronic medical record, including name, social security number and date of birth, were linked with the death data in order to ascertain the date, cause and location of death of our study cohort.

Outcomes

The primary endpoint was survival up to 5 years based on available data using initial date of ICU admission as the index time. Secondary endpoints included 28-day mortality, one-year mortality, ICU and hospital length of stay, discharge disposition and costs.

Statistical Analysis

Baseline demographic characteristics and clinical variables were compared between the patients receiving a rescue therapy versus those not using a two-sample Student's t-test with assumption of unequal variances (Satterthwaite's degrees of freedom) for continuous variables and Fisher's exact or chi-square tests for categorical variables.

For the primary analysis (long-term survival) we chose to use survival analysis because patients contributed different lengths of time at risk and we were interested in long-term outcomes beyond hospital discharge. The index time was date of first ICU admission. Duration of follow-up differed for each patient based on the date of ICU admission and available death data. Censored data were assumed to be independent of the survival times and censored patients included patients who neither died in the hospital nor were located in the WA State death registry and had a primary residential address outside WA State. Because we only linked with the WA

State Death Registry, we conservatively considered non-WA State residents to be lost to follow-up (Figure 1). The estimation of the survival function was computed using the Kaplan-Meier product limit estimator and graphically displayed using Kaplan-Meier curves (Figure 2A-C).

Cost data were analyzed using the Lin method for censored data without cost histories in which weighted costs were summed over the hospitalization period.(21) We divided the hospitalization period into 5-day intervals and for each time interval, calculated the average total hospital costs for patients who died during that interval. The average costs for each interval were then multiplied by the probability of dying during the interval to determine weighted costs. (20, 21) We used the bootstrap resampling method to obtain percentile-based 95% confidence intervals.

A Cox's proportional hazards model was used to compare the survival among patients who received a rescue therapy versus those who did not. The model was adjusted for observed, *a priori* defined potential confounders, including age, Caucasian race, admission SAPS II and primary admission diagnosis of sepsis or pneumonia.

Out of concern for residual confounding by indication, we conducted *a priori* planned secondary analyses using propensity adjusted for mortality up to 5 years, 28-day mortality and one-year mortality between patients receiving a rescue therapy and not receiving a rescue therapy. The propensity score was calculated using age, gender, BMI, Caucasian race, patient population (medical, trauma, surgical non-trauma), admission diagnosis of sepsis or pneumonia, mechanical ventilation within 24 hours of ICU admit, SAPS II, PaO_2/FiO_2 ratio at ICU admission, highest glucose and lowest hemoglobin. Injury severity scores (ISS), including AIS-Head and AIS-Chest were not included as these scores are only pertinent to trauma patients.

A two-sided alpha level of .05 was considered statistically significant. Statistical analyses were performed using STATA statistical software, version 12.0 (StataCorp., College Station, TX), and R statistical software, version 2.14.1 (Comprehensive R Archive Network). Data are presented as mean ± standard deviation unless otherwise noted.

Results

Study population

The final cohort included 428 patients meeting severe ARDS criteria according to the Berlin definition; 62 patients were exposed to a rescue therapy and 366 were treated conventionally (Figure 1). Demographic and clinical characteristics are displayed in Table 1. The mean age was 51 years (± 17.7). Roughly 85% of patients were admitted to the medical ICU with sepsis or pneumonia being the most common primary admission diagnosis. The mean SAPS II score was 60.8 (± 18). Within 24 hours of ICU admission, 38% of patients were mechanically ventilated with an average PaO2/FiO2 ratio of 160 mm Hg (± 108). The mean study qualifying PaO2/FiO2 ratio for the entire cohort was 76 mm Hg (± 16).

Primary outcome

The Kaplan-Meier survival plots are shown in Figure 2. Survival up to 5 years since ICU admission was 54.9% (95% CI: 50.2%, 60.1%). Survival at 28 days from ICU admission was 67.2% (95% CI: 62.9%, 71.9%); among those surviving to hospital discharge, 84.5% (79.8%, 89.4%) were alive 5 years post-hospital discharge. Median follow-up time from ICU admission was 449 days (IQR: 13, 1138). Most deaths occurred within 28 days of ICU admission with very few additional deaths occurring post-hospital discharge in our follow-up period.

Secondary outcomes

Median ICU length of stay was 15 days (IQR: 8, 25) and median hospital length of stay was 20 days (IQR: 10, 34). Mean total hospital cost for the cohort was $701K (95% CI: 97K, 846K).

Patients treated with a rescue therapy compared to those who were not were significantly younger (41.7 years ± 19.0 vs. 52.6 years ± 17.0, $p<.01$), more likely to have ARDS secondary to an infectious etiology (pneumonia or sepsis) ($p<.01$), and to be mechanically ventilated within 24 hours of ICU admission ($p=.01$) (Table 2). Baseline severity of illness scores, SAPS II, ISS, AIS-Head and AIS-Chest, were not significantly different between groups. There was no significant difference in the patient population in terms of type of ICU admission. The PaO_2/FIO_2 ratio at ICU admission was also similar in both groups ($p=.47$), however the study qualifying PaO2/FiO2 ratio within 72 hours of ICU admission was significantly different (68 mm Hg ± 18 versus 78 mm Hg ± 16, $p<.01$).

Physiologic variables pertinent to degree and onset of hypoxemia are displayed in Table 3. Lowest PaO_2/FIO_2 ratios within 24 hours of ICU admit were not different, however, the nadir PaO_2/FIO_2 ratio within 72 hours was lower in the group exposed to a rescue therapy (54 mm Hg ± 17 mm Hg vs. 69 mm Hg ± 17 mm Hg; $p<.01$). Patients treated with a rescue therapy spent a greater number of days mechanically ventilated and a significantly higher number of days on an $FIO_2 > 60\%$ when compared to the group not receiving a rescue therapy (median (IQR): 8 days (4, 17) versus 5 days (3, 8); $p<.01$).

Survival curves for patients treated with a rescue therapy and those treated conventionally are displayed in Figure 3. By 28 days, 45% of patients treated with a rescue therapy died, compared to 30% in the conventionally treated group. We found that 47% of patients treated with a rescue therapy died during their hospitalization, compared to 32% in the group receiving

conventional treatment. Among patients treated with a rescue therapy, 13% were eventually discharged home from the hospital compared to 29% in the conventionally treated group.

In unadjusted analyses, patients treated with a rescue therapy had a non-statistically significant 30% higher risk of death up to 5 years following their ICU admission (HR: 1.31, 95% CI: 0.89, 1.94; p = 0.17) (Table 4). Statistically significant mortality difference was seen at 28 days (HR 1.67 95% CI: 1.10, 2.53; p = .02). Results from adjusted analyses and our propensity adjusted analyses were similar to our unadjusted analyses.

Discussion

Overview. We evaluated the long-term survival of 428 patients with severe ARDS and found that while in-hospital mortality was high, patients who survived to hospital discharge had overall good 5-year survival.

We found that patients treated with a rescue therapy were young, had rapidly progressing hypoxemia and a high risk of death. Our data indicate that, unlike the setting of randomized controlled trials, in clinical practice, therapy is not initiated until severe ARDS patients have a declining PaO_2/FIO_2 ratio within 72 hours. (13-15, 17, 18)

Context with previous studies. Meta-analyses have suggested that prone position ventilation is associated with a mortality benefit in patients with a PaO_2/FIO_2 ratio ≤ 100. (22) Additionally, in a trial conducted by Mancebo *et al*, early initiation of prone ventilation in severe ARDS patients demonstrated a trend towards a reduced mortality. (16) Based on these observations, Guerin and colleagues recently reported the results of a prospective, multicenter, randomized trial of 466 severe ARDS (defined as PaO_2/FIO_2 ratio < 150) patients assigned to early initiation of prone position ventilation or supine position.(19) Early application of prone positioning significantly decreased 28-day and 90-day mortality.(19)

Despite restricting our eligibility criteria to severe ARDS according to the Berlin definition, our results are consistent with the results of a prospective, matched parallel cohort study conducted by Davidson *et al* in which no difference in long-term survival between ARDS survivors and their matched controls was found. (23, 24) In contrast to these results, our finding that patients treated with a rescue therapy versus conventional treatment might have a higher risk of death reflects that physicians delay initiation of therapy until patients become more critically ill.

Implications. It remains uncertain whether delaying initiation of therapy constitutes a missed window of opportunity for benefit from a rescue therapy in severe ARDS patients. Our study is unable to address whether outcomes would have been even worse had rescue therapies not been initiated. Future studies should continue to investigate whether or not there is a benefit to beginning rescue therapies earlier in the course of severe ARDS, for example immediately after a patient's PaO_2/FIO_2 ratio drops below 100 mm Hg.

Limitations. We acknowledge the challenges associated with retrospective data collection and the limitations of observational studies. Despite our attempts to control for indication bias via restriction of the cohort to development of ARDS within 72 hours of ICU admit, adjusting for potential confounders defined *a priori*, and secondary propensity adjusted analyses, residual confounding likely remained. This is because our admission characteristics did not capture the severity of hypoxemia that patients placed on a rescue therapy later developed. Therefore, in this study, we are unable to comment on the association between rescue therapies and outcomes due to the inability to entirely account for indication bias. Observational studies investigating critically ill patients are universally challenged with this difficulty. Severe ARDS patients, including those placed on a rescue therapy, represent a small

proportion of ICU patients, resulting in difficulty with subject accrual and small sample sizes. High quality prospective observational studies or randomized controlled trials are needed to investigate the actual effects of rescue therapies on outcomes in patients with critical hypoxemia. Despite the persistent biases, describing clinical practice patterns and long-term outcomes of patients with severe ARDS provides valuable information and can be used to generate hypotheses for future prospective trials. Due to the single center setting, these data may not generalize to institutions with different practices.

Conclusion

Severe ARDS patients have high hospital mortality, however, survivors to hospital discharge have relatively good long-term survival. The subset of severe ARDS patients who have a rapidly declining PaO_2/FIO_2 ratio and are often selected to be treated with a rescue therapy are at an even higher risk of death in the short-term; however, provided they survive to hospital discharge, they also have relatively good long-term survival. Historically, "rescue" therapies earned this name because they were used as a last resort effort to improve oxygenation in life-threatening situations. (3, 4, 11, 14, 15, 17, 18, 22, 25, 26) Future prospective studies should continue to investigate whether or not routine initiation of a rescue therapy in patients who have severe ARDS prior to the development of life-threatening critical hypoxemia would improve survival to hospital discharge.

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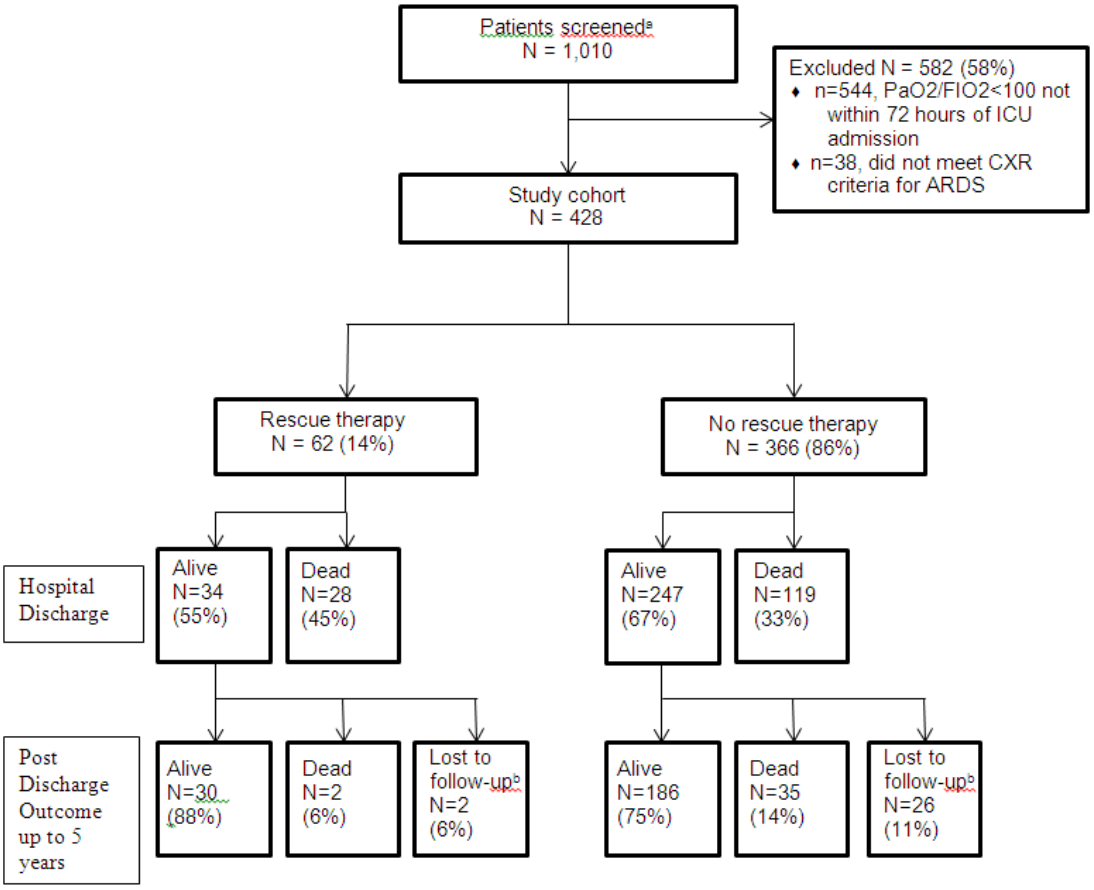
Figure 1: Flow chart of study cohort



[a]Included any patient with a PaO2/FiO2 ratio <100 at any time during the first ICU admission
[b] Includes subjects that neither appeared in the Washington State Death Registry nor died in the hospital AND had an address of residence outside of Washington State.

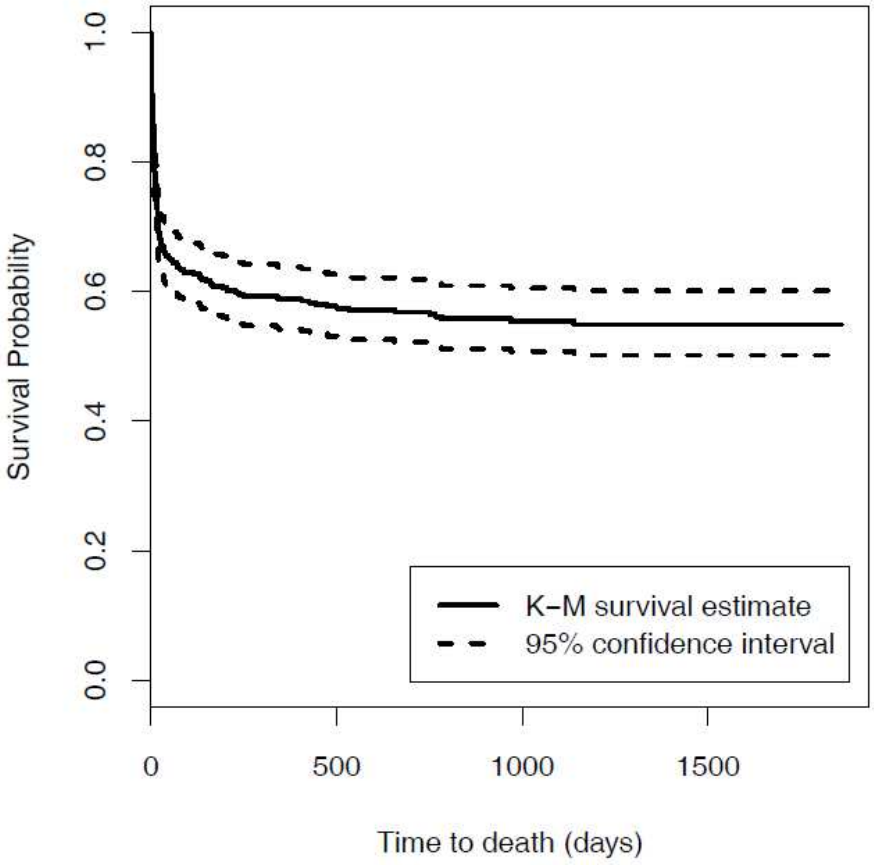
Table 1: Demographic and clinical characteristics of the study population

Characteristics	All patients
N (%)	428 (100)
Age, y, mean ± SD	51. 0 ± 17.7
Male gender, n (%)	310 (72)
Body mass index	29.5 ± 8.7
Race/Ethnicity, n (%)	
Caucasian	296 (69)
African American	40 (9)
Asian	46 (11)
Hispanic	15 (4)
Native American	22 (5)
Unknown	9 (2)
Patient population, n (%)	
Medical	363 (85)
Trauma	27 (6)
Surgical, non-trauma	38 (9)
Primary admission diagnostic category, n (%)	
Sepsis or Pneumonia	141 (33)
Trauma	113 (26)
Neurological injury	42 (10)
Other	132 (31)
Mechanically ventilated within 24 of ICU admit, n (%)	163 (38)
SAPS II, mean ± SD	60.8 ± 18
ISS in trauma patients, mean ± SD (n=169)	32.1 ±15.8
AIS – Head, mean ± SD (n=102)	3.44 ± 1.29
AIS – Chest, mean ± SD (n=113)	3.77 ± 0.76
PaO_2/FIO_2 ratio at ICU admission	160 ± 108
Study qualifying PaO2/FiO2 ratio[a]	76 ± 16
PEEP (cm H_2O)[b]	13 ± 6
ICU length of stay (days), median (IQR)	15 (8, 25)
Hospital length of stay (days), median (IQR)	20 (10, 34)
Hospital costs, mean (95% CI) [c]	701K (97K, 846K)

SD: standard deviation; SAPS II: simplified acute physiology score II; ISS: injury severity score; AIS: abbreviated injury severity; ISS and AIS applicable only for trauma patients

[a] Value of first PaO_2/FIO_2 ratio <100 within 72 hours of admission to ICU
[b] Amount of PEEP delivered at time of study qualifying PaO_2/FIO_2 ratio
[c] Mean hospital costs, adjusted for inflation and reported in 2012 U.S. Dollars. Bootstrap resampling method used to obtain a percentile-based 95% confidence interval.

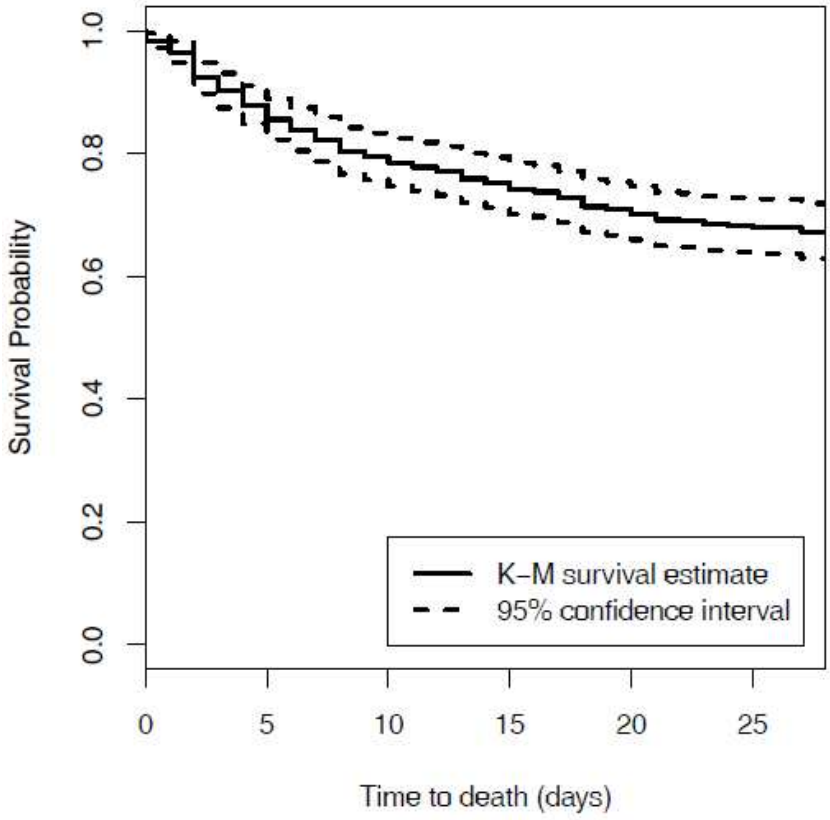
Figure 2A: Overall survival



Overall survival from date of ICU admission

	Time interval (days)					
	(0, 99)	(100, 199)	(200, 299)	(300, 399)	(400, 499)	(500, 1860)
Alive at start of interval	428	244	235	230	226	206
Dead during interval	156	9	5	2	4	8
Censored during interval	28	0	0	2	16	198

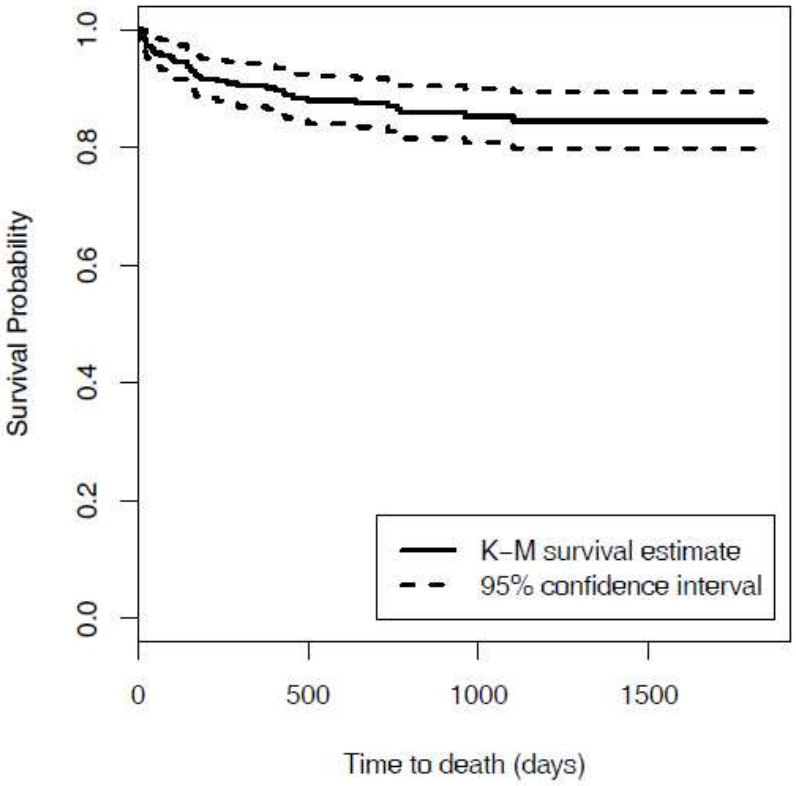
Figure 2B: Survival in first 28-days



Overall survival in first 28-days from date of ICU admission

	Time interval (days)			
	(0, 6)	(7, 13)	(14, 20)	(21, 28)
Alive at start of interval	428	358	320	291
Dead during interval	69	34	24	12
Censored during interval	1	4	5	6

Figure 2C: Survival post-hospital discharge



Overall survival from date of hospital discharge

	Time interval (days)					
	(0, 99)	(100, 199)	(200, 299)	(300, 399)	(400, 499)	(500, 1860)
Alive at start of interval	252	240	231	228	217	200
Dead during interval	12	9	3	1	5	6
Censored during interval	0	0	0	10	12	194

Table 2. Baseline characteristics of patients treated and not treated with a rescue therapy

Characteristics	Rescue Therapy	No Rescue Therapy	P value[a]
N (%)	62 (14)	366 (86)	
Propensity score, mean ± SD	0.28 ± 0.18	0.12 ± 0.12	<.01
Age, y, mean ± SD	41.7 ± 19.0	52.6 ± 17.0	<.01
Male gender, n (%)	42 (68)	268 (73)	.36
Body mass index	30.1 ± 10.7	29.4 ± 8.3	.54
Race/Ethnicity, n (%)			.01
Caucasian	36 (58)	260 (71)	
African American	5 (8)	35 (9)	
Asian	7 (11)	39 (11)	
Hispanic	8 (13)	7 (2)	
Native American	4 (7)	18 (5)	
Unknown	2 (3)	7 (2)	
Patient population, n (%)			.57
Medical	55 (89)	308 (84)	
Trauma	4 (6)	23 (6)	
Surgical, non-trauma	3 (5)	35 (10)	
Primary admission diagnostic category, n (%)			<.01
Sepsis or Pneumonia	32 (52)	109 (30)	
Trauma	10 (16)	103 (28)	
Neurological injury	9 (14)	33 (9)	
Other	11 (18)	121 (33)	
Mechanically ventilated on ICU admit, n (%)	33 (53)	130 (36)	.01
SAPS II, mean ± SD	60.8 ± 17.1	60.8 ± 18.3	.99
ISS in trauma patients, mean ± SD (n=169)	35.0 ± 14.7	31.7 ± 16.0	.36
AIS – Head, mean ± SD (n=102)	3.9 ± 1.3	3.4 ± 1.3	.15
AIS – Chest, mean ± SD (n=113)	3.9 ± 0.74	3.8 ± 0.77	.64
PaO_2/FIO_2 ratio at ICU admission	150 ± 127	162 ± 104	.47
Study qualifying PaO_2/FIO_2 ratio[b]	68 ±18	78 ± 16	.001
PEEP (cm H_2O)[c]	14 ± 6	9 ± 4	.01

SD: standard deviation; SAPS II: simplified acute physiology score II; ISS: injury severity score; AIS: abbreviated injury severity; ISS and AIS applicable only for trauma patients

[a] Two-sample t-test with assumption of unequal variance or Fisher's exact chi-square statistics
[b] Value of first PaO_2/FIO_2 ratio <100 within 72 hours of admission to ICU
[c] Amount of PEEP delivered at time of study qualifying PaO_2/FIO_2 ratio

Table 3: Physiologic variables during ICU stay

	Rescue Therapy (N = 62)	No Rescue Therapy (N = 366)	P value[¥]
Study qualifying PaO_2/FIO_2 ratio[a]	68 ±18	78 ± 16	<.01
Time from ICU admit to qualifying PaO_2/FIO_2 ratio (hours), median (IQR)	8 (4,34)	14.5 (5,39)	.12
Lowest PaO_2/FIO_2 ratio within 24hours[b]	93 ± 83	102 ± 62	.41
Lowest PaO_2/FIO_2 ratio within 72 hours[c]	54 ± 17	69 ± 17	<.01
Days spent with FIO2>60%, median (IQR)	8 (4, 17)	5 (3, 8)	<.01
Total number of ABGs collected, median (IQR)[d]	8 (6,12)	6 (5,9)	.01
Number of ABGs with PaO2/FiO2 <100, median (IQR)[d]	4 (3,10)	2 (1,4)	<.01
Days of mechanical ventilation			
median (IQR)	13 (6,27)	11 (6,19)	.18
mean ± SD	19.2 ± 19.3	14.9 ± 14.8	.04
Use of vasopressors[e], n (%)	51 (82)	240 (66)	.01
Use of neuromuscular blockade, n (%)	40 (65)	83 (23)	<.01
Mean SOFA	13.2 ± 3.0	13.9 ± 2.8	.10
Max SOFA	18.0 ± 3.2	18.8 ± 3.3	.06

IQR: Interquartile range; SD: Standard deviation; ABG: Arterial blood gas;
SOFA: Sequential Organ Failure Assessment

¥ Two-sample t-test with assumption of unequal variance for mean± SD; Fisher's exact chi-square test statistic for categorical variables and Wilcoxon rank sum test statistics for median (IQR). Values expressed as mean± SD unless otherwise specified.

[a] Value of first PaO_2/FIO_2 ratio <100 within 72 hours of admission to ICU
[b] Lowest PaO_2/FIO_2 ratio within 24 hours of admission to ICU
[c] Lowest PaO_2/FIO_2 ratio within 72 hours of admission to ICU
[d] Within 24 hours of first PaO2/FiO2<100
[e] Within 24 hours of ICU admission

Figure 3: Survival in first 28-days stratified by therapy

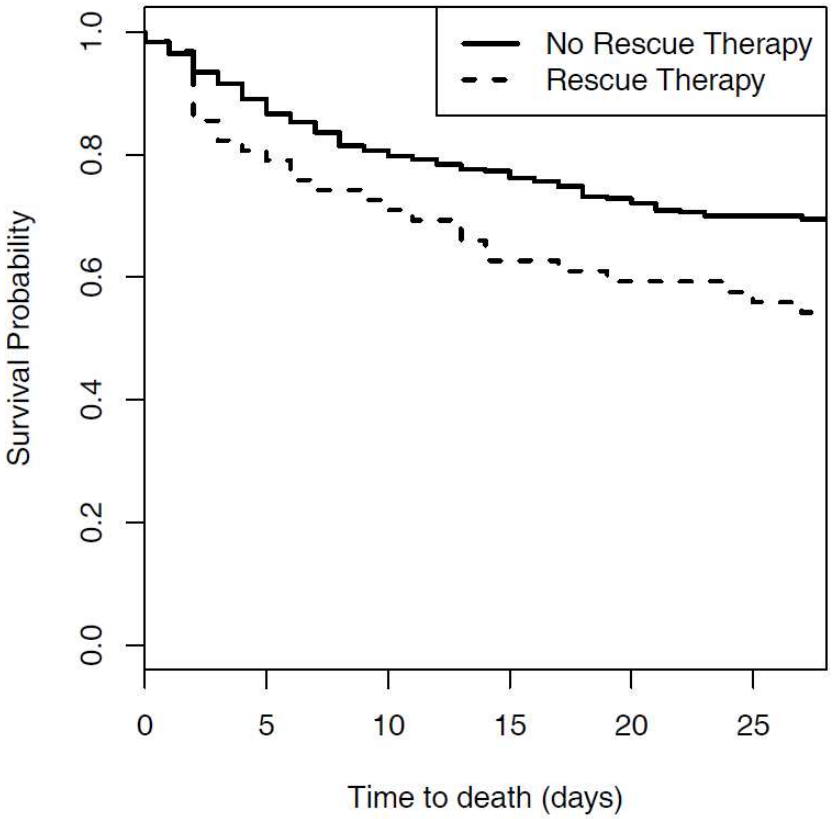


Table 4. Outcomes in patients treated and not treated with a rescue therapy

Study Endpoint	All Patients N = 428	Rescue Therapy N = 62	No Rescue Therapy N = 366	Hazard Ratio[a] (95% CI)	P value[a]
Primary endpoint					
Mortality, n(%)					
Crude				1.31 (0.89, 1.94)	.17
Adjusted				1.49 (0.98, 2.25)	.06
Propensity adjusted				1.40 (0.90, 2.18)	.14
Secondary endpoints					
28-day hospital mortality, n(%)	139 (32)	28 (45)	111 (30)		
Crude				1.67 (1.10, 2.53)	.02
Adjusted				1.80 (1.15, 2.80)	.01
Propensity adjusted				1.75 (1.08, 2.82)	.02
One-year mortality, n(%)	172 (40)	30 (48)	142 (39)		
Crude				1.42 (0.96, 2.10)	.08
Adjusted				1.61 (1.06, 2.44)	.03
Propensity adjusted				1.51 (0.96, 2.36)	.07
					P-value[b]
Discharge disposition, n (%)					.05
Death	148 (35)	29 (47)	119 (32)		
Home	115 (27)	8 (13)	107 (29)		
Skilled nursing facility	94 (22)	14 (22)	80 (22)		
Distinct rehab unit	34 (8)	6 (10)	28 (8)		
Other	37 (9)	5 (8)	32 (9)		

CI: Confidence interval

[a]Cox proportional hazard model adjusted for age, Caucasian race, admission SAPS II, diagnosis of sepsis or pneumonia. Propensity adjusted model is adjusted for propensity score which includes Age, Gender, BMI, Caucasian race, Patient population, Admission

diagnosis of sepsis or pneumonia, Mechanically ventilated on ICU admit, SAPS II, PaO_2/FIO_2 ratio at ICU admission, Highest glucose, Lowest Hemoglobin. ISS, AIS-Head and AIS-Chest not included as only pertinent to trauma patients.
[b]Pearson's chi square