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ACUTE RESPIRATORY DISTRESS SYNDROME OUTCOMES IN NON-RESEARCH SUBJECTS ASSESSED BY GENERALIZED PROSPECTIVE TRIAL ELIGIBILITY CRITERIA AND ADHERANCE TO LUNG-PROTECTIVE VENTILATION

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Abstract

Background. Acute respiratory distress syndrome (ARDS) mortality is lower among subjects participating in randomized controlled trials (RCT) versus those in observational studies. Excluding potential subjects with inordinately high mortality risk is necessary to prevent masking the impact of potentially effective treatments. We inquired whether observed mortality differed between RCT-eligible and RCT-ineligible subjects managed with varying degrees of lung-protective ventilation (LPV) in a non-research setting.

Methods. This single-center, retrospective, observational study utilized quality assurance data for monitoring LPV practices based upon National Institutes of Health ARDS Network (ARDSNet) protocols. Between 2002-2017, 1975 subjects meeting 1994 consensus criteria for ALI/ARDS (later reclassified by the Berlin definition) were prospectively identified and classified as RCT-eligible or RCT-ineligible based upon the original ARDSNet exclusion criteria for co-morbidities or moribund condition. Demographic and physiologic data from the day of ARDS onset and outcome data were. Survival was modeled by mixed-effect Cox proportional hazard model adjusted for age, both illness and lung injury severity plateau pressure (P_{plat}) and formal use of the ARDSNet ventilator protocol. The primary outcome of interest was all-cause mortality during the first 90 days following ARDS onset.

Results. Day 90 mortality was 27.6% in RCT-eligible patients vs. 50.4% in RCT-ineligible patients: HR (95% CI) of 0.47 (0.41-0.54), $P < 0.001$. Regardless of RCT-eligibility or ineligibility criteria, achieving a $P_{plat} \leq 30$ cmH_2O was associated with lower mortality. Overall, mortality risk was lower in patients managed by protocol vs. clinician-directed LPV (HR = 0.60 (95%CI = 0.52 – 0.69), $p < 0.001$), even among those in whom P_{plat} was ≤ 30 cmH_2O (HR = 0.64 (0.54-0.76), $p<0.001$).

Conclusion. Mortality in non-research, RCT-eligible patients was substantially lower compared to RCT-ineligible patients. Managing non-research ARDS patients by keeping Pplat $\leq$ 30 cmH_2O and formal use of a lung-protective ventilation protocol significantly reduces mortality risk.

Introduction

Since publication of the seminal trial on low tidal volume (V_T) ventilation by the National institutes of Health ARDS Clinical Trials Network (ARDSNet),[1] studies have reported higher mortality in the general ARDS population managed with lung-protective ventilation (LPV) compared to those in randomized controlled trials (RCT).[2, 3] This was largely attributed to exclusion criteria used in the later to prevent masking the effects of potential useful treatments due to subjects with exceptionally high mortality risk. In addition, rigorous adherence to treatment protocols in RCTs are speculated to enhance mortality reduction.[3, 4] Furthermore, delayed recognition of ARDS in observational studies along with the small fraction of screened subjects enrolled into RCTs are cited as additional factors that limit generalizing beneficial RCT results to clinical practice.[3]

We previously reported that adopting the ARDSNet LPV protocol for clinical management of ARDS significantly reduced mortality r both in those meeting RCT-eligibility and RCT-ineligibility criteria compared to traditional mechanical ventilation practices.[5] The current study reexamines in more detail, and with a larger sample, how mortality and other patient-centered outcomes are influenced by RCT-eligibility and ineligibility criteria.[1]

Methods

Population

All consecutive subjects treated at San Francisco General Hospital for acute lung injury or ARDS based on for the American-European Consensus Conference criteria [6] (and subsequently reclassified according to the Berlin Definition[7]) were entered into a quality

assurance database used to monitor adoption of the ARDSNet ARMA ventilator protocol.[1] Beginning in 2005 the PEEP/F_{IO2} grid from the ARDSNet ALVEOLI trial protocol was incorporated as an option for 91% of our subjects managed by protocol.[8] Volume assist-control ventilation was the primary ventilator mode used when implementing these protocols. Protocolized management was at the intensive care unit (ICU) attending's discretion and over a 16-year period protocol usage averaged 74%; ranging annually between 61-85%. Patients undergoing clinician directed LPV typically received a V_T of 7-8 mL/kg. By policy V_T was set according to predicted body weight and corrected for compressible volume loss in the circuit.

RCT eligibility

One investigator (RHK) who was site clinical coordinator for the ARDSNet clinical trials group (1996-2007) screened and entered each subject into the database according to the primary source of lung injury, as well as sepsis as a co-diagnosis. Patients were classified as either meeting RCT-eligibility or RCT-ineligibility criteria as defined in the ARDSNet ARMA trial.[1] Ineligibility criteria used for quality-assurance purposes were restricted to comorbid conditions likely to increase mortality, duration of mechanical ventilation or ICU length-of-stay (LOS) (**Supplementary Table 1**). No patients had been co-enrolled into any ongoing ARDSNet clinical trials between 2002-2008.

Measurements

The quality assurance database consisted primarily of information gathered from the day of ARDS onset including mechanical ventilation and gas exchange data, initial illness severity scores, use of ancillary ARDS therapies, as well as other demographic and outcome data. In the

subset of 1230 patients managed with the ARDSNet protocol, additional ventilator data was collected approximately 24h after protocol initiation to assess protocol adherence.

Acute physiology and chronic health evaluation score (APACHE II),[9] simplified acute physiology score (SAPS II),[10] and lung injury score (LIS)[11] were calculated on the day of ARDS onset. Ventilator systems status checks with contemporaneous arterial blood gas data were collected within four hours after ARDS onset. Measurements included respiratory system compliance (C_{RS}) calculated as $V_T \div$ the difference between end-inspiratory plateau pressure and positive end-expiratory pressure (P_{plat} - PEEP), which also was recorded as elastic driving pressure (P_{DR}).[12]

Oxygenation was assessed both as the ratio of arterial oxygen tension-to-inspired oxygen fraction (P_{aO2}/F_{IO2}), and oxygenation Index (OI) calculated as the product of mean airway pressure and the percent of inspired oxygen divided by P_{aO2}.[13] Ventilation efficiency was assessed using the ventilatory ratio (VR = measured minute ventilation x measured arterial carbon dioxide tension ÷ normalized minute ventilation x 37.5 mm Hg).[14]

Temporal measurements included days from ICU admission to initiation of invasive mechanical ventilation, and from its initiation to ARDS onset. Duration of mechanical ventilation, ICU length-of-stay (LOS), and hospital LOS from ARDS onset were calculated for survivors only. Approval to use our quality assurance data was granted by the University of California, San Francisco Institutional Review Board (Approval Reference number: 268589).

Statistical Analysis

Statistical analysis was done using PRISM 8.2.3 (Graphpad Software, La Jolla CA) and R (Package survival for R - Therneau T (2021). *A Package for Survival Analysis in R*. R package version 3.2-10, https://CRAN.R-project.org/package=survival). Continuous variables were expressed as either mean ± standard deviation (sd) or median and interquartile range (IQR) and were compared using either unpaired t test or the Mann-Whitney test. Paired comparisons were made using either paired t-test or Wilcoxon Sign-Rank test. Categorical variables were compared using Chi Square-test with Yates correction. Kruskall-Wallis test was used to compare more than two groups.

The primary outcome of interest was all-cause mortality during the first 90 days following ARDS onset. The primary comparison was between RCT-eligible and RCT-ineligible subjects. Additional prospectively planned comparisons included: P_{plat} below or above 30 cmH_2O; Berlin classes; protocol-based vs. clinician-based ventilator management and use of ancillary therapies to support gas exchange.

Actuarial survival was displayed using Kaplan Meier plots and compared using the log rank test. Survival was modeled using a mixed-effect Cox proportional hazard model adjusted for age, APACHE II score, Berlin class, LIS, P_{plat}, ARDS etiology, concomitant sepsis, type of ICU (medical, neurologic or surgical-trauma), number of ancillary therapies employed as fixed effect and the year of hospitalization as random intercept. Secondary outcomes focused on the duration of mechanical ventilation, ICU length of stay and hospital length of stay in survivors from the onset of ARDS. Alpha was set at 0.05.

Results

Population Characteristics

This study analyzed data from 1,975 consecutive subjects between July 2002 and December 2017. This sample comprised 1136 (58%) RCT-eligible and 839 (42%) RCT-ineligible subjects. The most frequent reasons for RCT ineligibility were acute brain injury 292 (34.8%), end-stage liver disease (ie. Child's Class C) 153 (18.2%) and perceived moribund condition at the time of initial assessment (ie. apparent refractory shock not based upon pre-hoc formal criteria) 124 (14.8%) of which 35 subjects also had end-stage liver disease. Significantly more RCT-eligible subjects received care in either the medical or surgical-trauma ICU setting, whereas significantly more RCT-ineligible subjects were managed in the neurocritical care setting and also were older (**Table 1**). Neither gender nor racial-ethnic background were different between groups.

Although RCT-eligible subjects had significantly lower APACHE II and SAPS II scores, ARDS severity at onset was not different between eligibility groups either by Berlin Category, LIS, or by those with a LIS > 3 (ie. eligibility criteria for extracorporeal membrane oxygenation).[15] RCT-eligible subjects had a higher incidence of pancreatitis, non-pulmonary sepsis, and sepsis as a co-diagnosis (**Table 1**).

Respiratory Mechanics and Quality of Lung Protective Ventilation

RCT-eligible subjects had significantly higher P_{aO2}/F_{IO2} and lower OI, weight-adjusted V_T and C_{RS} compared to RCT-ineligible subjects. However, PEEP, F_{IO2}, mean airway pressure, P_{plat} and VR were not different (**Table 2**). Use of the ARDSNet ventilator protocol was significantly higher in the RCT-eligible vs. RCT-ineligible group (73% vs. 58.2% (P <0.0001). ARDSNet

ventilator protocol was initiated either on the day of ARDS onset or on the following day in 92.8% of RCT-eligible subjects and 90.6% of RCT-ineligible subjects (P = 0.20).

There was a small, significant difference in PEEP among RCT eligible patients managed with the ARDSNet protocol between pre- and post-ALVEOLI study years (2002-2004 vs. 2005-2017): (8 [5-10] vs. 10 [5-10] respectively, P<0.0001). A similar trend also was observed in RCT-ineligible patients managed with the protocol (8 [5-10] vs. 10 [5-12] respectively, P = 0.06).

The quality of LPV was not different between RCT-eligible and RCT-ineligible groups in terms of achieving P_{plat}, and V_T targets (**Supplementary Table 2**). In addition, there was no difference between groups at ARDS onset in incidences when V_T, P_{plat} or P_{DR} reached levels believed to substantially increase ventilator-induced lung injury risk (i.e. $V_T \geq 12$ mL/kg, $P_{plat} \geq 35$ cmH_2O and $P_{DR} > 20$ cmH_2O). [1, 12, 16, 17] In both study cohorts subjects managed by protocol experienced further significant reductions in V_T, P_{DR} and F_{IO2} and increased PEEP over the first 24hr following protocol initiation (**Supplementary Table 3**). There was no difference in the frequency or number of ancillary therapies used to support gas exchange between RCT-eligible and RCT-ineligible subjects (**Supplementary Table 4**).

Primary Outcome

The predicted mortality based on the APACHE II scores was 40% and 55% for both RCT-eligible and RCT-ineligible subjects respectively. Observed mortality was markedly lower in RCT-eligible vs. RCT-ineligible subjects at Day 90: 27.6% vs. 50.4% respectively (HR = 0.47 (95%CI = 0.41-0.54), P < 0.001) **(Figure 1**). This was the case across both Berlin classifications and ARDS etiology, with one exception: those with pneumonia (**Supplementary Figures 1 and 2**

respectively). Among the 15% of RCT-ineligible subjects considered moribund at ARDS onset the mortality was 83% and was significantly greater than other RCT-ineligible subjects (44.8%, P < 0.0001) (**Supplementary Table 5**). Nonetheless, after excluding moribund subjects from the analysis, the mortality risk between RCT-eligible and RCT-ineligible remained significant (HR = 0.57 (0.49 – 0.67), p < 0.001). In addition, there was no pattern suggesting a consistent reduction in mortality over the 16-year study period (**Supplementary Figure 3**).

Regardless of RCT-eligibility or ineligibility, achieving a $P_{plat} \leq 30$ cmH_2O was associated with lower mortality (**Figure 2**). However, even when stratified by P_{plat}, RCT eligibility remained strongly associated with 90-day mortality. Overall, mortality risk was lower in subjects managed by protocol driven vs. clinician driven LPV (HR = 0.60 (95%CI = 0.52 – 0.69), p < 0.001), even among subjects whose P_{plat} was ≤ 30 cmH_2O (HR = 0.64 (0.54-0.76), p<0.001). Among RCT-ineligible subjects, mortality also was significantly lower among protocol-managed subjects with $P_{plat} \leq 30$ cmH_2O versus clinician-driven management with a $P_{plat} \leq 30$ cmH_2O (HR: 0.67 (0.54-0.83), P < 0.001).

Factors contributing to 90-day mortality in multivariate analysis included age, APACHE II score, RCT-ineligibility status, Berlin Classification severity and number of ancillary therapies (**Figure 3**). In contrast a $P_{plat} \leq 30$ cmH_2O and development of ARDS in either a surgical or neurocritical care setting were associated with decreased 90-day mortality.

Secondary Outcomes

Among survivors, mechanical ventilation duration, ICU and hospital LOS (following ARDS onset) were significantly shorter in the RCT-eligible group (**Table 1**). However, these differences

may be attributable to acute brain injury patients whose mechanical ventilation duration, ICU and hospital LOS were significantly longer than non-brain injured RCT-ineligible subjects, as well as RCT-eligible subjects (**Supplementary Table 6**). When acute brain injury subjects were removed from the analysis there was no differences in any of these variables between other RCT-ineligible and RCT-eligible subjects.

Discussion

Our main finding was RCT-eligible subjects managed with LPV had markedly lower mortality compared to RCT-ineligible subjects at Day 90 despite having similar severity of acute lung injury and benefiting from similar quality of LPV. This remained true after excluding subjects deemed moribund because of apparent refractory shock. Consistent with other studies, we found RCT-ineligible subjects had significantly higher illness severity scores at ARDS onset. In those who survived to hospital discharge, RCT-eligible subjects had significantly less days of mechanical ventilation, and both decreased ICU and hospital LOS compared to the RCT-ineligible subjects. These particular findings may be partly explained by the presence of acute brain injury subjects who accounted for ~35% of the RCT-ineligible study cohort.

Mortality was extraordinarily high among RCT-ineligible subjects in specific subsets, namely: Berlin Classification of severe ARDS (62%), non-pulmonary sepsis (72%), other less common etiologies (67%), end-stage liver disease (73%) and those deemed moribund (83%). In contrast, subgroups of RCT-ineligible subjects with acute brain, pneumonia and trauma had lower mortality rates of 43%, 37%, and 36% respectively that were similar to crude mortality rates reported in the general ARDS population.[18-22] Overall mortality risk among RCT-ineligible subjects was more than twice that of RCT-eligible subjects (HR: 2.26 (1.95-2.63), P< 0.0001).

A systematic review and meta-analysis of studies between 1994-2006 reported significantly lower pooled mortality among subjects enrolled into RCTs versus observational studies (36.2% vs. 44.0% respectively); with observational studies associated with a substantially higher mortality risk: OR of 1.36 (1.08-1.73).[2] Observational study subjects included both those who would have met RCT-eligibility as well as RCT-ineligibility criteria. Moreover, approximately half of the time period covered by these studies was prior to publication of the seminal ARDSNet study,[1] and more widespread adoption of LPV.

In contrast, our study sample spanned approximately 16 years at an original ARDSNet study site that quickly adopted the ventilator protocol for clinical management,[5] and in which the majority of subjects (58%) were RCT-eligible. These factors likely account for our lower crude mortality rate of 37% for the entire study sample. Despite less-rigid adherence to the ARDSNet protocol, mortality among our RCT-eligible subjects (with some exceptions) was similar to that reported in several ARDSNet studies: the exception being the aerosolized albuterol trial (**Supplementary Table 7**).[1, 8, 23-26]

Generalizing our findings are limited because of three factors, some of which may be unique to our institution. First, we approach ARDS surveillance consistent with our participation as an ARDSNet clinical trials site from 1996-2008. This being daily screening for early identification of at-risk patients, rapidly detecting ARDS onset and strongly advocating use of the ARDSNet protocol. Second, our highly skilled respiratory care practitioners were individually trained in (and had used) the ARDSNet ventilator protocols continuously since 1996. Third, these efforts were facilitated by consistent, strong cross-disciplinary physician support for LPV.

Others have speculated that mortality rates between therapeutic RCT and observation studies might be reduced by more stringent adherence to LPV protocols.[3] Our study supports this notion. Within hours of ARDS recognition 73% of our subjects were ventilated at a $V_T \leq$ 8mL/kg and 92% $\leq$ 9 mL/kg. P_{plat} was universally monitored and 85% of subjects had a $P_{plat} \leq 30$ cmH_2O within that time frame. Furthermore, 74% of subjects managed by protocol, experienced additional reductions in V_T, P_{plat} and P_{DR} within 24h of protocol initiation.

In contrast, a 50-nation observational study reported less than 67% of ARDS subjects were managed with a $V_T \leq 8$ mL/kg, while P_{plat} was monitored in less than 40% with corresponding hospital mortality rates of 34.9% (31.4%-38.5%) for mild, 40.3% (37.4%-43.3%) for moderate, and 46.1% (41.9%-50.4%) for severe ARDS.[18] When comparing our RCT-eligible data to multi-center RCT data used by Force et al.,[7] our hospital mortality was below the 95%CI for mild (19.5% vs. 24-30%) moderate (24.4% vs. 29-34%), and severe ARDS (38.3% vs. 42-48%).[7]

Our study addresses some previously cited limitations of applying RCT study results to the general ARDS population: these being the prevalence of higher non-enrollment into RCTs among public hospitals caring for vulnerable populations.[3] San Francisco General Hospital provides care primarily to this patient population. Early identification and enrollment of RCT-eligible subjects also is another factor that limits generalizing RCT trial results of LPV to the ARDS population at large.[3] Following announcement of the seminal ARDSNet study results in the Spring of 1999, we made a concerted effort to identify patients with ARDS quickly and encourage implementation of the ARDSNet ventilator protocol.[5]

Previously we reported that our formal adoption of the ARDSNet ventilator protocol (2000-2003) reduced hospital mortality compared to clinical practice (1998-1999) both in RCT-

eligible (40% to 23% ,P =0.019) and RCT-ineligible subjects (78% to 48%, P = 0.031): demonstrating that the ARDS Net protocol improved survival regardless of mortality risk categorization.[5] Our current study extends these findings and suggests that even initiating less structured LPV soon after ARDS onset reduces mortality risk.

Our study is limited by our reliance upon data gathered for quality assurance purposes. That data had to be abstracted by hand necessitated practical limitations on the amount that could be collected. Therefore, our data lack much of the "granularity" that would have provided greater control of important confounders, and therefore, a more refined interpretation of our results (eg. our inability to collect Sequential Organ Failure Assessment scores, fluid balance, ventilator settings over an extended time period, sedative use, etc.). Although our impression was that day-to-day ventilator management was reasonably constant, we have no data to support it.

In summary, Among ARDS subjects identified early and managed primarily using the ARDSNet ventilator protocol, those who met RCT enrollment eligibility criteria had a mortality rate similar to that reported in several ARDSNet trials. Moreover, RCT-eligible subjects had a greater than 50% reduction in mortality risk compared to RCT-ineligible subjects.

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Figure Legends

Figure 1. Kaplan-Meier plots of the probability of 90-day survival with 95% CI between patients meeting randomized control trial eligibility vs. ineligibility criteria.

Figure 2. Kaplan-Meier plots of the probability of 90-day survival with 95% CI between subjects meeting randomized control trial eligibility vs. ineligibility criteria. and a plateau pressure cut-off of 30 cmH_2O.

Figure 3. Forest plot of adjusted Cox proportional hazard model for 90-day mortality

Supplementary Figure 1. Comparisons of 90-day mortality between RCT-eligible (EL) and RCT-ineligible (IN) subjects across Berlin Classifications of mild, moderate (MOD) and severe (SEV) ARDS. Data represented as mean with 95% confidence interval.

Supplementary Figure 2. Comparisons of 90-day mortality between RCT-eligible (EL) and RCT-ineligible (IN) subjects across ARDS etiologies aspiration (ASP), pancreatitis (PAN), pneumonia (PNA), non-pulmonary sepsis (SEP), trauma (TRA) and other less-common sources (OTH). Data represented as mean with 95% confidence interval.

Supplementary Figure 3. Hospital mortality patterns across 16 years for RCT-eligible, RCT-ineligible and all subjects combined.

Quick Look

Current Knowledge

Mortality reported in the general ARDS population managed with lung-protective ventilation is higher than that reported in randomized controlled trials (RCT) because of the need to exclude subjects with co-morbid conditions and excessive mortality risk. This limits the generalizing of these findings to the ARDS population in general that includes both those eligible and non-eligible patients.

What this paper contributes to our knowledge:

In a non-research setting, early identification of ARDS patients and use of NIH ARDSNet ventilator protocol produced similar mortality rate in those who would meet RCT eligibility criteria to that reported in several ARDSNet trials. These RCT-eligible subjects had a greater than 50% reduction in mortality risk compared to RCT-ineligible subjects.

Table 1. Demographic, pulmonary mechanics and gas exchange characteristics on day of ARDS onset and outcomes between subjects meeting eligibility criteria for participation in a randomized clinical trial vs. those meeting exclusion criteria.*

	RCT Eligible	RCT Ineligible	P
N	1136	839	
Setting			
MICU	714 (62.9%)	438 (52.2%)	0.0008
NCCU	13 (1.1%)	211 (25.1%)	< 0.001
SICU	409 (36%)	190 (22.6%)	< 0.001
Age	50.6 ± 16.6	52.4 ± 17.0	0.022
Gender			
Male	849 (74.7%)	612 (72.9%)	0.97
Female	310 (27.3%)	227 (27.1%)	0.92
Descent			
African	227 (20%)	170 (20.3%)	0.74
Asian/Pacific	190 (16.7%)	143 (17%)	0.85
European	460 (40.5%)	331 (39.4%)	0.78
Hispanic	245 (21.6%)	180 (21.4%)	0.82
Middle Eastern	11 (1%)	12 (1.4%)	0.49
Native American	2 (0.2%)	4 (0.5%)	0.22
Berlin Category			
Mild	181 (15.9%)	111 (13.2%)	0.06
Moderate	572 (50.4%)	419 (49.9%)	0.94
Severe	383 (33.7%)	309 (36.8%)	0.17
LIS	2.5 (2.3,3.0)	2.5 (2.3,3.0)	0.91
LIS > 3.0†	237 (20.9%)	170 (20.3%)	0.79
Primary ARDS Etiology			
Aspiration	165 (14.5%)	148 (17.6%)	0.056
Pancreatitis	49 (4.3%)	7 (0.8%)	< 0.001

Pneumonia	381 (33.5%)	256 (30.5%)	0.26
Non-Pulmonary Sepsis	252 (22.2%)	142 (17%)	0.008
Trauma	220 (19.4%)	174 (20.7%)	0.58
Other	69 (6.1%)	112 (13.3%)	< 0.001
Sepsis as Co-Diagnosis‡	223 (19.6%)	131 (15.6%)	0.025
APACHE II	21 (15,27)	25 (19,31)	<0.001
SAPS II	45 (34,59)	51 (40,64)	<0.001
Days ICU Admit to MV Initiation	0 (0,0)	0 (0.0)	0.0497
Days MV to ARDS Onset	0 (0,1)	0 (0,2)	< 0.001
Days Onset to Protocol Initiation	0 (0,0)	0 (0,0)	0.06
Days MV with ARDS (Survivors)	9 (4,18)	11 (6,21)	< 0.001
ICU-LOS with ARDS (Survivors)	12 (6,22)	15 (8,25)	< 0.001
Days from ARDS Onset to Hospital Discharge (Survivors)	23 (13,44)	29 (15, 47)	0.02
Mortality (Day 90)	314 (27.6%)	423 (50.4%)	<0.0001

Key: APACHE = acute physiology and chronic health evaluation score, LIS = lung injury score, LOS = length-of-stay, MICU = medical intensive care unit, MV = mechanical ventilation, NCCU = neurologic critical care unit, SAPS = simplified acute physiology score, SICU = surgical intensive care unit. *Data are presented either as mean ± standard deviation or median (25-75% interquartile range). † ECMO enrollment criteria. ‡Incidence in those with primary ARDS etiologies of aspiration, pancreatitis, pneumonia, trauma and other.

Table 2. Mechanical ventilation and gas exchange variables on the day of ARDS onset.*

	RCT-Eligible	RCT Ineligible	p
N	1136	839	
ARDSNet Protocol Use	829 (73%)	489 (58.2%)	< 0.0001
Protocol use in:			
MICU	516 (72.3%)	260 (59.4%)	< 0.0001
NCCU	7 (53.8%)	102 (48.3%)	0.92
SICU	306 (74.8%)	127 (66.8%)	0.053
V_T (mL)	455 (398, 520)	460 (400, 533)	0.21
V_T (mL/kg)†	7.1 (6.1, 8.1)	7.4 (6.2, 8.2)	0.003
Pplat (cm H_2O)	24 (21, 28)	24 (21, 28)	0.78
PEEP (cm H_2O)	8 (5, 10)	8 (5, 10)	0.25
P_{DR} (cm H_2O)	16 (13, 19)	15 (12, 19)	0.047
Mean Paw (cm H_2O)	15 (12, 18)	15 (12, 18)	0.63
C_{RS} (mL/cmH_2O)	29 (24, 36)	31 (24, 38)	0.013
V_E (L/min)	10.1 (8.1, 12.4)	10.0 (8.1, 12.2)	0.58

Pa_{CO2} (mm Hg)	40 (35, 46)	40 (35, 45)	0.95
VR	1.7 (1.4, 2.1)	1.6 (1.4, 2.1)	0.72
pH	7.35 (7.25, 7.41)	7.35 (7.27, 7.42)	0.47
BE (mEq/dL)	-3.8 (-8.3, 0.4)	-3.3 (-8.5, 1.2)	0.15
F_{IO2}	0.80 (0.60, 1)	0.80 (0.60, 1)	0.17
Pa_{O2} (mm Hg)	87 (71, 114)	84 (70, 107)	0.03
Pa_{O2}/F_{IO2} (mm Hg)	125 (90, 180)	120 (87, 162)	0.001
OI	11.6 (7.2, 17.5)	12 (7.7, 19.5)	0.013

Key: ARDS Net = acute respiratory distress syndrome [clinical trials] network, BE = base excess, C_{RS} = respiratory system compliance, LIS = lung injury score, OI = oxygenation index, Pa_{CO2} = arterial carbon dioxide tension, P_{aO2}/F_{IO2} = arterial oxygen tension-to-inspired oxygen fraction ratio, Paw = airway pressure, Pplat = end-inspiratory plateau pressure, PEEP = positive end-expiratory pressure, P_{DR} = Pplat-PEEP, V_E = minute ventilation, VR = ventilatory ratio, V_T = tidal volume, *Data are presented as median (25-75% interquartile range). † based upon predicted body weight.

Supplementary Table 1. NIH ARDS Clinical Trials Network (ARDSNet) exclusion criteria for the trial comparing 12 vs. 6 mL/kg tidal volume study and those adopted for quality assurance purposes at San Francisco General Hospital.*

Adopted Criteria	Criterion adopted in order to:
Clinical evidence of left atrial hypertension. If measured pulmonary arterial occlusion pressure > 18 mmHg	Indicate subjects with an ARDS risk factor in whom hydrostatic pulmonary edema likely contributed to hypoxemia. Based upon medical history and/or magnitude of fluid resuscitation. Also used to indicate patients in whom mortality risk might be increased due to severity of cardiac dysfunction and the additional stress of acute lung injury.
C5 or higher spinal cord injury	Indicate subjects likely to have prolonged duration of mechanical ventilation or ICU LOS rather than mortality risk.
Increased intracranial pressure	Indicate subjects likely to have poorer prognosis and limited goals of care at some point after ARDS onset. This criterion was expanded to include any subject with acute brain injury regardless of whether intracranial pressure monitoring was used.
Severe chronic respiratory disease	Indicate subjects likely to have prolonged duration of mechanical ventilation or ICU LOS as well as potential for mortality risk because of the additional stress of acute lung injury.
Morbid Obesity	Indicate subjects likely to have prolonged duration of mechanical ventilation.
Malignancy or other irreversible disease or *condition* for which 6-month mortality is estimated > 50%	Indicate subjects likely to have poorer prognosis and therefore limited goals of care.
Perceived moribund condition	Indicate subjects with increased mortality risk based upon ad hoc empirical evidence (i.e. MAP $\leq$ 55 mmHg

	with pH ≤ 7.15 and/or base deficit ≥ 15 mEq/dL) despite initial resuscitation efforts.
Severe chronic liver disease (Childs-Pugh Score ≥ 10)	Increased mortality risk. Note: scores were calculated for all subjects diagnosed liver disease (or noted to have elevated total bilirubin) but were not entered into the database

Key: ARDS = acute respiratory distress syndrome, C5 = fifth cervical vertebrae, ICU-LOS = intensive care unit length-of-stay, MAP = mean arterial pressure, * criteria from the internal NIH ARDS Network study manual issued December 1st 1995.

Supplementary Table 2. Distribution of both lung-protection factors and ventilator-induced lung injury risk factors at ARDS onset

	RCT-Eligible	RCT Ineligible	P
Enhanced Lung Protection			
$V_T \leq 6$ mL/kg	214 (18.8%)	153 (18.3%)	0.79
$V_T \leq 8$ mL/kg	844 (74.3%)	595 (71.0%)	0.12
Pplat ≤ 30 cm H_2O	974 (85.7%)	708 (84.4%)	0.44
$P_{DR} \leq 15$ cm H_2O	561 (49.4%)	456 (359 (54.4%)	0.03
Enhanced Lung Injury Risk			
$V_T \geq 12$ mL/kg	5 (0.4%)	7 (0.8%)	0.41
Pplat ≥ 35 cmH_2O	74 (6.5%)	49 (5.7%)	0.60
$P_{DR} > 20$ cmH_2O	191 (16.8%)	132 (15.7%)	0.56

Key: Pplat = end-inspiratory plateau pressure, PEEP = positive end-expiratory pressure, P_{DR} = Pplat-PEEP, V_T = tidal volume,

Supplementary Table 3. Comparisons between RCT-eligible and RCT-ineligible subjects managed with an ARDSNet ventilator protocol: initial baseline measurements following protocol initiation and on the following day (Day 1).*

	RCT-Eligible		RCT-Ineligible	
	Baseline	Day-1	Baseline	Day-1
Pplat (cmH_2O)	24 (21, 28)	24 (21, 28)†	24 (21, 29)	25 (22, 28)
PEEP (cmH_2O)	8 (5,10)	10 (8,12)‡	10 (5,12)	10 (10,14)‡
P_{DR} (cmH_2O)	15 (13, 19)	14 (11, 17)‡	15 (12, 19)	13 (11, 16) §
V_T mL/Kg	6.8 (6.1, 7.9)	6.2 (5.9, 6.6)‡	7.0 (6.0, 8.0)	6.1 (5.9, 6.5) §
F_{IO2}	0.80 (0.60, 1)	0.50 (0.50, 0.70)§	0.80 (0.60, 1)	0.60 (0.50, 0.80) §

Key: *Data are presented as median (25-75% interquartile range).†P = 0.003 vs. baseline, ‡P < 0.001 vs. baseline §P < 0.001 vs. baseline, F_{IO2} = inspired oxygen fraction, Pplat = end-inspiratory plateau pressure, PEEP = positive end-expiratory pressure, P_{DR} = Driving pressure (Pplat-PEEP), V_T = tidal volume.

Supplementary Table 4. Use of ancillary therapies for oxygenation and/or buffer support

	RCT-Eligible	RCT-Ineligible	P
NMB	173 (15.2%)	145 (17.4%)	0.24
Aerosolized Prostacyclin	154 (13.6%)	137 (16.4%)	0.095
Prone Positioning	48 (4.2%)	23 (2.8%)	0.10
THAM Rx	39 (3.4%)	40 (4.8%)	0.17
Recruitment Maneuvers	29 (2.6%)	34 (4.1%)	0.084
HFOV	7 (0.6%)	1 (0.1%)	0.17
ECMO	9 (0.8%)	1 (0.1%)	0.078
Received at Least 1 Ancillary Therapy	267 (23.5%)	227 (27.1%)	0.08
Received $\geq$ 2 Ancillary Therapies	117 (10.3%)	98 (11.7%)	0.27
Mortality in Those Receiving at Least 1 Ancillary Therapy	109 (40.8%)	128 (56.4%)	<0.0001
Mortality in Those Not Receiving Ancillary Therapy	205 (23.6%)	295 (48.2%)	< 0.0001

Key: ECMO = Extracorporeal Membrane Oxygenation, HFOV = High Frequency Oscillatory Ventilation, NMB = Neuromuscular Blockade, THAM = tris-hydroxymethyl aminomethane

Supplementary Table 5. Characteristics of subjects excluded due to perceived moribund condition (ie. not based on any formal pre-hoc definition) at the time of assessment.*

Variable†	Median (IQR)
MAP (mmHg)	47 (42,53)
SAP (mmHg)	66 (60,73)
pH	7.09 (7.03,7.15)
BE (mEq/dL)	-16.7 (-20, -14.7)

Key: BE = base excess, SAP = systolic arterial pressure, MAP = mean arterial blood pressure. *Data are presented as median (25-75% interquartile range). †Represent the lowest values measured on the day of ARDS onset.

Supplementary Table 6 Comparison of mechanical ventilation duration, intensive care until length-of-stay and ARDS-associated hospital length of stay among survivors between RCT-Ineligible subjects with acute brain injury, other RCT-ineligible subjects and RCT-eligible subjects.*

	RCT-Ineligible ABI	RCT-Ineligible	RCT-Eligible
N	195	215	822
MV Days	14 (8,24)†	9 (4,17)	9 (4-18)
ICU LOS	18 (12,28)†	12 (6,19)	12 (6,22)
Hospital Days	30 (19,49)‡ §	27 (12,43)	23 (13,44)

Key: ABI = acute brain injury, ICU = intensive care unit, LOS = length-of-stay, MV = mechanical ventilation, RCT = randomized controlled trial, *Data are presented as median (25-75% interquartile range). †P < 0.0001 vs. both other RCT-Ineligible and RCT-Eligible, ‡P = 0.016 vs. other RCT-Ineligible subjects, §P = 0.0006 vs. RCT-Eligible subjects.

Supplementary Table 7 Mortality comparisons between RCT-eligible subjects managed clinically with the ARDSNet ventilator protocol vs. ARDSNet clinical trials.

Mortality Evaluation	SFGH Mortality RCT-Eligible	ARDS Net Mortality	Trial
Hospital Discharge	28.3%	31.0%	ARMA[1]
Hospital Discharge	28.3%	24.9% (lower PEEP) 27.5% (higher PEEP)	ALVEOLI[8]
Day 60	26.9%*	25.5% (fluid conservative) 28.4% (fluid liberal)	FACTT[23]
Day 90	27.6%	24.3% (albuterol) 18.5% (placebo)	ALTA[26]
Day 90	31.3%†	42.5% (NMBA) 42.8% (Control)	PETAL[25]

Key: NMBA = neuromuscular blocking agent, RCT = randomized controlled trial. *reflects mortality adjusted to Day 60, †reflects mortality of subjects delimited to inclusion criteria of PEEP $\geq$ 8 cmH_2O and P_{aO2}/F_{IO2} < 150 mmHg.

Fig 1

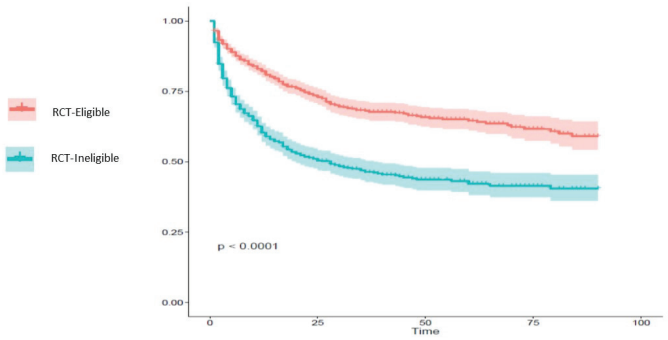

Figure 1. Kaplan-Meier plots of the probability of 90-day survival with 95% CI between patients meeting randomized control trial eligibility vs. ineligibility criteria.

338x190mm (96 x 96 DPI)

Fig 2

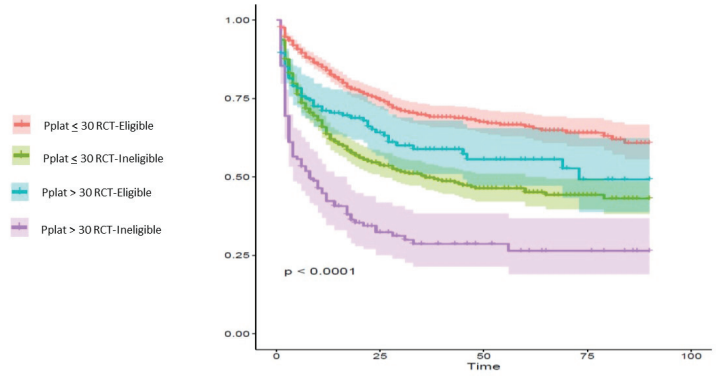

Figure 2. Kaplan-Meier plots of the probability of 90-day survival with 95% CI between subjects meeting randomized control trial eligibility vs. ineligibility criteria. and a plateau pressure cut-off of 30 cmH2O

338x190mm (96 x 96 DPI)

Fig 3

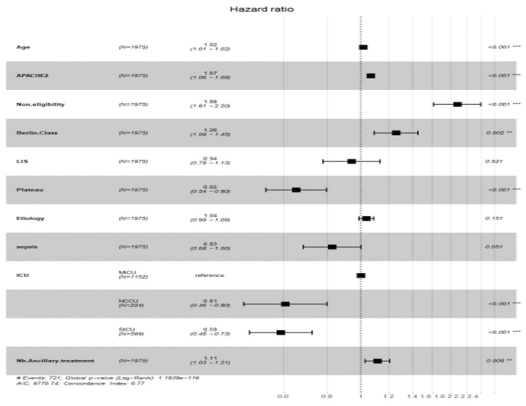

Figure 3. Forest plot of adjusted Cox proportional hazard model for 90-day mortality

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