Influence of Clinical Factors and Exclusion Criteria on Mortality in ARDS Observational Studies and Randomized Controlled Trials

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ARDS has a high mortality in the acute setting, with long-term disability among disease survivors. In 1967, David Ashbaugh and colleagues first described the clinical features of ARDS, which were notably similar to the infantile respiratory distress syndrome. Half a century later, ARDS remains underrecognized and is associated with high mortality rates. Valuable insights from observational studies fail to demonstrate a mortality benefit in randomized controlled trials (RCTs). In the absence of a pharmacologic cure, supportive ventilator strategies limit rather than treat the ongoing lung injury. Interestingly, ARDS has higher mortality rates in observational studies compared to RCTs. Comparing mortality rates between ARDS studies and trials is problematic, partly due to varying time-points at which mortality is reported. Discerning the true mortality attributable to ARDS is also difficult. The diagnostic criteria for ARDS are mainly clinical and lack the objectivity of a laboratory test or biomarker. Nonetheless, these factors are common to both studies and trials, and fail to explain the higher mortality rate of ARDS observational studies. Disease heterogeneity and complex patient characteristics can also confound mortality estimation in ARDS. We therefore examined patient and trial factors that could influence mortality outcomes in ARDS observational studies and RCTs. Unlike RCTs, observational studies include ARDS subjects with severe comorbidities and those requesting limited care. Less stringent selection criteria could thereby contribute to high mortality rates in ARDS observational studies. In contrast, exclusion criteria in RCTs meticulously scrutinize patient characteristics, confining the type and number of eligible subjects. As a result, the task of identifying, consenting, and randomizing eligible patients within the enrollment window is challenging, further decreasing the number of subjects enrolled. Moreover, ARDS RCTs strictly adhere to lung-protective strategies, while ARDS observational studies continually demonstrate variable compliance. This review highlights the impact of patient- and trial-related factors on influencing mortality rates in ARDS observational studies and RCTs. *Key words: ARDS; mortality; observational studies; randomized; controlled trials; acute respiratory distress syndrome network; cancer; liver disease; limitation of care.* [Respir Care 2018;63(8):1060–1069.

Introduction

ARDS is a rapidly progressive and often fatal cause of respiratory failure, first described in 1967 by Ashbaugh and colleagues.[1] In 1972, a National Heart, Lung, and Blood Institute (NHLBI) task force estimated an annual incidence of 150,000 ARDS cases, with mortality rates of up to 70%. Over the last 50 years, extensive research efforts have led to a significant improvement in the understanding of the disease, but they have failed to produce a pharmacologic cure. In 2016, mortality rates of 35%, 40%, and 46% for mild, moderate, and severe ARDS, respectively, were described,[2] emphasizing the high mortality rate associated with the disease. Unfortunately, only supportive measures with lung-protective ventilation,[3] alongside a few others,[4,5] have demonstrated a mortality benefit in ARDS randomized controlled trials (RCTs).

Directly comparing mortality rates across ARDS observational studies and RCTs or analyzing trends in mortality rate is challenging. ARDS mortality is reported over different time points in both observational studies and RCTs. Heterogeneity among ARDS patients and the lack of a definitive diagnostic test obscures the mortality truly attributable to ARDS.

Despite these limitations, recent ARDS studies reveal an underrecognized yet interesting pattern in mortality reporting: ARDS observational studies have a higher mortality rate compared to ARDS RCTs.[6] To date, reasons for this discrepancy have not been well described. With the advent of lung-protective ventilation, we examined the ARDS literature, re-confirming the higher mortality rate in ARDS observational studies compared to ARDS RCTs. We hypothesized that clinical factors and exclusion criteria could contribute to the difference in mortality rates. Known predictors of mortality in ARDS observational studies were then analyzed in relation to the exclusion criteria of RCTs. Common clinical factors and trial-related factors were identified, and their influence on ARDS mortality in observational studies and RCTs were investigated. In this review, we discuss the influence of clinical and trial-related factors, in an attempt to explain the striking difference in mortality rates between ARDS observational studies and RCTs.

Review of Literature

In the era of lung-protective ventilation, ARDS observational studies continue to have a higher mortality rate compared to ARDS RCTs. This is evident when the mortality rates from observational studies by Bellani et al[2] and Sakr et al[7] (Table 1) are compared to the mortality rates reported by the NHLBI-sponsored ARDS Network (ARDSNet) trials[8-12] (Table 2).

Observational Studies

Observational studies by design do not have well-defined exclusion criteria and hence include heterogeneous subjects. To effectively capture the diversity of an observational study, we selected 2 large prospective cohort studies, one by Bellani et al[2] and another by Sakr et al.[7] These multinational observational studies were conducted in the era of lung-protective ventilation and enrolled mechanically ventilated subjects with ARDS based on the American-European Consensus Conference[13] or Berlin[14] criteria. Subjects with coexisting severe liver disease, cancer, high-predicted mortality, trauma, or sepsis were also included. These studies were conducted at different times, in separate geographic locations, thus proving a global perspective of real-life, non-trial ARDS patients.

Randomized Controlled Trials

ARDS RCTs have strict exclusion criteria that differ based on the specific trial design. To effectively compare the exclusion criteria of RCTs and the predictors of mortality in observational studies, we examined the NHLBI-sponsored ARDS Network trials: Fluid and Catheter Treatment Trial (FACTT),[8] Albuterol for Treatment of Acute Lung Injury Trial (ALTA),[9] Omega Nutrition Supplement Trial (OMEGA),[10] Early versus Delayed Enteral Nutrition Trial (EDEN),[11] and Statins for Acutely Injured Lungs from Sepsis Trial (SAILS). These trials had similar exclusion criteria and mortality reporting at 60 d, and lung-protective ventilation with low tidal volumes of 6 mL/kg predicted body weight (PBW) were used. The Alveoli[15] trial was not included, as a modified low tidal volume ventilation (low V_T) protocol was used, and the inability to comply with low V_T was not listed as a specific exclusion criterion. Across these 5 trials,[8-12] common exclusion criteria

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Table 1. Mortality at 28, 60, and 90 Days in Observational Studies Using Either AECC or Berlin Definitions for ARDS

Study	Definition	Subjects, *n*	ALI/Mild ARDS, *n*	*ARDS, *n*	Day of Mortality Evaluation	All Mortality, *n* (%)	ALI/Mild ARDS, *n* (%)	ARDS, *n* (%)
Bellani et al[2]	Berlin	2,377	714	1,663	28	828 (34.8)	211 (29.6)	617 (37.1)
Sakr et al[7]	AECC	393	59	334	60	179 (45.5)	20 (33.9)	159 (47.6)
Bellani et al[2]	Berlin	2,377	714	1,663	90	952 (40)	249 (34.9)	703 (42.3)

* All subjects encompassed under AECC ARDS definition as well as Berlin criteria for moderate and severe ARDS.
ALI = acute lung injury
AECC = American-European Consensus Conference

Table 2. Mortality at 60-Days in NHLBI ARDS Clinical Trials Network Studies

	Total Subjects, *N*	Experimental Arm, *n*	Control Arm, *n*	Mortality Experimental Arm, %	Mortality Control Arm, %	Overall Mortality, %
Fluid and Catheter Treatment Trial (FACTT)[8]	1,000	503	497	25.5	28.4	26.9
Albuterol for Treatment of Acute Lung Injury Trial (ALTA)[9]	282	152	130	23.0	17.7	20.6
Omega Nutrition Supplement Trial (OMEGA)[10]	272	143	129	26.6	16.3	21.7
Early versus Delayed Enteral Nutrition Trial (EDEN)[11]	1,000	508	492	23.2	22.2	22.7
Statins for Acutely Injured Lungs from Sepsis Trial (SAILS)[12]	745	379	366	28.5	24.9	26.3
Weighted Mean				25.3	23.9	24.6

NHLBI = National Heart, Lung, and Blood Institute

Table 3. Common Disease and Enrollment Specific Exclusion Criteria in the ARDS Network RCTs

Disease-Specific Exclusions	Enrollment-Specific Exclusions
Liver dysfunction: Child-Pugh score 12–15	Refusal of consent by physician, patient, or family
Malignancy, irreversible disease: estimated 6-month mortality > 50%	> 48 h since all inclusion criteria were met
Bone marrow or lung transplant	Patient, surrogate, or physician not committed to full support
Moribund condition: expected survival < 24 h	No intent to monitor intravascular pressures
Neuromuscular disease impairing spontaneous breathing*	Unwillingness or inability to use V_T = 6 mL/kg PBW
Vasculitis, diffuse alveolar hemorrhage	Pregnancy or breastfeeding
Body surface area burns ≥ 30%	Body mass > 1 kg/cm of height
Severe chronic respiratory disease	

* Cervical spinal cord injury (≤ C5), amyotrophic lateral sclerosis, Guillain-Barre syndrome, myasthenia gravis.
RCT = randomized controlled trial
PBW = predicted body weight
V_T = tidal volume

were identified and grouped based on reasons specific to the underlying disease or enrollment process (Table 3). Exclusion criteria specific to individual trials were addressed independently (Table 4).

Mortality Rates

In the era of low V_T, observational studies demonstrate a higher mortality rate compared to the ARDSNet RCTs.[8-12] Bellani et al[2] enrolled 2,377 subjects with ARDS, with a reported 28-d mortality of 35% and 90-d mortality of 40%, while Sakr et al[7] enrolled 393 subjects with ARDS with a reported 60-d mortality of 46% (Table 1). The ARDS mortality in the two observational studies ranged between 35% and 46%. In both studies, the ARDS mortality rate was calculated at different intervals. Thus, specifying an average or weighted-average mortality rate would be inaccurate.

In the 5 ARDSNet trials,[8-10,12] the weighted 60-d average mortality rate was 25% in the treatment arm and 24% in the control arm. The overall weighted 60-d average mortality rate was 24.6% (Table 2).

For RCTs using low V_T, mortality rates are typically 25–31%.[16] The 25% mortality rate in the 5 selected

Table 4. Trial-Specific Exclusion Criteria in ARDS Network RCTs

Fluid and Catheter Treatment Trial (FACTT)[8]	Albuterol for Treatment of Acute Lung Injury Trial (ALTA)[9]	Omega Nutrition Supplement Trial (OMEGA)[10] and Early versus Delayed Enteral Nutrition Trial (EDEN)[11]	Statins for Acutely Injured Lungs from Sepsis Trial (SAILS)[12]
Presence of pulmonary artery catheter after onset of acute lung injury	> 72 h since initiation of mechanical ventilation	> 72 h since initiation of mechanical ventilation	> 7 d since initiation of mechanical ventilation
Renal failure requiring renal replacement therapy	Contraindication to aerosolized albuterol	No enteral access or high-output entero-cutaneous fistula	Unable to receive or unlikely to absorb enteral study drug
Acute myocardial infarction within past 30 d	Daily use of inhaled β agonist, corticosteroid, or oral leukotriene modifier	Bowel obstruction, ischemia, infarction; short bowel syndrome or no gastrointestinal tract	Received statin medication within 48 h of randomization
Allergy to furosemide	Inability to stop β agonist	TPN use or intent to use in 7 d	Allergy or intolerance to statins
	Severe congestive heart failure	BMI < 18.5 or loss of > 30% total body weight in 6 months	Physician refusal to use or avoidance of statin therapy
	Acute coronary syndrome within past 30 d	Laparotomy expected in 7 d	CK, ALT, or AST level > 5 times ULN
	New-onset atrial fibrillation requiring anticoagulation	Unable to raise head of bed 30–45°	Untreated hypothyroidism
	> 5 PVCs per min within 4 h before randomization	Central nervous system hemorrhage, coagulopathy, or bleeding disorder	Medications interacting with study drug or statin
	Heart rate > 85% predicted or 140 beats/min	Allergy to enteral formula	NYHA class IV cardiac disease
	Use of high-frequency oscillatory ventilation	Need for enteral formula with omega-3 fatty acids or gamma-linolenic acid	Myocardial infarction within past 6 mo
	Participation in medication trials within past 30 d (except OMEGA trial)	Refractory shock	Intracranial hemorrhage within past 1 mo

RCT = randomized controlled trial
ALT = alanine transaminase
AST = aspartate transaminase
CK = creatine kinase
NYHA = New York Heart Association
PVC = premature ventricular contractions
TPN = total parenteral nutrition
ULN = upper limit of normal

ARDSNet trials[8-12] was in this expected range. However, the mortality for observational studies[2,7] ranged between 35% and 46%, distinctly higher than the mortality rate in the RCTs. A similar pattern was reported in a systematic review of ARDS observational studies and RCTs conducted between 1984 and 2006.[6] The review included studies and trials before and after the era of lung-protective ventilation,[3] and described similarly higher mortality rates in ARDS observational studies compared to ARDS RCTs.[6] More recently, a Spanish observational study of subjects with ARDS receiving low V_T also reported a mortality rate of 48%.[17] These data suggest that even in the era of low V_T, ARDS observational studies[2,7] have a higher mortality rate compared to ARDS RCTs.[8-12]

An average of 10% of the total screened subjects were randomized into 1 of the 5 ARDSNet trials[8-12] (Table 5). Subjects were eliminated based on exclusions that related to a co-existing illness, issue with enrollment, or the trial design. Here, stringent pre-requisites for trial participation not only limited the initial pool of potentially eligible patients, but also limited the final number of subjects randomized. Furthermore, ARDS patients with limited access to clinical trials are not represented in the RCTs. Restrictive exclusion criteria can alter the subject cohort, inadequately reflecting the heterogeneous and complex attributes of real-life ARDS patients. ARDS observational studies have fewer constraints, permitting greater diversity in patient enrollment. Of the numerous factors that influence the observed differences in mortality between observational studies and RCTs, exclusion related to enrollment is likely one of the key factors (Tables 3 and 4). Presented below is an in-depth analysis of the leading causes for patient exclusion from RCTs.

Disease-Specific Exclusion Criteria

Clinical trials often eliminate ARDS patients based on the presence or increased severity of a comorbid illness (Table 3).

Liver Disease. Approximately 8% of ARDS patients with severe liver disease, defined as a Child-Pugh score of 10–

Table 5. Proportion of Screened Versus Enrolled Subjects in the ARDS Network RCTs

ARDSNet Trial, Year	Subjects Enrolled, *n*	Patients Screened, *n*	Proportion of Patients Enrolled, %
Fluid and Catheter Treatment Trial (FACTT), 2006[8]	1,000	11,512	8.69
Albuterol for Treatment of Acute Lung Injury Trial (ALTA), 2011[9]	282	2,688	10.49
Omega Nutrition Supplement Trial (OMEGA), 2011[10]	272	2,778	9.79
Early versus Delayed Enteral Nutrition Trial (EDEN), 2012[11]	1,000	7,968	12.55
Statins for Acutely Injured Lungs from Sepsis Trial (SAILS), 2014[12]	745	7,491	9.95
Total	3,299	32,437	10.17

RCT = randomized controlled trial

15, were excluded from the ARDSNet trials.[8-12] In the observational LUNG SAFE study,[2] mortality was 71% (73 of 103 subjects) with an odds ratio of 3.28 (95% CI 1.99–5.40) in subjects with coexisting ARDS and liver disease.[18] Prior ARDS observational studies have consistently recognized chronic liver disease to be an independent predictor of mortality in subjects with ARDS.[19-22]

Estimating the true mortality attributable to ARDS is overall challenging; additionally, this seems to be true in patients with ARDS and cirrhosis. Cirrhosis is associated with immune dysfunction,[23] higher risk of developing sepsis,[24] and sepsis-induced ARDS.[25] ARDS patients with end-stage liver disease and septic shock have mortality rates of up to 100%.[26]

Smoking[27] and alcohol use[28] can also confound mortality estimation in ARDS and liver disease. Oxidant stress from direct cigarette smoke exposure incites epithelial and endothelial cell injury,[27] predisposing patients to develop ARDS. Chronic alcohol use independently increases the risk for ARDS, and it also increases the severity of nonpulmonary organ dysfunction in ARDS patients with septic shock.[29] A mortality rate of 65% compared to 35% has been reported in ARDS subjects with chronic alcohol use compared to ARDS patients without substantial alcohol use.[28]

In complex critically ill patients, the increased-permeability pulmonary edema and severe respiratory failure characteristic of ARDS may be more of a response to widespread systemic inflammation rather than the primary inciting process, which means that lung-specific therapies may have a lower chance of success. In contrast, strategies targeted specifically at lung injury in primary causes of ARDS (pneumonia and aspiration) may have a significant impact on reducing overall mortality rates. Conversely, a RCT conducted in a select patient population with limited diversity may fail to produce similar results when performed in a general, clinically heterogeneous, group of non-trial patients. Nonetheless, conducting a well-powered study in a highly select cohort of critically ill ARDS patients is challenging and laborious.

Improvements in the overall management of sepsis has resulted in a decline in mortality rates in patients with cirrhosis and septic shock,[31] while the use of low V_T in patients with severe comorbidities such as liver disease does have a significant mortality benefit.[32] Hence, it may be reasonable to consider including ARDS subjects with severe liver disease into future RCTs.

Cancer and Immune Incompetence. Patients with active cancer, predicted 6-month mortality rate of 50%, and bone marrow or lung transplant recipients were excluded from the ARDS network trials. The LUNG SAFE study[2,18] reported an increased hospital mortality in subjects with ARDS who had active cancer (odds ratio 1.83, 95% CI 1.31–2.57); hematological malignancies (odds ratio 4.77, 95% CI 2.82–8.04); and immunosuppression (odds ratio 1.42, 95% CI 1.04–1.93). Similar findings were also reported by Sakr et al.[7] In previous studies, 85% of subjects with hematological malignancies and 15% of subjects with solid tumors developed ARDS, with an overall hospital mortality of 64%.[33] Bone marrow/hematopoietic stem cell transplantation was identified as an independent predictor of hospital mortality (odds ratio 1.71, 95% CI 1.07–2.71). Similar to ARDS patients without cancer,[2] infection-related direct lung injury and extra-pulmonary septic shock were the most common risk factors for developing ARDS.[33,34] However, therapeutic success in these immunocompromised patients may be impaired by a higher risk of invasive fungal infections, drug-resistant bacterial infections,[33,34] and neutropenia from chemotherapy or radiation.[35]

Some ARDS patients with a history of cancer were eligible for enrollment in the ARDSNet trials. Interestingly, these subjects also demonstrated higher 28-d and 60-d mortality rates compared to ARDS patients without cancer (55% vs 24% and 60% vs 28%, respectively; $P < .001$).[34] Notably, despite the inclusion of the ARDS subjects with cancer in some of the ARDSNet trials, the combined overall trial mortality remained at 26%.[34] A total of 2,631 ARDS subjects were enrolled in these trials, but only 116 (4.4%) ARDS subjects had cancer. The observational LUNG SAFE study

enrolled a comparable number of ARDS subjects, although 600 of the 2,377 (25%) were immunosuppressed, had active cancer, or had hematological malignancies. Stringent exclusion criteria eliminate a majority of cancer patients from participating in RCTs. Thus, although the ARDS patients with cancer in the RCTs also have higher mortality rates, the limited number of cancer patients who have been enrolled may be insufficient to cause a significant difference in the overall trial mortality.

The 2017 Cancer Statistics[36] reported an increase in the 5-y relative survival rate for all cancers. Moreover, studies in patients with ARDS and cancer have also demonstrated a trend toward improved survival.[33,37] Thus, enrolling cancer patients in randomized clinical trials is important.[38]

Enrollment-Specific Exclusion Criteria

Exclusions within the enrollment process are designed to ensure the validity of the data generated while also protecting a patient's rights and wishes (Table 3).

Consent. Obtaining consent from eligible ARDS patients within a highly constrained time window is challenging. Patients may not be able to consent for themselves, or they may lack well-documented advance directives. Family members are often overwhelmed with the intensity of the clinical situation and may be unable to make decisions about participation in a research trial.[39] In the selected RCTs, 21% of the total screened patients were excluded owing to the lack of consent from a family member, a surrogate decision-maker, or the treating physician. Hence, a majority[8–12,15,38–41] of patients, although eligible, are not enrolled. Higher rates of non-enrollment are more prevalent at public hospitals than at higher referral centers. The absence of a surrogate decision maker is the most common reason for non-enrollment, followed by refusal from the treating physician or family.[41] Slow recruitment can increase costs, prolong therapeutic uncertainty, or produce insignificant results if the sample size is not adequate.[40] Furthermore, the generalizability of the trial results can be affected,[39] especially if the trials do not represent underserved populations well.[41]

Timing. Timely identification of patients with ARDS is crucial. In the LUNG SAFE study,[2,18] the diagnosis of ARDS was often delayed, with only 34% of subjects being diagnosed when the ARDS criteria were first met.[2] In the selected RCTs, on average 14% of screened patients were excluded because they were outside the trial-stipulated time frame for diagnosis or mechanical ventilation. Excluding eligible patients in RCTs can once again decrease generalizability and efficiency[38] of the trial, although quantifying a direct mortality impact becomes difficult.

Limited-Care Directives. A majority of ICU deaths occur after withdrawal of or from withholding life-sustaining treatments.[42-45] The ARDSNet trials[8-12] excluded otherwise eligible patients if their family or treating physician was not committed to full support. Some patients who were not amenable for invasive procedures including central venous pressure monitoring were excluded. In the LUNG SAFE study,[2,18] 578 (24%) subjects had decided to limit therapy, and of these subjects, 498 (86%) died in the hospital. Of note, in 525 (91%) subjects, the decision to limit life-sustaining therapy was made after ARDS was diagnosed. Subjects with immunosuppression, low pH, and chronic liver disease were found to be more likely to opt for limited care.[18] Factors such as older age, higher sequential organ-failure scores, immunosuppression, hematological and non-hematological cancers, severe pancreatitis, and poor neurological status were also reported to independently influence the decision to limit care.[45] It is not surprising that these factors also overlap with the determinants of poor outcomes identified in ARDS observational studies (Table 6). The incidence of subjects with poor prognostic comorbidities is higher in ARDS observational studies than in ARDS RCTs. Although difficult to prove, excluding patients with limited care requests maybe also be a factor in the lower mortality rates observed in RCTs.

Compliance With Lung-Protective Ventilation. Noncompliance with the ARDS network recommendation of 6 mL/kg PBW ventilation protocol or low V_T was listed as a specific exclusion criteria in the 5 selected ARDS network trials.[8-12] In the observational study by Sakr et al,[7] only 44% of the mechanically ventilated subjects received a mean tidal volume of 5–7 mL/kg PBW, and the use of tidal volumes $>$ 7.4 mL/kg PBW independently increased mortality. In a prospective study, Needham et al[46] showed that every 1-mL/kg PBW increase in initial tidal volumes above 6.5 mL/kg PBW[3] was associated with a 23% increased risk of ICU mortality, and subsequent increases of 1 mL/kg PBW from the initial tidal volume were associated with a 15% higher risk of ICU mortality. Over the years, supportive management with low V_T[3] has been one of the few supportive[4,47] strategies shown to reduce the short-term and likely long-term ARDS mortality rates.[48] In the multi-center LUNG SAFE study,[2] although lower tidal volumes were used overall, more than one third of subjects received tidal volumes $>$ 8 mL/kg PBW, and approximately 60% received tidal volumes $>$ 7 mL/kg PBW. Additionally, compliance with lung-protective ventilation in emergency departments has also been a concern,[49,50] especially when mechanical ventilation is often begun in the emergency setting while patients wait for beds in the ICU.[2]

Subjects enrolled in ARDSNet RCTs had lower mortality rates than in the original high tidal volume arm of the

Table 6. Mortality Predictors in Observational Studies Compared to Common Exclusion Criteria in ARDS Network RCTs

Mortality Predictors in Observational Studies	Common Exclusion Criteria in RCTs
Chronic liver disease	Liver dysfunction with Child-Pugh score of 12–15
Severity of multi-organ failure	Moribund, patient not expected to survive 24 h
Active cancer	Malignancy or other irreversible disease or condition for which 6-month mortality is estimated at 50%
Hematological malignancies	Bone marrow transplant or lung transplant
Immune-incompetence	Burns ≥ 40% of total body surface area
Older age	Patient, surrogate, or physician not committed to full support
Lower pH	No consent from treating physician or patient or family
Lower P_{aO_2}/F_{IO_2}*	Chronic lung disease
Higher mean fluid balance (ICU)†	No intent to obtain central venous access
Increased tidal volume‡	Unwillingness or inability to use 6 mL/kg PBW ventilation
Increased breathing frequency	Neuromuscular disease impairing spontaneous ventilation
PEEP < 12 cm H_2O in moderate ARDS	Pregnancy or breast feeding
Higher plateau and driving pressures§	Body mass > 1 kg/cm of height
Lower number of ICU beds	> 48 h since all inclusion criteria were met

* Lower P_{aO_2}/F_{IO_2} (120–150 mm Hg) was associated with increased hospital mortality.[2,18]
† Increased mean ICU fluid balance was an independent predictor of ICU mortality.[7]
‡ Tidal volumes of > 7.4 mL/kg PBW was associated with increased ICU and hospital mortality.[2,18]
§ At ARDS onset, a Plateau pressure ≥25 cm H_2O (severe ARDS), and driving pressure (Pplat-PEEP) ≥ 14 cm H_2O (moderate and severe ARDS) was associated with increased hospital mortality.[2,18]
RCT = randomized controlled trial
PBW = predicted body weight

ARMA trial.[38] The use of lower tidal volumes in the post-ARMA[3] ARDSNet RCTs[8-12] was strictly enforced. Although a trend toward using lower tidal volumes is apparent,[18,51,52] the consistent use at recommended levels is still a problem in observational studies.[2,7] The effect of low V_T on long-term outcomes is debatable, although an absolute risk reduction in 2-y mortality of 7.8% with 100% adherence and 4% with 50% adherence to low V_T has been reported.[48] Given the higher tidal volumes in observational studies, more stringent adherence to low V_T could, in theory, narrow the mortality differences between observational studies and RCTs.

Trial-Specific Exclusion Criteria

To minimize adverse events resulting from the trial intervention or trial design, RCTs have additional exclusion criteria that are specific to the individual trial (Table 4). In drug trials, allergy or known harmful interactions of the study drug with a patient's current medication regimen is a clear exclusion.[9,12] In the SAILS trial,[12] approximately 33% of the screened patients were excluded given an overall concern for statin use.

A specific trial design can eliminate ARDS patients with clinical conditions that are often present in critically ill patients. The presence of new-onset atrial fibrillation requiring anticoagulation,[9] myocardial infarction in the past 6 months (9% of patients in ALTA and 6% in FACTT),[12] untreated hypothyroidism, the need for renal replacement therapy,[8] or the foreseeable need for a laparotomy in the ensuing 7 d[10,11] are part of the underlying reasons that a patient is critically ill and also determines the severity of the illness. In the FACTT trial,[8] 21% of the screened patients had a pulmonary artery catheter placed after the onset of acute lung injury and were therefore ineligible for trial participation. It therefore does not come as a surprise that only 10.2% of the screened patients were eventually randomized into one of the ARDSNet trials[8-12] (Table 5). To accurately determine the extent to which exclusion criteria affect trial outcomes may be problematic, but the effect that exclusion criteria have on subject selection in RCTs is highly evident. Exclusion criteria significantly reduce the number of ARDS subjects enrolled in clinical trials. Trial subjects are an imperfect representation of the general, critically ill ARDS population and may partly explain the difference in mortality rates between observational studies and RCTs.

Predictors of Mortality in Observational Studies

Increasing severity of multi-organ failure was identified as a predictor of mortality in observational studies,[7,18] a finding that is consistent with ARDS observational studies conducted prior to low V_T[20,21,53]. Although the selected ARDSNet trials[8-12] did not exclude patients with multi-organ failure, they did exclude patients with estimated 6-month mortality of > 50%, severe congestive heart failure, refractory shock, moribund, or severe neuromuscular

disorders that impaired spontaneous respiration. ARDS patients with morbid obesity or chronic lung disease as well as breastfeeding or pregnant women were also excluded (Table 6). Approximately 11% of the screened patients in FACTT[8] and 9% of the screened patients in ALTA[9] were excluded due to a high predicted 6-month mortality. The Acute Physiology and Chronic Health Evaluation III score was used by RCTs, while the sequential organ failure assessment or the Simplified Acute Physiology Score II score was used by the selected observational studies to represent illness severity. The inability to objectively compare the severity of illness between observational studies and RCTs adds to the lingering uncertainty that observational studies enroll more seriously ill subjects than RCTs.

Older age and a lower P_{aO_2}/F_{IO_2}, especially between 120–150 mm Hg, was associated with higher ARDS mortality in the LUNG SAFE study.[18] However, definitive evidence linking age and P_{aO_2}/F_{IO_2} to mortality outcomes in ARDS is lacking.[7,54-56] In both the observational studies and the RCTs, there was no specified age cutoff, and all ARDS patients with a P_{aO_2}/F_{IO_2} ratio $<$ 300 mm Hg were enrolled. Of note, the ARDSNet trials[8-12] excluded patients with other causes of respiratory failure, like chronic intrinsic lung disease, severe neuromuscular weakness, and morbid obesity. Given the insufficient data and dissimilar patient populations, the independent contribution of age and significance of the P_{aO_2}/F_{IO_2} ratio on mortality differences in ARDS observational studies and RCTs rates remains unclear.

Increased plateau pressures $\geq$ 25 cm H_2O in severe ARDS, driving pressures $\geq$ 14 cm H_2O in moderate and severe ARDS,[18] elevated breathing frequency,[18] and higher mean ICU fluid balance[7] were independent predictors of increased mortality in observational studies (Table 6). The decreased availability of ICU beds was also shown to increase hospital mortality. Although it is evident that these factors increase mortality rates in ARDS observational studies, the corresponding effect on RCTs is yet to be determined. The care for ARDS subjects enrolled in clinical trials is based on predetermined, clearly outlined treatment protocols, including input from interdisciplinary teams.

Limitations

In this retrospective review, the influence of individual factors on mortality outcomes could not be quantified. It is not clear how many patients in RCTs were not included in the trial because of one or more than one exclusion criteria. A lack of sufficient data in both groups prevented any analysis of ARDS patients with chronic lung disease, morbid obesity, or women who were pregnant or breastfeeding. The ARDSNet trials were conducted in patients with similar characteristics across designated hospitals within the United States, while the observational studies enrolled diverse groups of ARDS patients from multiple hospitals in several countries.

Summary

ARDS observational studies have a higher mortality rate compared to ARDS RCTs. Exclusion criteria in ARDS RCTs influence the clinical attributes of subjects enrolled. For example, RCTs exclude ARDS patients with high predicted mortality rates, severe underlying disease, requests for limited care, and other factors that can potentially interfere with trial outcomes. The treatment approach in trial subjects is based on well-standardized, evidence-based strategies. All subjects in the ARDSNet trials[8-12] received low V_T as directed. Patients unable to comply with the prespecified treatment protocols or ventilatory strategies were excluded. In contrast, observational studies had a delay in ARDS recognition and insufficient compliance with low V_T. Subjects with multiple comorbidities, regardless of severity, were also included. Death in ARDS subjects who opted for limited care further contributed to the higher overall mortality in observational studies. In RCTs, the exclusion criteria are designed in part to reduce heterogeneity, but this inadvertently results in a cohort of subjects with similar clinical characteristics. Such cohorts of trial subjects do not represent the general ARDS population and thus have different mortality rates. In conclusion, this review highlights the potential clinical and trial-related factors that can influence mortality reporting in both ARDS observational studies and RCTs.

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