Understanding Causes of Death in Patients With Acute Respiratory Distress Syndrome: A Narrative Review

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OBJECTIVES: To provide a comprehensive summary of the published data on cause of death in patients with acute respiratory distress syndrome (ARDS).

DATA SOURCES: PubMed (January 2015 to April 2024), bibliographies of relevant articles, and ARDS Network and Prevention & Early Treatment of Acute Lung Injury (PETAL) network websites.

STUDY SELECTION: Observational studies and clinical trials that reported on cause of death in greater than or equal to 30 patients with ARDS, not obtained from death certificates. Animal studies, case reports, review articles, study protocols, and studies in pediatrics were excluded.

DATA EXTRACTION: Causes of death among ARDS patients who died were extracted and tabulated along with other pertinent study characteristics.

DATA SYNTHESIS: We identified 15 observational studies (nine non-COVID ARDS, five COVID-related ARDS; one both) and five clinical trials (all non-COVID ARDS). Mutually exclusive prespecified categories were used for recording the cause of death in only eight studies although studies differed in the categories included and their definitions. When multiple organ failure was a predetermined category, it was the most common cause of death recorded (~50% of deaths), followed by respiratory causes with proportions varying from 16% to 42% depending on nomenclature (e.g., refractory hypoxemia, pulmonary causes) and definitions. However, the largest observational study in non-COVID ARDS (964 deaths), did not include multiple organ failure as a predetermined category, and found that pulmonary failure (42%) and cardiac failure (37%) were the most common causes of death. In COVID-related ARDS observational studies, pulmonary reasons were the most reported cause of death (up to 88%).

CONCLUSIONS: Few studies have reported cause of death in patients with ARDS. In those that do, cause of death categories and definitions used are heterogeneous. Further research is needed to see whether a more rigorous and unified approach to assigning and reporting cause of death in ARDS would help identify more relevant endpoints for the assessment of targeted treatments in clinical trials.

KEYWORDS: critical care; death; mortality; respiratory distress syndrome; review

A cute respiratory distress syndrome (ARDS) is a clinical syndrome characterized by acute refractory hypoxemia with bilateral infiltrates on chest imaging as a result of diffuse lung inflammation and pulmonary edema (1, 2). Pathophysiology of the condition is complex but ultimately involves injury to both layers of the alveolar-capillary barrier resulting in impaired gas exchange (1, 2). Causes of ARDS are either direct lung injury, such as pneumonia (most common) or gastric aspiration, or indirect lung injury,

⊕ KEY POINTS

Question: We aimed to review published data on causes of death in acute respiratory distress syndrome (ARDS).

Findings: Of 20 studies, only eight used mutually exclusive prespecified categories; those included (and definitions) differed between studies. When multiple organ failure was a predetermined category, it was the most common cause of death (~50% in non-COVD ARDS), when not, pulmonary failure (42%) and cardiac failure (37%) were the most common causes.

Meanings: A more rigorous and unified approach to reporting cause of death in ARDS could potentially better guide the selection of clinical trial endpoints, especially in the development of targeted treatments.

such as nonpulmonary sepsis (most frequent) or major trauma (1, 2). In around 8% of patients, the causes of ARDS are not immediately recognizable (3). The condition is commonly seen in the ICU as shown in the global international Lung Safe study where 10.4% of patients admitted to ICU fulfilled ARDS criteria (3). Specific pharmacotherapies for ARDS are lacking, with patient management focused on providing best supportive care through incremental respiratory support to increase blood oxygen levels—high-flow nasal oxygen, noninvasive respiratory support, and invasive mechanical ventilation, conservative fluid management, corticosteroids, and prone positioning (4, 5). Despite best supportive care, the condition continues to carry significant morbidity, and an approximately 40% in-hospital mortality rate (3, 6).

Due to the complexity of assigning cause of death for critically ill patients, all-cause mortality is most often the primary endpoint in the assessment of ARDS interventions, including within the clinical development of pharmaceutical treatments (7–9). Clinical trials have thus far been unsuccessful in demonstrating efficacy for ARDS treatments. Identifying death primarily due to a respiratory cause could help support the assessment of efficacy of interventions targeting lung function. Few studies have been designed to identify the cause of death in ARDS, but data on this topic have been reported in studies that had a broader aim. Identification and synthesis of these data could inform a better understanding of the most common cause(s) of death, and how they are recorded/categorized. Therefore, we sought to provide a comprehensive summary of the published data by conducting a narrative analysis and review.

MATERIALS AND METHODS

We performed a search of the MEDLINE database to identify original articles (either prospective/retrospective observational studies or clinical trials) that reported on cause of death in patients with ARDS (**eFig. 1A**, http://links.lww.com/CCX/B392). We combined keywords for ARDS with those relating to death or clinical outcomes (see the **eMethods** for the search string, http://links.lww.com/CCX/B392), restricting to studies published in the English language from January 1, 2015, to April 12, 2024 (the date of the search) and with an available abstract. During screening of article titles and abstracts, we disregarded animal studies, case reports, review articles, study protocols, clinical guidelines, and studies in pediatrics (where ARDS is defined used the specific pediatric ARDS [Pediatric Acute Lung Injury Consensus Conference] criteria as opposed to the Berlin/American-European Consensus Conference criteria used in adults) (10). For the remaining articles retrieved, we obtained the whole publication and searched for the terms "death," "died," and "mortality" anywhere in the article. We retained studies where cause of death was reported in greater than or equal to 30 patients and not obtained from death certificates. The accuracy of death certificates for specific cause of death is known to be unreliable in many cases (11); for example, cardiac arrest is the ultimate cause of death in many disease states. However, investigators developing targeted treatments would have interest in the preceding dysfunction that led to cardiac arrest; for example, the sustained need for high levels of oxygen supplementation and mechanical ventilation. For this present analysis, we therefore assumed data from death certificates alone would not provide sufficient granularity for our purposes. Further, bibliographies of relevant publications were scanned to identify further articles on the topic, including those published pre-2015 if deemed particularly relevant. As it became apparent that the search largely retrieved articles from observational studies, we performed an additional search of PubMed (**eFig. 1B**, http://links.lww.com/CCX/B392),

specifically designed to capture relevant data (if available) from clinical trials. To maximize sensitivity, we combined the keywords for ARDS with the keyword "trial" (eMethods, http://links.lww.com/CCX/B392), applying the same inclusion and exclusion criteria, and searches for "death" keywords in the whole publication, as undertaken following the initial database search. Additionally, publications listed on the ARDS Network (ARDSNet) (12) and Prevention & Early Treatment of Acute Lung Injury (PETAL) network (13) websites (back to 2010) were obtained and screened for any further relevant articles. Due to the more limited number of clinical trials with data on this topic, we included studies that reported on cause of death in at least ten patients (as compared with the 30 for observational studies); however, we excluded those where cause of death was not reported for all patients who died.

RESULTS

From over 900 articles retrieved from the initial database search and 185 retrieved from the additional search, 20 were deemed relevant (15 observational studies and five clinical trials) and included in this review (eFig. 1, A and B, http://links.lww.com/CCX/B392). Only two cohort studies (one prospective and one retrospective study) were designed specifically to categorize cause of death in patients with ARDS as the study objective (14, 15). Another investigation focused on death in patients with ARDS but was a secondary analysis from three prospective observational studies not designed to evaluate cause of death specifically (16). The remaining studies were designed to answer other research questions in ARDS research, with cause of death briefly reported in either the main results of the article or in the supplement.

Non-COVID ARDS

Observational Studies. Causes of death reported from observational studies of patients with non-COVID ARDS are summarized in **eTable 1** (http://links.lww.com/CCX/B392) for large-sized studies (≥ 100 deaths) and **eTable 2** (http://links.lww.com/CCX/B392) for moderate-sized studies (30 to < 100 deaths). Further study details can be found in **eTables 3** and **4** (http://links.lww.com/CCX/B392). Mutually exclusive prespecified categories (between five and nine) were used for recording the cause of death in six (four large and

two moderate in size) studies (**eTable 5**, http://links.lww.com/CCX/B392) (15–19). In the largest of these, the international multicenter Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE (LUNGSAFE) study (18), the most common factors leading to death among 964 of 2813 ARDS patients who died in the ICU, across all regions, were respiratory failure (42%) and cardiovascular failure (37%). Notably, multiple organ failure (MOF) refractory hypoxemia and sepsis were not included among the prespecified categories. Instead, categories were based on the organ system deemed as the most pertinent in contributing to death in the ICU (e.g., "pulmonary," "neurologic," and "cardiac"). In comparison, in the prospective studies by Villar et al (16) and Gacouin et al (17), which reported on 778 and 572 ARDS deaths, respectively, MOF (a predefined category) was the most commonly recorded cause of death, accounting for around 50% of deaths in both studies (16, 17). In these two studies, pulmonary causes accounted for 16–23% of deaths captured by the category "refractory hypoxemia" (16, 17). In the largest retrospective study—one of the two studies specifically designed to evaluate cause of death in ARDS—Ketcham et al (15), used prespecified categories based on the organ system deemed responsible for death (similar to those used by Stapleton et al [14]), although they also included sepsis (using a different definition to Stapleton et al [14]) but not MOF as a distinct option (**Table 1**). Twenty-eight percent of deaths in this study were categorized as due to pulmonary dysfunction, and 29% were due to sepsis (which was not a category included in LUNGSAFE or the Gacouin et al [17] study). In comparison, sepsis accounted for 17% of deaths (independent of MOF) in the study by Villar et al (15, 16). It is also of note that unlike the other large observational studies, Gacouin et al (17) designated "withdrawal of life support/end of life decision" (6% of ARDS deaths) as a cause of death category.

In moderately-sized studies (eTable 2, http://links.lww.com/CCX/B392), MOF was the most commonly recorded cause of death, ranging from 26% to 89% depending on the categories used and whether these were mutually exclusive (14, 20–23). Among these, the prospective study by Stapleton et al (14)—the only other study designed specifically to evaluate cause of death in ARDS—used nine prespecified categories based on the organ system deemed responsible for death, although

TABLE 1.
Study Characteristics and Reported Causes of Death in Ketcham et al (15) and Stapleton et al (14)

	Ketcham et al (15) (Retrospective Cohort Study)	Stapleton et al (14) (Prospective Cohort Study)
Study design	Retrospective cohort study	Prospective cohort study
Setting, time period	Five ICUs within a single center; January 2016 to December 2017	Single level I trauma center; 1998
ARDS patients	Patients with ARDS (number NR; median age 62 yr; who experienced in-hospital death were identified using a query tool of patients' EHR)	205 patients with ARDS (median age 48 yr; identified via daily ICU surveillance)
ARDS definition	Berlin criteria	American-European Consensus Conference criteria
Deaths	127[a]	30
Data collection method	Data regarding causes and circumstances of death were collected from the patients' EHR using a structured abstraction form and allocated to one of the prespecified categories	Review of medical charts, rigorous inspection of temporal relationships of laboratory data, hemodynamic and respiratory parameters, and nursing and physician notes to identify one of the prespecified categories
Data abstractors	EHR data were reviewed by one of five internal medicine-trained physicians who did not participate in the adjudication of ARDS and were blinded to adjudicated ARDS status (excellent inter-rater reliability was demonstrated on an initial test set of ten charts). Cause of death was documented by checking a tick box against one of the prespecified categories[c]	Three critical care physicians individually abstracted data from patients' medical charts following daily ICU surveillance. One physician further reviewed the charts of six patients initially reviewed by one of the other physicians
Causes of death (prespecified categories used)	Categories based on patient assessment in the 72 hr before death:	Categorized as due to the presenting injury/illness or ARDS risk factor progression, associated with conditions preceding ARDS onset:
	Sepsis[b]: 29%	Sepsis with multiple organ failure[d]: 30%
	Pulmonary[c]: 28%	Respiratory failure: 13%
	Neurologic[c]: 17%	CNS: 29%
	Cardiac[c]: 10%	Cardiac: 8%
	Hepatic[c]: 6%	Hepatic: 7%
	Gastrointestinal[c]: 4%	Gastrointestinal: 3%
	Hemorrhagic[c]: 4%	Hemorrhagic: 4%
	Other[c]: 2%	Renal: 5%

ARDS = acute respiratory distress syndrome, EHR = electronic health record, NR = not reported.

[a]Eighty-two percent died while receiving substantial respiratory support.

[b]Sepsis-3 definition.

[c]Primary syndrome or organ system that was considered as most directly contributing to death or withdrawal of life support.

[d]Sepsis with multiple organ failure was defined as sepsis syndrome in combination with two other severe organ system dysfunctions. Sepsis syndrome could be present without any direct evidence of infection (i.e., it could be reflective of a systemic inflammatory state from any cause).

they also included sepsis with MOF (but not MOF or sepsis separately) as a separate option (Table 1).

Clinical Trials. None of the five clinical trials mentioned that cause of death had been prespecified

(**eTable 6**, http://links.lww.com/CCX/B392). In the largest trial, which included patients with moderate-to-severe ARDS, of whom 107 died, 64% of deaths were related to underlying disease, 34% were directly

related to ARDS, with the remaining deaths classed as due to unknown cause (similar percentages were reported for patients with focal or nonfocal ARDS) (24). In a trial of 277 patients with moderate-to-severe ARDS, of whom 69 died, multisystem organ failure (51%), irreversible shock (16%), and refractory hypoxemia (16%) were the most frequently recorded causes of death (25). MOF (with sepsis) was similarly the most frequently cause of death in two smaller trials (26) and was mentioned as a reported cause of death in another small trial where the numbers of deaths from each cause were not stated (27).

COVID-Related ARDS

Causes of death reported from observational studies of patients with COVID-related ARDS ($n = 6$) are summarized in **eTable 7** (http://links.lww.com/CCX/B392). Prespecified categories (between four and nine) for recording cause of death were used in four of the six studies, being mutually exclusive in three (eTable 5, http://links.lww.com/CCX/B392). Among these six studies, the largest were two prospective studies conducted by Estenssoro et al (28, 29) in Argentina, who reported the most common cause of death to be refractory hypoxemia (43–47% of patients) (28, 29), and septic shock (31% of patients) (28). Irreversible respiratory failure was the reported cause of death in four smaller studies (one prospective, two retrospective, and one ambispective) with estimates of 50% ("refractory hypoxemia") (23), 16% ("irretractable respiratory failure") (30), 65% ("refractory respiratory failure and persistent hypoxemia [Pao_2/Fio_2] < 100") (31), and 88% ("irreversible respiratory failure during extracorporeal membrane oxygenation resulting in palliation") (32).

Evaluation of the Evidence

Because only two of the 20 studies included in this review were designed specifically to describe causes of death in ARDS and hence included details on their methodology, it was not possible to systematically critique the methods used in each study and thereby evaluate the strength of the evidence provided. However, further details of the Ketcham et al (15) and Stapleton et al (14) studies are shown in Table 1. In both studies, experts in the field used standardized methods to collect details relating to cause of death from patients'

records and assign cause to a predetermined category, along with a level of validation (from a second reviewer). Stapleton et al (14) also used a prospective design, which minimizes biases related to secondary data collection. However, the sample sizes were small in both—notably smaller than some other studies included in this review. In terms of external validity, both are limited in being conducted from a single center in the United States, especially the Stapleton et al (14) study, which was set in a trauma center, with the latest data collected more than 2 decades ago when clinical practice may have differed to the present day. The patients studied (median age 48 yr) are unlikely to be representative of the broad range of ARDS patients that would be drawn from wider populations in terms of demographic/clinical characteristics and, potentially, cause of death.

DISCUSSION

To our knowledge, our narrative literature provides the first comprehensive summary of causes of death in patients with ARDS. We found that few studies reported the cause of death and that those that did differed in the categories used, whether these were prespecified and how they were defined. Only two studies (both observational cohort studies), with study periods 2 decades apart were designed specifically to evaluate cause of death in ARDS patients and thereby reported sufficient methodological details for critique; both were limited in terms of the generalizability of their findings. Very few clinical trials were identified for inclusion.

In most studies of non-COVID-related ARDS, the most commonly reported cause of death was MOF when this was a predetermined category, accounting for approximately 50% of deaths. In the large international LUNGSAFE study, respiratory failure was the most recorded cause of death (42%), followed by cardiac failure (42%), likely because the category of MOF was unavailable (18). Among patients with COVID-related ARDS, death from respiratory causes—refractory hypoxemia/respiratory failure—were the most reported, followed by sepsis.

Heterogeneity seen in the categories used for cause of death was particularly notable for MOF and pulmonary reasons. In some studies, MOF was a distinct category but was an either/or category with sepsis/shock in others (14, 21, 22). When it came to respiratory

failure. Stapleton et al (14) defined refractory hypoxemia as insupportable respiratory failure. In the study by Gacouin et al (17), refractory hypoxemia was defined as the inability to obtain an oxygen saturation of at least 92% in patients who received mechanical ventilation with F_{IO_2} set at 90% or more (Gacouin A, personal communication, August 11, 2023), and in the study by Villar et al (16), it was defined as hypoxemia due to unresolved ARDS without further explanation. Such differences in the definitions of ARDS death categories between studies likely explains the wide range of proportion of death due to respiratory failure reported across studies from 13% (14) to 23% (16), and more than 40% when categorized as "pulmonary cause of death" (18). As pointed out in the secondary analysis of unpublished data from seven ARDSNet studies by Bosch et al (33), if the proportion of ARDS patients who die of refractory respiratory failure is low, the feasibility of enriching ARDS clinical trials for interventions targeting oxygenation is low and would require very large sample sizes. This could explain, in part, why finding effective treatments has been elusive thus far. In their analysis, which focused on identifying the rate of death due to irreversible respiratory failure (defined as $Pao_2/F_{IO_2} < 40$ mm Hg within 24 hr of death), the overall mortality rate due to irreversible hypoxemic respiratory failure was 1.1% (95% CI, 0.8–1.4%). The authors concluded that large pragmatic trial designs would be needed to achieve the necessary power with such low rates of respiratory failure attributable death and suggest that investigators could, instead, consider testing therapies that do not specifically target oxygenation. However, as found in several studies in our literature review, if other criteria are used to define death caused by respiratory failure or due to pulmonary failure, close to 50% of patients are considered to die of this cause. Although most of these patients most likely do not have the severity of respiratory failure as defined by Bosch et al (33) and in other studies, these patients are unable to be liberated from mechanical ventilation often due to an inability to adequately decrease supplemental oxygen levels.

There is no question that multiple organs are affected in the syndrome of acute respiratory failure (ARDS). In terms of aiding drug development, however, it is important to understand what ultimately caused a patient to succumb to their illness and/or the relative contribution of pulmonary vs. other morbidities and at what stage of disease). All-cause mortality reported in most clinical trials represents a heterogeneous pool of death causes that include those not potentially modifiable by a therapy with a lung-specific mechanism of action (e.g., death due to stroke, myocardial infarction, internal bleeding, etc.) Several pulmonary endpoints have been proposed to assist drug developers in demonstrating proof concept in phase 2 studies in patients with ARDS, which typically have a modest sample size. One such endpoint is ventilator-free survival (VFS) at day 28 (The European Medicines Agency has also suggested that VFS could potentially have a role in support of marketing approval for ARDS therapies) (34). We believe that an endpoint of "death due to lung organ failure" or clearly defined "refractory hypoxemia" could help support efficacy assessment of therapies that would ameliorate or prevent lung injury in ARDS. However, scientific and clinical community-based consensus is needed on these terms, for example, using Delphi methodologies among relevant stakeholders (35) and trials that examine these outcomes using these standards. Although a recent article (36) reports that among patients with sepsis, ARDS likely explained a high proportion of mortality (high attributable mortality fraction in those with co-existent ARDS), it is still unclear what the predominant "cause" of mortality is among patients with ARDS (i.e., refractory hypoxemia, ventilator dependence, MOF, etc.) and how this varies among patients with/without sepsis.

As mentioned, only two studies in this review were specifically designed to evaluate cause of death in ARDS, which differed in their approach, and with limited generalizability to patients dying with ARDS in current clinical practice. More studies designed with this objective, with an expert-based consensus on categories and definitions of cause of death are needed. Additionally, researchers in the ARDS field should consider cause of death as an outcome of interest wherever this is operationally feasible, with transparency on how, and by whom, the data were captured. Further, to minimize bias, we would encourage cause of death data to be collected prospectively, in real-time, by respiratory/critical care physicians or trained researchers.

CONCLUSIONS

Few studies have reported cause of death in patients with ARDS. In those that do, cause of death categories

and definitions used are heterogeneous leading to disparate results. Further research is needed to see whether a more rigorous, standardized, and transparent approach to assigning and reporting the cause of death in ARDS, in particular, death due to respiratory failure, would better guide clinical trial endpoint selection and, ultimately, the development of targeted treatments.

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