Acute respiratory distress syndrome: Prognosis and outcomes in adults

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a type of respiratory failure characterized by the acute onset of bilateral alveolar opacities and hypoxemia. The prognosis of ARDS is reviewed here. Other issues related to ARDS are discussed separately. (See "Acute respiratory distress syndrome: Clinical features, diagnosis, and complications in adults" and "Acute respiratory distress syndrome: Epidemiology, pathophysiology, pathology, and etiology in adults" and "Acute respiratory distress syndrome: Ventilator management strategies for adults" and "Acute respiratory distress syndrome: Fluid management, pharmacotherapy, and supportive care in adults" and "Acute respiratory distress syndrome: Investigational or ineffective therapies in adults".)

MORTALITY

ARDS is associated with appreciable mortality, with the best estimates from a multicenter, international cohort study of 3022 patients with ARDS, suggesting an overall rate of death in the hospital of approximately 40 percent [1-4]. Mortality increases with disease severity; unadjusted hospital mortality was reported to be 35 percent among those with mild ARDS, 40 percent for those with moderate disease, and 46 percent for patients with severe ARDS [4]. Similar to other studies, mortality directly correlated with driving pressure (ie, the difference between plateau

[ie, end inspiratory] and positive end expiratory pressures) [5]. (See "Acute respiratory distress syndrome: Ventilator management strategies for adults", section on 'Further titration/increase in PEEP (high PEEP)'.)

The underlying cause of the ARDS is the most common cause of death among patients who die early [6-9]. In contrast, nosocomial pneumonia and sepsis are the most common causes of death among patients who die later in their clinical course [8]. Patients uncommonly die from respiratory failure [7].

Numerous studies suggest that survival has improved over time [2,9-11]. As an example, an observational study of 2451 patients who had enrolled in ARDSNet randomized trials found a fall in mortality from 35 to 26 percent between 1996 and 2005 [10]. To the extent that mortality may be decreasing with time, several issues should be considered:

- It is not known if mortality has decreased among patients who received their care outside of a specialized center or a clinical trial.
- The improved mortality may be attributable to patients who have ARDS related to risk factors other than sepsis, such as trauma [9].
- To the extent that mortality has decreased, the reasons are uncertain. Likely causes include better supportive care and improved ventilatory strategies, such as low tidal volume ventilation [10,12,13]. (See "Acute respiratory distress syndrome: Ventilator management strategies for adults", section on 'Low tidal volume ventilation: Initial settings'.)

Predictors — Many studies have sought to identify factors during the acute illness that predict mortality. Such factors can be categorized as patient-, disease-, or treatment-related. No single factor has proven to be superior to the others.

Patient-related — Older patients appear to be at an increased risk for death [14-16]. This was illustrated by a multicenter cohort study that followed 1113 patients with ARDS for 15 months [14]. The mortality rate increased progressively with age, ranging from 24 percent among patients 15 to 19 years of age to 60 percent among patients 85 years of age or older. The overall mortality rate was 41 percent. Although it has been suggested that obesity may impact the mortality of critically ill patients with or without ARDS, evidence is conflicting, although poorly controlled meta-analyses suggested lower mortality in association with obesity [17-25]. Underlying comorbidities, such as cancer, immunosuppression, and chronic liver failure, are also associated with increased hospital mortality [16].

Disease-related — Disease-related predictors of mortality include severe hypoxemia, failure of oxygenation to improve, pulmonary vascular dysfunction, increased dead space, infection, a high severity of illness score, a non-traumatic cause of the ARDS, and certain biomarkers and gene polymorphisms.

- Gas exchange – The severity of hypoxemia determines whether the patient has mild ARDS (arterial oxygen tension/fraction of inspired oxygen [PaO_2/FiO_2] >200 but ≤300 mmHg), moderate ARDS (PaO_2/FiO_2 >100 but ≤200 mmHg), or severe ARDS (PaO_2/FiO_2 ≤100 mmHg). Mortality appears to increase as ARDS becomes more severe, according to an observational study of 3670 patients with ARDS that found that patients with mild, moderate, and severe ARDS had mortality rates of 27, 32, and 45 percent, respectively [26]. Preliminary data suggest that the oxygen saturation index (OSI), calculated as FiO_2 x mean airway pressure [MAP] x 100) / peripheral oxygen saturation [SpO_2], may be a superior predictor of mortality because it takes MAP into account; in that study higher OSI correlated with increased mortality [27]. Similarly, there is general agreement that improvement of oxygenation during the early intensive care unit (ICU) course correlates with survival [28] and that deterioration in oxygenation correlates with mortality as shown in a recent analysis of patients with mild ARDS [29]. Severe hypercapnia (partial arterial pressure of carbon dioxide [$PaCO_2$] ≥50 mmHg) may also indicate increased mortality, higher complication rates, and more organ failures [30].

- Pulmonary vascular dysfunction – Pulmonary vascular dysfunction is indicated by an elevated transpulmonary gradient (ie, ≥12 mmHg) or pulmonary vascular resistance index (ie, >285 dyne s/cm). The transpulmonary gradient is the difference between the mean pulmonary artery pressure and the pulmonary artery occlusion pressure, while the pulmonary vascular resistance index is the transpulmonary gradient divided by the cardiac index. Pulmonary vascular dysfunction appears to be an independent risk factor for 60-day mortality and fewer ventilator-free, ICU-free, and hypotension- or vasopressor-free days [31].

- Higher extravascular lung water and pulmonary vascular permeability indices correlate independently with 28 day mortality [32]. As an example, the Radiographic Assessment of Lung Edema (RALE) score, which measures the extent and density of alveolar opacities chest radiographs, was shown to correlate with overall survival, 28-day, and 90-day mortality rates and warrants further study [33].

- Dead space – Dead space ventilation early in the course of ARDS appears to correlate with mortality. This was illustrated by a series of 179 patients with early ARDS who had their ratio of dead space to tidal volume (ie, the dead space fraction or Vd/Vt) determined by

measuring exhaled carbon dioxide (CO_2) levels [34]. The dead space fraction was markedly elevated (mean 0.58, normal <0.30) and there was a linear correlation between the degree of dead space ventilation and mortality. For every 0.05 increase in dead space fraction, the odds of death increased by 45 percent. A bedside variable, the ventilatory ratio (VR), defined as (minute ventilation (mL/min) x $PaCO_2$ (mmHg)]/(predicted body weight x 100 x 37.5), was shown to correlate with Vd/Vt as well as increased mortality, even after adjusting for other factors such as PaO_2/FiO_2 ratio and severity of illness [35].

- Infection – Infection and/or multiorgan dysfunction are better predictors of mortality than respiratory parameters [9,36-41]. This is probably because they predict death from a nonrespiratory cause, which is more common than death due to respiratory failure.

- Severity of illness score – Severity of illness scores appear to correlate with mortality. As an example, patients with a higher APACHE III score have an increased likelihood of death (odds ratio 1.78 per 25-point increase, 95% CI 1.16-2.73) [15]. Among those who present with mild ARDS, approximately half worsen within the first week, while one third remain mild and the remainder (<20 percent) improve [29]. (See "Predictive scoring systems in the intensive care unit", section on 'Acute Physiologic and Chronic Health Evaluation (APACHE)'.)

- Underlying cause of the ARDS – Patients with trauma-related ARDS appear to have a lower likelihood of death at 90 days than patients with ARDS that is unrelated to trauma [42]. Severe but not mild or moderate alcohol misuse, in patients with acute lung injury, is associated with an increased risk of death or persistent hospitalization at 90 days (adjusted odds ratio, 1.7; 95% CI 1.00 to 1.87) [43]. The presence of diffuse alveolar damage (DAD) on lung biopsy is also associated with a worse prognosis compared with those who had non DAD-associated ARDS [44]

- Laboratory – Routine laboratory parameters are not helpful for predicting the outcome of ARDS. However, a large body of emerging evidence suggests that many biomarkers and gene polymorphisms are associated with both susceptibility to ARDS and outcome from ARDS [45]. The practical utility of these observations is uncertain, but the research may lead to new preventative and therapeutic strategies in the future. Other analyses have suggested the existence of two biologically and clinically distinct subphenotypes of ARDS, hypo-and hyper-inflammatory subtypes (Type 1 and Type 2 respectively), with increased mortality associated with the hyper-inflammatory subtype [46,47].

Treatment-related — Treatment-related predictors of mortality include a positive fluid balance, glucocorticoid therapy prior to the onset of ARDS, packed red blood cell transfusions,

and being in an ICU that does not mandate care by an intensivist.

- Fluid balance – A positive fluid balance may be associated with higher mortality [48,49]. This was demonstrated by the ARDSNet low tidal volume trial, which found that a negative fluid balance at day 4 was associated with decreased mortality compared to a positive fluid balance, after adjustment for factors such as age, severity of illness, and ventilator strategy (adjusted odds ratio 0.50, 95% CI 0.28-0.89) [49]. (See "Acute respiratory distress syndrome: Fluid management, pharmacotherapy, and supportive care in adults", section on 'Conservative fluid management'.)

- Treatment with glucocorticoids – Patients who received glucocorticoids prior to the onset of ARDS may have an increased likelihood of death (odds ratio 4.65, 95% CI 1.47-14.7) [15]. (See "Acute respiratory distress syndrome: Fluid management, pharmacotherapy, and supportive care in adults", section on 'Glucocorticoids'.)

- Packed red blood cell transfusion – Patients who receive packed red blood cell transfusions may have an increased likelihood of death (odds ratio 1.10 per unit transfused, 95% CI 1.04-1.17) [15,50].

- Organization of the ICU – Patients cared for in an ICU that mandates transfer to an intensivist or co-management by an intensivist may have a decreased likelihood of death (odds ratio 0.68, 95% CI 0.53-0.89) [51]. Patients cared for in hospitals with fewer ICU beds may have increased mortality [16].

- Late intubation – Patients who are intubated late in the course of the disease may have a higher risk of death from ARDS when compared with patients who are intubated early and those who are never intubated (56 versus 26 versus 26 percent) [52]. Although unproven, it suggests that initial strategies (eg, noninvasive ventilation and high flow oxygen) may impact the timing of intubation, to ultimately affect mortality.

Predictors of improved survival include lung protective ventilation strategies, which are discussed separately. (See "Acute respiratory distress syndrome: Ventilator management strategies for adults".)

MORBIDITY AMONG SURVIVORS

Cognitive, psychologic, and physical morbidity is common among survivors of ARDS [53]. Similar to that observed in survivors of any critical illness, morbidities are usually evident upon discharge from the intensive care unit (ICU). Many of the cognitive, psychiatric, and physical

manifestations are present for at least five years and they tend to resolve slowly. The occurrence and resolution of symptoms are frequently co-dependent. Neuropsychologic and physical impairments after ARDS are discussed in this section. The epidemiology, diagnosis, clinical manifestations, outcome, and treatment of post-intensive care syndrome, much of which overlaps with ARDS, and long-term symptoms in critically ill patients with COVID-19 are discussed separately. (See "Post-intensive care syndrome (PICS) in adults: Clinical features and diagnostic evaluation" and "COVID-19: Evaluation and management of adults with persistent symptoms following acute illness ("Long COVID")".)

Cognitive — Rates of cognitive dysfunction following ARDS varies among studies, ranging from 30 to 55 percent [53-56]. In two observational studies of a total of 310 ARDS survivors, impaired neurocognitive function was reported in 30 percent and 49 percent of patients at 12 months following the acute illness [54,55]. These rates are similar to that reported in the largest study of survivors of critical illness where 40 percent had neurocognitive deficits at three months; these persisted at 12 months in the vast majority [56]. Severity of hypoxemia may be associated with an increased risk of cognitive impairment following ARDS [56]. Factors which may be associated with long-term cognitive impairment include pre-existing impairment, neurological injury, delirium, mechanical ventilation, duration of sedative use, and systemic inflammation [57]. (See "Evaluation of cognitive impairment and dementia".)

Psychiatric — Psychiatric illnesses also appear to be common among survivors of ARDS, with depression, anxiety, and post-traumatic stress disorder as the most common disorders reported [53,55,58,59]. The absolute risk varies between studies. One prospective cohort study of ARDS survivors estimated that the incidence of depressive symptoms was 40 percent during the two years following the acute illness [58]. In another observational cohort, depression, post-traumatic stress disorder, and anxiety were present in 36, 39, and 62 percent of survivors at one year [55]. In a study reporting psychiatric symptoms, 66 percent of ARDS survivors had substantial symptoms of depression, anxiety, or posttraumatic stress disorder (PTSD) during one year follow up [59]. The majority of symptomatic patients experienced morbidity in two or more domains. Risk factors for symptoms included younger age, female sex, unemployment, alcohol misuse, and greater opioid use in the ICU, whereas there was no association between symptoms and severity of illness or ICU length of stay. In a study focusing on ARDS survivors up to five years out from their illness, 52 percent had continuous or recurring symptoms with 38, 21, and 23 percent having prolonged anxiety, depression, and PTSD symptoms, respectively, with median durations of 33 to 39 months [60]. Risk factors for long-term psychiatric morbidity included worse pre-ARDS mental health, including previous depression and psychological distress in the period preceding ARDS. (See "Comorbid anxiety and depression in adults: Epidemiology, clinical manifestations, and diagnosis" and "Co-occurring substance use disorder

and anxiety-related disorders in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis".)

Physical — Survivors of ARDS frequently have persistent, abnormal exercise endurance and physical disabilities [53,58,61-69]. The persistent nature of this abnormality was demonstrated by a prospective cohort study that followed 109 survivors of ARDS for five years [63]. The six minute walking distance (6MWD) at one, three, and five years was 66, 67, and 76 percent of predicted, respectively. During a two-year follow-up study of 186 ARDS survivors, the cumulative incidence of impaired physical function was as high as 66 percent [58]. Another prospective cohort study reported that 38 percent of patients with ARDS had muscle weakness at discharge, which was associated with worse five-year survival [68]. One meta-analysis of 48 studies (over 11,000 patients) survivors of ARDS reported a lower than predicted 6 minute walk distance in 57 percent at three months, 63 percent at six months and 66 percent 12 months [53]. Risk factors for physical dysfunction were longer ICU stay and prior depressive symptoms. In one meta-analysis of ARDS survivors the 6MWD at three months following discharge was 300 meters, which improved to 410 meters at 12 months [69]. Female sex and pre-existing comorbidity were associated with lower 6MWD. (See "Cardiac rehabilitation programs".)

Data suggest that many ARDS survivors experience additional physical decline after their critical illness. For example, in one prospective cohort study, 69 percent of 193 ARDS survivors experienced decline in >1 physical measure such as muscle strength, exercise capacity, and physical functioning [70]. Significant risk factors for subsequent physical decline included increased age and pre-ARDS comorbidity.

A longitudinal prospective cohort study of 156 ARDS survivors showed an association between muscle weakness at hospital discharge and increased five-year mortality [68]. Thirty-eight percent of patients had demonstrable muscle weakness at discharge, and this was associated with worse five-year survival. Fifty percent experienced either persistent or resolving weakness trajectories during the follow up period, and these were associated with more than a threefold greater hazard of death compared to patients without weakness.

Lung function — Lung function following ARDS is commonly compromised for as long as five years [61,63,71]. However, it is uncertain whether decreased lung function results in physical impairment. The degree of compromise depends on which parameter of lung function is measured (spirometry, lung volumes, diffusing capacity). For example, upon discharge, approximately 80 percent of patients will have a reduction in diffusing capacity and a smaller percentage will have airflow obstruction (20 percent) or restriction (20 percent) on spirometry and lung volumes [61]. In most patients, lung volumes and spirometry will normalize (ie, measure within 80 percent of predicted values) by six months, and diffusion capacity should

normalize by five years [61,63,71]. A small percentage of patients are left with residual deficits and supplemental oxygen is rarely required [61,62,64-67]. (See "Overview of pulmonary function testing in adults".)

Other — Additional sequelae of ARDS include complications of endotracheal intubation, minor imaging abnormalities, increased risk of death, poor quality of life, and family stress (also known as post-intensive care syndrome-family [PICS-family]]) [3,72-74].

- Complications of intubation – Patients with ARDS may experience complications associated with prolonged intubation including laryngotracheal stenosis, tracheomalacia, and speech or swallowing impairment, the details of which are discussed separately. (See "Complications of the endotracheal tube following initial placement: Prevention and management in adult intensive care unit patients".)

- Imaging abnormalities – Although most patients experience excellent radiologic recovery, at 180 days post diagnosis, abnormalities persist in a significant minority and correlate with worse pulmonary function and quality of life [72,74].

- Increased mortality – One multicenter prospective cohort of 646 ARDS survivors reported mortality at one year that was substantially higher than in-hospital mortality (41 versus 24 percent) [3]. Important predictors of death were the presence of comorbidities and discharge to another facility (eg, hospital, long term acute care facility, nursing home, hospice).

- PICS-family – All of these morbidities place substantial stress on family members many of whom are in decision-making and caregiving roles for their loved ones [73]. (See "Management and prognosis of patients requiring prolonged mechanical ventilation" and "Post-intensive care syndrome (PICS) in adults: Clinical features and diagnostic evaluation", section on 'Post-intensive care syndrome-family'.)

Returning to work — Despite these abnormalities, some survivors are able to return to work. In a prospective five-year follow-up cohort study, 77 percent of those who were working at the time of their acute illness returned to work, while 17 percent did unpaid work within the home, and six percent became full-time students [63]. Most of those who returned to work did so within two years after ICU discharge, although many required a gradual transition back to work. In a multicenter longitudinal study, nearly half of previously employed ARDS survivors were jobless 12 months following ARDS [75]. Older patients and those with a longer hospital stay were at increased risk of delayed return to work. In another study, among long-term survivors who were previously employed, 51, 45, and 31 percent had not returned to work at one, two, and five years after ARDS, respectively [76]. Factors associated with a slower return to work

included comorbidity burden preceding ARDS, longer duration of mechanical ventilation (up to five days), and discharge to a healthcare facility [76].

Predictors — Several studies have sought factors during the acute illness that predict long-term sequelae [66,71,77,78]:

- Persistent symptoms one year after recovery correlate with the duration of mechanical ventilation and the lowest static thoracic compliance during the acute illness [66].
- Abnormal lung function one year after recovery correlates with the following factors measured during the acute illness: lowest static thoracic compliance, mean pulmonary artery pressure, positive end-expiratory pressure (PEEP), initial intrapulmonary shunt fraction, and requirement of a fraction of inspired oxygen (FiO_2) >0.6 for more than 24 hours [77,78].
- A better functional outcome at one year appears to correlate with the absence of illness acquired during the ICU stay and rapid resolution of multiple organ failure and lung injury [71].
- There is no known correlation between ventilatory strategies and either long-term pulmonary function or health-related quality of life [61,79].

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Acute respiratory distress syndrome (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Acute respiratory distress syndrome (ARDS) is a type of respiratory failure characterized by the acute onset of bilateral alveolar infiltrates and hypoxemia. Diagnostic criteria for ARDS are provided separately. (See "Acute respiratory distress syndrome: Clinical features, diagnosis, and complications in adults", section on 'Diagnosis'.)

- ARDS is associated with appreciable mortality, estimated at approximately 40 percent. In-hospital survival appears to have improved over time. (See 'Mortality' above.)

- The underlying cause of the ARDS is the usual cause of death among patients who die early. In contrast, sepsis due to nosocomial pulmonary infection is the most common cause of death among patients who die later in their clinical course. Patients seldom die from respiratory failure. (See 'Mortality' above.)

- There are numerous factors that can be assessed during the acute illness that may predict mortality. However, no single factor appears to be superior to the others. (See 'Predictors' above.)

- Survivors of ARDS can develop cognitive, psychological, and physical impairments that may last for months to years following their acute illness. In addition many have abnormalities in pulmonary function that are generally mild, as well as reduced quality of life and impaired ability to return to work for at least two to five years following the acute illness. (See 'Morbidity among survivors' above.)

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