The Epidemiology of Acute Respiratory Distress Syndrome Before and After Coronavirus Disease 2019

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KEYWORDS

- ARDS • Epidemiology • Incidence • Subtypes • Mortality • COVID-19

KEY POINTS

- Acute respiratory distress syndrome (ARDS) is heterogeneous.
- ARDS has high incidence among intensive care unit patients.
- ARDS has high morbidity and mortality.
- Improved supportive care has decreased ARDS incidence and mortality.
- Coronavirus Disease 2019–associated ARDS is a syndrome within the known ARDS spectrum.

INTRODUCTION

Acute respiratory distress syndrome (ARDS) occurs when a diverse array of triggers cause acute, bilateral pulmonary inflammation and increased pulmonary capillary permeability leading to acute hypoxemic respiratory failure. Pulmonary biopsy (or autopsy) classically demonstrates diffuse alveolar damage (DAD).[1] Recognizing that ARDS is a syndrome and that research and benchmarking require reproducible definitions, a 2011 consensus conference in Berlin proposed a practical, updated definition (the "Berlin Definition"),[2] In summary, this requires,

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1. An acute process developing within 1 week of a known clinical insult or new or worsening respiratory symptoms;
2. Radiographic images showing bilateral opacities not fully explained by effusions, lobar or lung collapse, or nodules; and
3. Impairment in oxygenation as measured by a $Pao_2/Fio_2 \leq 300$ mm Hg in the presence of a positive end-expiratory pressure (PEEP) of at least 5 cm H2O.

Despite many advances in the understanding of ARDS, morbidity and mortality remain high with few targeted therapies. In this epidemiologic review, we consider the etiology, subtypes and phenotypes, incidence, mortality, long-term outcomes, and the relationship(s) between Coronavirus Disease 2019 (COVID-19) and prepandemic ARDS.

ETIOLOGY

Admitting that patients would not have survived long enough to be diagnosed with ARDS before the widespread use of intensive care unit (ICU) ventilators for hypoxemic respiratory failure, Ashbaugh and colleagues first reported on ARDS as a distinct syndrome in a 1967 series of 12 patients.[3] Despite suffering from heterogeneous primary insults, the patients all developed similar patterns of acute-onset respiratory failure with bilateral infiltrates and decreased pulmonary compliance accompanied by autopsy findings of acute inflammation and hyaline membranes.[3]

This initial report captured the heterogeneity of ARDS that continues to present challenges in diagnosis and treatment. Pneumonia is the most common trigger for ARDS, although nonpulmonary sepsis, aspiration pneumonitis, and trauma are also common. An assortment of less common triggers have been identified including pancreatitis and blood transfusion. Clinical syndromes compatible with ARDS but with no identifiable trigger are referred to as acute interstitial pneumonia (AIP) or sometimes Hamman-Rich syndrome rather than ARDS and may represent a response to an array of sometimes overlapping pulmonary insults.[1,4–15] In both ARDS and, presumptively, AIP, an insult elicits an inflammatory response which leads to increased-permeability pulmonary edema creating the hypoxemia and bilateral opacities on imaging required for diagnosis.[16,17] In its most severe forms, DAD results pathologically.

ARDS resulting from direct pulmonary insult such as pneumonia manifests pathologically as alveolar collapse, fibrinous exudate, and edema of the alveolar walls to a greater degree than ARDS resulting from nonpulmonary causes such as pancreatitis.[18] This may represent a spectrum of severity or alternative pathophysiological processes. What is less clear is why some patients with inciting conditions develop ARDS while others do not, and whether differences in genotype, phenotype, or therapeutic context play a role remains unclear.

Chronic conditions including obesity and diabetes have been associated with a decreased incidence of ARDS. In diabetes, some hypothesize that this observed association reflects a decreased inflammatory response among diabetics.[19,20] A potential association with obesity is less clear.[21–23] Importantly, collider bias may in fact account for the observed associations.[24]

On the contrary, chronic alcohol use has been associated with higher risk of ARDS. Kaphalia and Calhoun[25] found that chronic alcohol use leads to pulmonary immune dysfunction, epithelial dysfunction, and the inability to handle reactive oxygen species leading to the high permeability pulmonary edema and hyaline membrane formation seen in ARDS. Smoking is also associated with higher risks of ARDS. Not only are patients who smoke more likely to get pneumonia they also have higher rates of ARDS triggered by nonpulmonary causes.[26,27] Cigarette smoking may thus increase the

risk of the inflammatory cascade that results in ARDS. Interestingly, ozone exposure (but no other known pollutants) is also associated with increased risk of ARDS.[28] Consistently, older age,[8] non-white race (likely a surrogate for "social determinants of disease"),[29] and some genetic variants[30] have been described as host factors associated with risk of developing ARDS.

Although age is a risk factor for developing ARDS, it has not consistently been found to be associated with increased mortality. The multinational LUNG-SAFE (The Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) study showed older age to be a risk factor for mortality[31]; however, when controlling for risk, severity, and comorbidity, the independent relationship between age and mortality in ARDS is not consistent.[8] The association of race and ethnicity with ARDS mortality was studied in a retrospective cohort study in 2009 using patient data from three ARDS network randomized control trials. Black race and Hispanic ethnicity were found to have not only higher rates of ARDS than white individuals but higher mortality as well. The causes of race- and ethnicity-related differences are not well understood and likely vary between groups but, in all cases, likely derive substantially from "social determinants of disease" rather than genetic factors. For instance, the fact that higher mortality in Black patients resolves with adjustment for illness severity suggests barriers that hinder Black individuals from seeking early care, physician delay in diagnosis, and other factors worsen the severity mix in these groups.[29]

SUBTYPES

A defining characteristic of ARDS is its heterogeneity, from Ashbaugh's initial publication to the present day.[32,33] Traditional categorizations (as, eg, in the Berlin definition) are based on severity of hypoxemia, which correlates with mortality and the extent of DAD on pathologic examination.[34,35] The effects of some potential ARDS therapies may also vary with hypoxemia severity. For example, in 2018, Guo and colleagues[36] published a systemic review and meta-analysis showing a likely trend toward improved outcomes in patients receiving a high-PEEP protocol. For patients with a Pao_2/Fio_2 (P/F) ratio ≤ 200, there was a slightly lower risk of death; however, in patients with a P/F ratio 201 to 300, there was a possible higher risk of death. Of note this mortality benefit has not been seen in any individual randomized control trials[37–39] and remains a controversial topic. Another example is the 2019 study of therapeutic neuromuscular blockade to improve outcomes in ARDS. Although a previous trial hinted at decreased mortality in patients with P/F ratio less than 130,[40] this larger trial concluded no mortality benefit.[41]

ARDS can also be subdivided based on the initial insult, whether pulmonary (pneumonia, pulmonary contusion, and aspiration) or extrapulmonary (nonthoracic trauma, nonpulmonary sepsis, and transfusion).[7,42,43] Several pathologic, biologic, and physiologic differences have been identified on this basis.[18,44–47] However, in practice, it is difficult to differentiate between the two groups based on substantial overlap.[13] These pathologic, biologic, and physiologic differences are heavily influenced by underlying lung function and architecture, smoking status, chronic diseases, and other conditions, which inflate the heterogeneity of ARDS. No mortality difference has been found between the two groups, likely related to the complexities of the overlap between the two groups.[48]

More recently, "machine learning"-style techniques have been used to identify distinct subtypes. Post-hoc analysis (using latent class analysis) of the ARMA (ARDSnet: Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome) and ALVEOLI (Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure to Obviate Lung Injury)

trials revealed two phenotypes of ARDS.[37,49] Relative to phenotype 1, phenotype 2 was hyperinflammatory, with higher plasma levels of inflammatory biomarkers, a higher prevalence of vasopressor use, lower serum bicarbonate, and a higher prevalence of sepsis found in phenotype 2 than in phenotype 1.[50] Critically, in terms of its clinical utility, this hyperinflammatory phenotype was also associated with higher mortality. Phenotype may also predict response to therapies: A post-hoc analysis of a randomized controlled trial of statin therapy for ARDS suggested benefit for hyperinflammatory patients.[51] It will be important with the expanding use of novel statistical techniques for subtyping to ground them in reality and validate them in both prospective cohorts and within prespecified subgroups in prospective trials.

INCIDENCE

The incidence of ARDS varies globally by over 400%.[52] It is important to acknowledge in this context that ARDS as a syndrome reflects both patient physiology and clinical context. For example, where patients with hypoxemic respiratory failure are not routinely intubated (as may occur in certain institutional settings in USA/Europe or in low- and middle-income country settings with limited supplies of ventilators and/or resources and personnel for ICU-level care), ARDS incidence may appear lower than it actually is. Similarly, routine use of high-tidal-volume ventilation among patients at risk may increase the incidence of ARDS in a given setting. With those caveats in mind, incidence ranges from 10.1/100,000/y in Brazil in 2014 to 82/100,000/y in the United States in 2005 (**Table 1**).[5,7,8,10] Between-study differences in case ascertainment and local context may drive these observed differences.[53,54] Some studies, for instance, relied on clinician diagnosis while others used billing codes, both of which may be inaccurate. Both methods are likely to undercount ARDS cases, as only 60% of ARDS cases were appropriately identified by clinicians in one large study.[1] Differences in the prevalence of ARDS risk factors may account for some of the variation as well.

Likely the highest quality evidence on ARDS incidence and management patterns originates from LUNG-SAFE, a prevalence study conducted during a 4-week period in 459 ICUs in 50 countries. Overall, 10% of all ICU patients and 23% of mechanically ventilated patients met ARDS criteria, yielding an ICU incidence of 5.5 cases per ICU bed per year.

In 2011, the Prevention and Early Treatment of Acute Lung Injury (PETAL) Network developed the Lung Injury Prediction Score (LIPS) to help identify patients in the emergency department with high risk of developing ARDS. ARDS predictors included in the final score both triggers (ie, shock, aspiration, lung contusion) and risk modifiers (ie, smoking, diabetes mellitus, acidosis). This tool also works in hospitalized patients as a quick and effective way of identifying high-risk patients.[55–57] Hopes that this score would help enrich enrollment in trials of therapeutics to decrease incidence and death from ARDS, however, have so far not borne fruit. For instance, the LIPS-A trial, in which aspirin was tested as a possible intervention in this subgroup of patients, showed no difference in rates of ARDS and rates of death after receiving aspirin versus placebo.[58]

Between 2001 and 2008, rates of ARDS fell by half in two ICUs in Rochester, Minnesota, in a population-based, retrospective cohort study of the epidemiology of ARDS patients admitted during that time period. Severity of acute illness, greater number of comorbidities, and major predisposing conditions in patients with ARDS increased while mortality stayed the same during this time. Interestingly, the reduction in incidence occurred exclusively in patients with hospital-acquired ARDS. As noted by the authors, during this time, a separate hospital-wide program to limit risk factors for ARDS was undertaken which can explain this reduction in hospital-acquired ARDS. This indicates that ARDS may, in part, be a preventable hospital-acquired

Table 1
Main epidemiologic studies on ARDS incidence after AECC definition

Authors, Year of Publication [Reference]	Study Period	Country or Countries	Incidence of All ARDS Categories (per 100,000 Person-Years-Population-Based Studies) or Percentage (%, Hospitalization-Based Studies)	Incidence of Moderate and Severe ARDS Categories (per 100,000 Person-Years-Population-Based Studies) or Percentage (%, Hospitalization-Based Studies)
Sigurdsson et al,[15] 2013	1988–2010	Iceland		3.65–9.63
Nolan et al,[4] 1997	1990–1994	Australia		7.3–9.3
Luhr et al,[5] 1999	1997	Scandinavia (Sweden, Denmark, Iceland, Norway)	17.9	13.5
Bersten et al,[6] 2002	1999	Australia (South, Western, and Tasmania)	34	28
Brun-Buisson et al,[13] 2004	1999	Europe	7.1% (of all ICU admissions)	6.1% (of all ICU admissions)
Rubenfeld et al,[7] 2005	1999–2000	King County, WA, USA	78.9	58.7
Manzano et al,[8] 2005	2001	Granada, Spain	25.5	23
Sakr et al,[92] 2005	2002	Europe	12.5% (of all ICU admissions), 19.1% (of all mechanically ventilated patients)	10.6% (of all ICU admissions), 16.5% (of all mechanically ventilated patients)
Li et al,[9] 2011	2001–2008	Olmsted County, MN		81 (in 2001), 38.3 (in 2008)
The Irish Critical Care Trials Group,[14] 2008	2006	Ireland	19%	
Caser et al,[10] 2014	2006–2007	Vitoria Region, Brazil	10.1	6.3
Linko et al,[11] 2009	2007	Finland	10.6	5
Villar et al,[12] 2011	2008–2009	Spain		7.2
Bellani et al,[1] 2016	2014	50 Countries	10.4% of all ICU admissions, 5.5 cases per ICU bed per year	

ARDS was defined using the Berlin definition nomenclature: All ARDS categories include mild, moderate, and severe ARDS.

complication.[9] Multiple additional studies have shown that using LTVV in all visitors to the hospital and ICU have decreased incidence of ARDS arguing for the use of LTVV in all patients and not only on those with respiratory failure.[59,60]

ACUTE RESPIRATORY DISTRESS SYNDROME-ASSOCIATED MORTALITY

Despite improved mortality rates, ARDS continues to be a syndrome of high mortality. As noted previously, P/F ratio correlates with ARDS outcome, prompting the authors of the Berlin Criteria to maintain the traditional severity categories in their updated consensus definition. Mortality in cohorts analyzed by the Berlin Criteria authors was 34.9% (95% confidence interval [CI]: 24%-30%) in mild ARDS, 40.3% (95% CI: 29%-34%) in moderate ARDS, and 46.1% (95% CI: 29%-34%) in severe ARDS, as defined by P/F thresholds of 300, 200, and 100.[2] The LUNG-SAFE study reported similar findings, with 28-day mortality of 29.6% (95% CI: 26.2%-33.0%) in mild ARDS, 35.2% (95% CI: 32.4%-38.1%) in moderate ARDS, and 40.9% (95% CI: 36.8%-45.1%) in severe ARDS using the same P/F thresholds used in the Berlin definition.[1]

Reported ARDS mortality has decreased over recent decades. Compared to the late 1990s, when independent studies reported ARDS mortality of 58% to 59%,[4,13] mortality in contemporary studies is much lower (**Figs. 1** and **2**). ARDS mortality in 2014 in LUNG-SAFE was 10.4%,[1] and 28% in the LOTUS-FRUIT U.S. multicenter study conducted by the PETAL Network in 2019.[61] While imperfect,[62] death certificate data also suggest decreasing risk of death for ARDS patients, with annual attributable mortality in one U.S. death certificate analysis decreasing from 5.01 per 100,000 people in 1999 to 2.82 per 100,000 population in 2013.[63] While changes in ascertainment (diagnosing more patients with less-severe ARDS) and decreasing use of mechanical ventilation for patients near the end of life may contribute to this trend, it appears likely that increasing the use of LTVV since the publication of the seminal ARMA trial in 2000 is a key factor driving improved outcomes in ARDS.[49] In fact, among patients who do
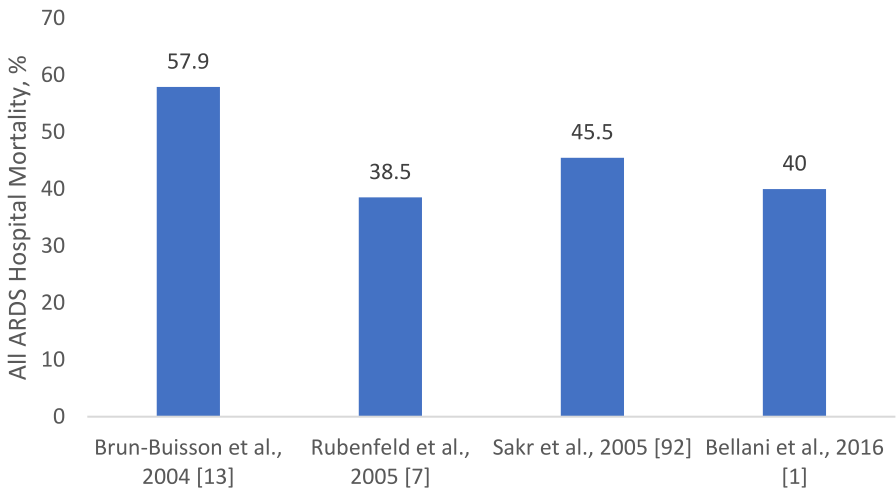

Fig. 1. Estimated overall hospital mortality rates for patients with ARDS of any severity. Hospital mortality reported in the main epidemiologic studies in all ARDS categories (mild, moderate, and severe). On the X-axis, the studies are chronologically ordered based on the study period.
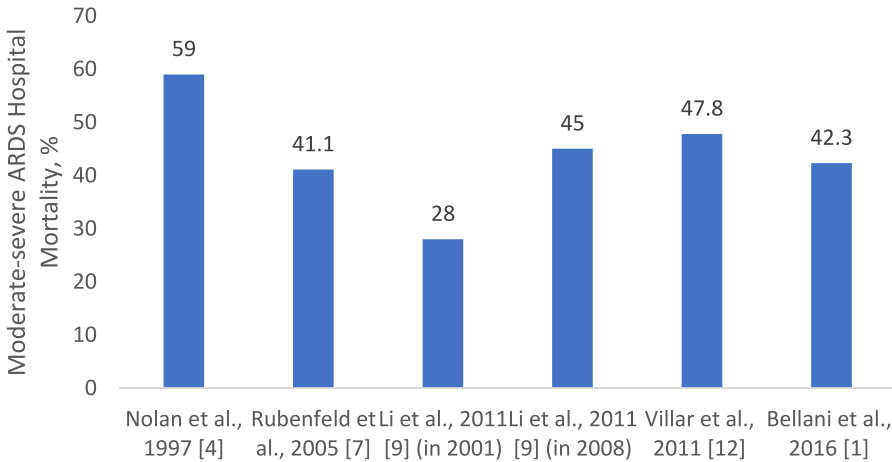
Fig. 2. Estimated mortality rates for patients with moderate-severe ARDS. Hospital mortality reported in the subgroups of moderate-severe ARDS. Moderate-severe ARDS hospital mortality in the study by Li *and colleagues* [2011] is reported in two different years of study, 2001 and 2008. On the X-axis, the studies are chronologically ordered based on the study period.

receive low tidal volume ventilation, there has been no change in mortality.[64] It is also important to note that, in some settings, apparent stability of crude ARDS mortality may mask changes in case mix (increasing illness severity and comorbidities) and therefore improving risk-adjusted mortality.[9]

LONG-TERM OUTCOMES

Despite the significant lung injury experienced during the course of a patient's illness with ARDS, postillness pulmonary function tests showed normalization at 5 years after ICU.[65] Despite this normalization in lung function, reported quality-of-life scores and exercise tolerance, measured by 6-minute walk test, remain lower than average at 5 years. Multiple factors likely contribute to this including persistent weakness and neuropsychologic impairments. These neuropsychologic issues are heterogeneous and affect both the patient and their caregivers.[65] These patients also accrue larger health care costs after hospitalization because of increased utilization of the health care system. ARDS is one of the most common reasons for admission to a long-term ventilator rehabilitation unit.[66]

COVID-19

The severe acute respiratory distress syndrome-associated coronavirus-2 was first identified in December 2019 in Wuhan, Hubei, China, as the agent causing what is now called COVID-19.[67] COVID-19 was officially declared a pandemic by the World Health Organization on March 11, 2020. As of November 21, 2020, 57,274,018 confirmed cases have been reported with 1,368,000 deaths worldwide.[68] While it is increasingly clear that COVID-19 is a multisystem disease, the primary manifestation is a viral pneumonia that, in some patients, progresses to ARDS, often complicated by protracted illness or death.

Mortality estimates for COVID-19-associated ARDS vary widely, ranging from 3.4% to 88.3% (**Table 2**).[69–74] These estimates are affected by the studied population,

Table 2
Twenty-eight-day mortality rate data of patients with ARDS from COVID-19

Authors, Year of Publication [Reference]	Study Period	City, Country	Mortality
Yang et al,[69] 2020	12/24/2019–01/26/2020	Wuhan, China	61.5%
Wang et al,[70] 2020	01/25/2020–02/25/2020	Shanghai, China	88.3%
Grasselli et al,[71] 2020	02/20/2020–03/18/2020	Milan, Italy	26%
Ferrando et al,[72] 2020	03/12/2020–06/01/2020	Spain and Andora	36%
Bhatraju et al,[74] 2020	02/24/2020–03/09/2020	Seattle, USA	50%*
Gupta et al,[73] 2020	03/04/2020–04/04/2020	Various cities, USA	6.6%-80.8% (35.4%)

All patients were admitted to the ICU with ARDS due to COVID-19. All mortalities are 28-d mortality except the study by *Batraju et al which includes a 14-d mortality.

health system factors (thresholds for hospitalization varied across cohorts substantially), therapeutic context (Early in the pandemic, large numbers of potentially toxic therapies were administered in cocktails.), institutional context (the degree to which the studied health care systems were strained by the pandemic surge), and patient-level risk factors (some sites predominantly cared for patients in nursing homes). For example, patients admitted to hospitals with fewer ICU beds had higher risk of death likely because of less training and comfort of caregivers in treating ARDS as well as limited resources in these settings, particularly in the pandemic context. Critically, some early mortality studies had insufficient follow-up to provide accurate estimates of morality, excluding patients without a final outcome (discharge or death) and thereby inflating mortality estimates by excluding patients alive and still in the hospital.

The question of whether and how COVID-19-associated ARDS differs from prior forms of ARDS has been surprisingly contentious.[75] Early anxiety about abrupt decompensation specific to this condition, the risk of aerosolization and consequent transmission to caregivers with high-flow nasal cannula oxygen, and lack of effective therapeutics all played a role, as did clinician perceptions that some patients with COVID-19 exhibit "happy hypoxemia" and/or higher-than-expected lung compliance for their degree of hypoxemia.[76] The opinion that ARDS resulting from COVID-19 might be exceptional and clinicians' frustration over the lack of proven treatments were sometimes associated with calls for application of therapies previously shown ineffective in general ARDS and even for the use of high-tidal-volume ventilation. Spring and summer 2020 witnessed a vigorous debate on the issues, with some thought leaders arguing for novel supportive care, and others arguing that standard supportive care for ARDS represented the best approach.[77,78]

While some prognostic factors differ and time from COVID-19 symptom onset to full ARDS is sometimes slightly longer than with some classic ARDS etiologies,[79] most evidence to date suggests that ARDS in COVID-19 lacks important differences from the syndrome generally. Contradicting the postulated "L-type" (high compliance) and "H-type" (low compliance) dichotomy advanced by some as unique to COVID-19 ARDS,[76,80] the spectrum of lung compliance in COVID-19 ARDS appears similar to that observed in prior studies of general ARDS.[81] Pathologic analysis also shows findings similar to ARDS generally, demonstrating hyaline membrane formation, edema, and DAD.[82] We therefore manage COVID-19 ARDS with the package of evidence-based care that we apply to ARDS generally, including strict adherence to low-tidal-volume ventilation,[49] consideration of prone positioning,[83] and high PEEP for more

severe ARDS,[36] conservative fluid management,[84] protocolized spontaneous breathing and awakening trial,[85] and early mobilization.[86] It is nevertheless plausible that, given its homogeneous trigger and potentially more homogeneous inflammatory phenotype, ARDS resulting from COVID-19 could respond to therapies that failed trials enrolling patients with a heterogeneous array of triggers and endotypes. The apparent efficacy of steroid therapy in several (imperfect) trials,[87,88] a treatment for which trials in general ARDS population had repeatedly yielded conflicting evidence,[89–91] may be one early example of this phenomenon.

SUMMARY

ARDS remains a common, deadly problem among critically ill patients around the world. It is a syndrome of significant heterogeneity, with sub-phenotypes requiring further characterization and tools for prompt clinical identification. COVID-19 has brought new challenges including a large, and relatively homogeneous, population of ARDS patients but does not seem to cause a truly unique respiratory failure syndrome distinct from ARDS generally nor even engender a truly homogenous subtype of ARDS. Further advances in ARDS care will likely require improved understanding of the epidemiology of this syndrome and its subtypes as well as innovative trials of focused therapeutics. Given the high mortality of the syndrome and its long-term morbidity, ongoing study into treatment and care of patients with ARDS is paramount.

CLINICS CARE POINTS

- Although acute respiratory distress syndrome (ARDS) has a high incidence among intensive care unit patients, with high morbidity and mortality, it remains underdiagnosed.
- The Berlin criteria were created to help clearly identify patients with ARDS.
- Supportive measures with low-tidal-volume ventilation, prone positioning, conservative fluid management strategies, high PEEP for severe disease, protocolized spontaneous breathing and awakening trials, and early mobilization have lowered the morbidity and mortality of ARDS and are the cornerstone of therapy.
- COVID-19-associated ARDS is a syndrome on the ARDS spectrum and should therefore be treated with the same strategies as classic ARDS while we await results of ongoing trials.

DISCLOSURE

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