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Long-Term Outcomes in Acute Respiratory Distress Syndrome

Epidemiology, Mechanisms, and Patient Evaluation

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KEYWORDS

- Acute lung injury • Physical function • COVID-19 • Cognitive function
- Mental health • Post-intensive care syndrome • Skeletal muscle

KEY POINTS

- Many ARDS survivors experience long-term impairments including limitations in physical and cognitive function, mental health symptoms, and decreased quality of life.
- Premorbid functional status and comorbidities are important contributors to post-ARDS long-term outcomes.
- Given the abrupt rise in ARDS incidence with the COVID-19 pandemic, the prevalence of long-term impairments following ARDS is expected to increase.

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a clinical syndrome of inflammatory lung injury characterized by the acute onset of hypoxemia, noncardiogenic pulmonary edema, and the need for mechanical ventilation. Since its first description by Ashbaugh and colleagues¹ in 1967, our understanding of its epidemiology, pathogenesis, and long-term impact has grown.² Estimates from the early 2000s suggest that ARDS affects more than 190,000 people in the United States each year and results in an estimated 74,500 deaths and 3.6 million hospital days.³ Over the past 50 years, care has improved for patients with ARDS; for example, randomized trials have provided evidence-based strategies for optimizing mechanical ventilation and fluid therapy.^{4,5} There are now a growing number of patients surviving to hospital discharge and

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beyond, an estimated 100,000 patients each year, a number that is expected to rapidly expand during the coronavirus disease 2019 (COVID-19) pandemic.^{6,7}

The advent of low tidal volume ventilation at the turn of the century heralded a new era in the management of ARDS.⁶ Multiple studies since that time have shown improved mortality and hospital-based outcomes, owing to low tidal volume ventilation and other advances in care.^{8–12} Modern management of ARDS may have also led to reduced long-term pulmonary complications, because more recent studies have failed to see the frequency of long-term pulmonary complications reported in the 1980s.^{6,13,14} These reductions in short-term mortality and longstanding pulmonary morbidity in survivors opened the door to a focus on other nonpulmonary complications that patients and their families experience as they recover from the acute illness.^{6,15} Peer-reviewed publications describing long-term outcomes of ARDS and critical illness have grown substantially from 3 in the 1970s to more than 300 since 2000.¹⁶ Professional and scientific societies, including the American Thoracic Society, Society of Critical Care Medicine, and funding agencies including the National Institutes of Health, have recommended prioritizing research on outcomes of survivors of critical illness, including survivors of ARDS after hospital discharge.^{16–20}

Recently, the rapidly emerging COVID-19 pandemic has created a massive surge of ARDS cases in the United States and worldwide. Of those patients hospitalized with COVID-19, approximately one-third develop ARDS.²¹ It is unclear what the rates of ARDS will be in 2020 to 2021 worldwide, but it is highly likely that the incidence will be significantly higher than in prior years. Most of the attention during the first 10 months of the pandemic has been focused on the acute management of COVID-19 ARDS and preventing early mortality, of which 60-day mortality estimates for patients with COVID-19 requiring intensive care unit (ICU) care are up to 60%.²² However, the long-term impairments in survivors of COVID-19 ARDS are likely to contribute to this ongoing major health crisis for years to come, even as the incidence of COVID-19 ARDS declines (**Fig. 1**).

In this review, we discuss the persistent impairments many ARDS survivors face following resolution of their critical illness, including decreased physical and cognitive function, mental health symptoms, and reduced quality of life. Given the high prevalence of these impairments following ARDS, we also discuss the clinical evaluation of the patient post-ARDS, with consideration of the ongoing and evolving knowledge of COVID-19 ARDS.

Impairments in Physical Function Following Acute Respiratory Distress Syndrome

Physical function is defined as the ability to perform basic and instrumental activities of daily living.²³ Physical function is an integrated output from a coordinated response of multiple organ systems. In the ARDS survivor, injury to the pulmonary, neuromuscular, and cardiac systems should be considered as critical organ systems that may influence physical function.

Pulmonary

Patients with ARDS experience severe problems with gas exchange, causing profound hypoxia and necessitating mechanical ventilation. Lung injury resolution is a complex and coordinated response that begins from the onset of injury and has been extensively reviewed by others.² When successful, lung injury recovery results in liberation from mechanical ventilation. However, residual pulmonary injuries such as fibrosis and pulmonary diffusion impairments may be present following hospital discharge and may influence a patient's long-term physical function. Through the mid-1990s, research in long-term outcomes following ARDS focused primarily on

Projected Changes in ARDS Landscape Over Time

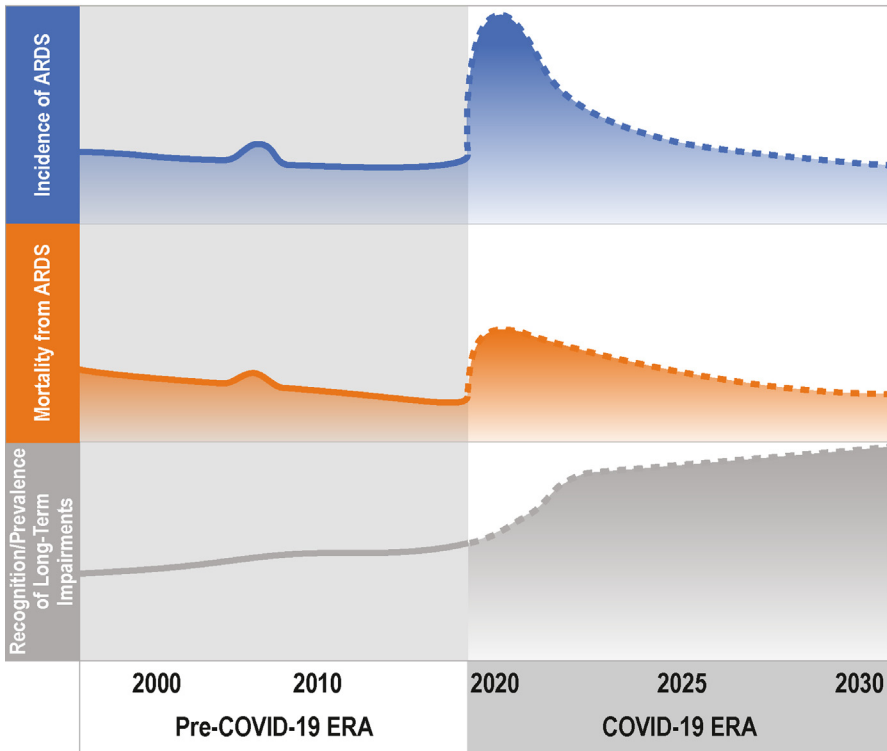


Fig. 1. In the pre-COVID-19 era, declining ARDS mortality was associated with an increase in recognition and prevalence of long-term impairments. In the post-COVID-19 era, there is an anticipated increase in long-term impairments following ARDS even as COVID-19 cases decline.

pulmonary recovery.^{13,24,25} In most survivors of ARDS, pulmonary function returns to normal within 6 to 12 months despite severe initial lung injury.²⁶ Residual pulmonary function impairments are often asymptomatic and include mild restriction or obstruction or mild reduction in diffusing capacity.^{14,27,28}

Radiographic evidence of ARDS often persists beyond symptomatic and pulmonary function recovery. In 1999, Desai and colleagues²⁹ described the acute- and late-phase computed tomographic (CT) scan patterns following ARDS. Ground glass opacification and consolidation are reported in the early phase, whereas a reticular pattern is more common in the late phase and associated with the duration of mechanical ventilation.²⁹ The Toronto ARDS Outcomes Study Group reported CT imaging findings 5 years after severe ARDS between 1998 and 2001.³⁰ Pulmonary CT imaging abnormalities were found in most patients (75% of 24 patients) but were generally minor and in the nondependent lung regions. In this study, no correlation was found between radiographic findings and symptoms, pulmonary function tests, or health-related quality of life measures, suggesting that the long-term impairments patients face following ARDS are complicated and are likely not secondary to structural lung disease in most patients.

The long-term pulmonary manifestations of COVID-19 ARDS will be realized as more COVID-19 ARDS survivors are studied in follow-up. Emerging data indicate

that many patients experience persistent respiratory complaints.³¹ Efforts are underway worldwide to enroll COVID-19 survivors in long-term follow-up. One such study in the United States, called BLUE CORAL, is prospectively enrolling patients with severe COVID-19 and includes long-term follow-up in a subset of these patients (<https://petalnet.org/studies/public/bluecoral>).

Neuromuscular

The skeletal muscle system, a major target in ARDS, has often been overlooked as an organ of injury. The loss of muscle mass and function during critical illness has long been recognized since the time of Osler, but it was not until the 1990s that case series emerged reporting profound neuromuscular weakness in heterogeneous cohorts of critically ill patients.^{32–38} A variety of terms, such as acute quadriplegic myopathy, thick filament myopathy, critical illness myopathy, and critical illness polyneuropathy, were used to describe the varied electrical and pathologic patterns of neuromuscular injury seen in these patients, often after receiving prolonged mechanical ventilation.^{39–42} In 2003, a landmark observational study carefully quantified injury to the neuromuscular system in a cohort of critically ill patients on mechanical ventilation for more than 7 days, using a clinical examination, electrophysiology, and muscle biopsies.⁴³ This work coined the term “Intensive Care Unit Acquired Paresis,” which later became known as “Intensive Care Unit Acquired Weakness (ICUAW).”⁴⁴ In the 25% of patients in this cohort who met the criteria for severe muscle weakness, characterized by Medical Research Council (MRC) sum score of less than 48 of 60, all patients had electrophysiologic or pathologic neuromuscular injury. Importantly, patients who met this clinical diagnosis of ICUAW had increased short- and long-term mortality, a finding confirmed in subsequent studies.^{45–47} Those who remained severely weak following hospital discharge had an increased risk of death in follow-up, highlighting ICUAW as a risk factor for subsequent mortality.

The mechanisms driving muscle wasting in ARDS are complex and incompletely understood. However, patients with ARDS universally experience muscle wasting (loss of muscle mass and function) of the limb and respiratory muscles to variable degrees. Electromyography and nerve conduction studies may reveal predominantly neuropathic (critical illness polyneuropathy), myopathic (critical illness myopathy), or mixed (critical illness neuromyopathy) patterns of injury in severe cases.⁴⁴ Even in patients who do not exhibit electrophysiological abnormalities, muscle atrophy (loss of muscle mass) is a ubiquitous feature of ARDS, driven by inflammation and disuse.^{45,48} Histologically, muscles of patients with ARDS may variably show type 2 myofiber atrophy, myosin loss, or immune cell infiltrates.^{48,49} Preclinical and human studies of ARDS-related muscle wasting support the concept that muscles have an imbalance in skeletal muscle homeostasis favoring increased protein degradation and decreased protein synthesis.^{45,48} Major pathways mediating protein degradation include the ubiquitin proteasome, calpain, and lysosomal pathways.⁵⁰ Increasing attention has also been turned to the influence of systemic and muscle metabolism in mediating muscle function in critical illness.^{51–53} The area of muscle metabolism may have important implications for nutrient delivery during ARDS and how nutrition may influence skeletal muscle function in the acute and longer-term follow-up.^{54–56}

Some ICU exposures may influence the development of ICUAW in ARDS, some of which may be modifiable. Early studies of tight glycemic control in the early 2000s found a reduced incidence of neuromuscular weakness with tight glycemic control.^{57–59} The subsequent NICE-SUGAR trial tempered enthusiasm for this approach when a signal for increased mortality emerged.⁶⁰ However, glycemic control remains

a potentially modifiable risk factor for the development of ICU-acquired weakness in the generally critically ill population, although further study here is needed. The use of corticosteroids and neuromuscular blocking agents has also been variably associated with the development of ICUAW, although confounding by indication for these exposures may limit interpretation in observational cohorts.⁶¹ Importantly, the ROSE randomized controlled trial of cisatracurium versus placebo in early ARDS found no increase in ICUAW incidence through day 28 (47% cisatracurium group vs 39% in placebo group), although missing data for this secondary outcome was common.⁶²

Skeletal muscle wasting that occurs during ARDS is likely a major driver of reduced physical function in ARDS survivors observed during long-term follow-up. Certain risk factors and ICU exposures have been variably implicated in the development of muscle weakness in long-term follow-up. In cohorts of patients with acute respiratory failure requiring mechanical ventilation, increased age, severity of illness, comorbid illness, and ICU length of stay have been associated with long-term physical function impairment.^{26,63–65} One study suggests that compliance with low tidal volume ventilation reduces long-term mortality, even when adjusting for hospital mortality.¹² Similarly, in a randomized trial of an ICU and hospital-based physical therapy intervention in patients with severe acute respiratory failure, patients randomized to the intervention arm had improved physical function in long-term follow-up, despite no measured benefit at hospital discharge.⁶⁶ Collectively these data suggest that ICU exposures during hospitalization with ARDS may influence long-term outcomes such as mortality and physical function.

One interesting observation is that ARDS survivors follow different physical function recovery trajectories. Risk factors such as age, male sex, longer lengths of stay, and hearing or vision loss are more likely to remain functionally impaired.^{63,64,67} The mechanisms underlying failed versus successful recovery are incompletely understood, although some clues are emerging. Muscle biopsies from humans with long-term weakness following critical illness show a transcriptomic signature consistent with failed muscle regeneration.⁶⁸ Patients with sustained muscle atrophy have decreased muscle stem (satellite) cell content.⁶⁹ Future work is needed to better understand potential mechanisms underlying the muscle recovery of ARDS survivors, and this mechanistic work and trajectory analyses will contribute to tailored approaches to study specific ARDS long-term endotypes.

Last, it is important to recognize that not all deficits identified following a critical illness are due to the critical illness itself.⁷⁰ Longitudinal cohorts that measured physical function and deficit accumulation before and following critical illness have demonstrated this finding.^{71,72} These studies found that many deficits were accumulating before the incident illness. Indeed, these pre-critical illness functional deficits influence mortality and long-term functional impairment.^{71,73,74} Failure to recognize pre-critical illness physical function in ARDS survivors results in misattribution and could lead to frustration on the part of both clinicians and patients.

Cardiovascular

Although less well described than pulmonary and muscle injury during ARDS, cardiac injury does occur in a subset of patients and may contribute to long-term morbidity and mortality. Troponin elevation can be found in up to 90% of patients hospitalized with ARDS or sepsis and appears to be correlated with the severity of illness.^{75,76} Elevated cardiac biomarkers during critical illness have been associated with long-term mortality.⁷⁷ Some patients with ARDS develop echocardiographic evidence of cardiac injury (septic or stress cardiomyopathy), during the critical illness, which

may be driven by adverse cardiopulmonary interactions or systemic inflammation.^{5,78} Cardiovascular events such as myocardial infarction or stroke are twice as likely in sepsis survivors compared with age-matched controls.⁷⁹ Significant interest exists in the relationship of COVID-19 with cardiac complications including acute myocardial injury and myocarditis, arrhythmias, and acute coronary syndrome.⁸⁰ Recent data suggest that the angiotensin-converting enzyme 2 receptor, which severe acute respiratory syndrome coronavirus 2 uses for cellular entry, is expressed in the heart.⁸¹ Accumulating data suggest that cardiovascular injury during ARDS likely contributes to reduced functional outcomes in ARDS survivors, although more research is needed in this area.

Cognitive Impairment, Mental Health Symptoms, and Quality of Life Following Acute Respiratory Distress Syndrome

The long-term impact of ARDS extends beyond impairments in physical functioning; observational studies have consistently shown that there are long-term neuropsychiatric impairments in many patients following resolution of the acute lung injury. Long-term cognitive impairment, new or worsening mental health symptoms, and reduced quality of life have all been reported.

Cognitive

Cognitive impairment following ARDS is common, profound, and often persistent. This impairment affects ARDS survivors of all ages. In observational cohort studies of ARDS survivors, the prevalence of cognitive impairment varies based on the subpopulation studied, timing of assessment, and cognitive assessment tool used. In a prospective study by Hopkins and colleagues⁸² (n = 106; 62 followed for 1 year), 78% of patients were cognitively impaired on a neuropsychological battery at 1-year follow-up. In a subsequent study (n = 120), participants underwent comprehensive neuropsychological testing at hospital discharge, 1 year, and 2 years. Most participants in this cohort (78%) were impaired at hospital discharge, 46% at 1 year, and 47% at 2 years.⁸³ In National Heart Lung and Blood Institute ARDSnet studies, longitudinal outcome data also support the conclusion that cognitive impairment following ARDS is common and persistent. In long-term outcome assessments following the Early versus Delayed ENteral feeding (EDEN) trial, 25% of patients were cognitively impaired on the Mini-Mental State Examination Telephone version at 6 months and 21% at 12 months.⁵⁶ Following the Statins for Acutely Injured Lungs in Sepsis (SAILS) study, cognitive impairment was present in 37% of ARDS survivors at 6 months and 29% at 12 months.⁸⁴ In a large multicenter prospective cohort study of a diverse population of patients in general medical and surgical ICUs, many of whom were intubated and likely had ARDS, one-quarter of patients had cognitive impairment 12 months after critical illness to the degree seen in patients with mild Alzheimer disease and one-third had impairment to the degree seen in patients with moderate traumatic brain injury.⁸⁵ In this cohort, impairments were found in a broad range of domains, more than just memory, including executive functioning. Although we do not yet know the prevalence of cognitive impairment following COVID-19 ARDS, early research suggests that neurologic features are often present during acute COVID-19 infection.⁸⁵⁻⁸⁷ Also, the population at highest risk for severe COVID-19 infection overlaps significantly with those at risk for cognitive decline (advanced age, obesity, diabetes), and we can expect that there may be an increase in long-term cognitive impairment reported following severe COVID-19 in the coming years.⁸⁸⁻⁹⁰

Although post-ICU cognitive impairment is commonly reported in ARDS, one challenge in determining the contributory impact of ARDS on cognitive function,

particularly in older adults, is that premorbid cognition is generally unknown in observational cohort studies. The development and the duration of delirium are strong predictors of post-ARDS cognitive decline.^{85,91,92} Pre-existing cognitive impairment or dementia is a risk factor for the development of delirium in the ICU as well as cognitive decline after critical illness.^{85,93} Delirium and cognitive impairment are clearly intertwined; patients who develop delirium during an ARDS hospitalization are a high-risk group for post-ICU cognitive impairment and merit screening postdischarge.⁹⁴

There are multiple pathways by which critical illness may lead to new or worsening cognitive impairment. Hypoxemia is common in patients with ARDS, and the hippocampus is susceptible to hypoxic insults.⁹⁵ Neuroimaging studies of ARDS survivors demonstrate accelerated cerebral and hippocampal atrophy.⁹⁶ Autopsy studies of patients with ARDS whose critical illness was complicated by delirium have also shown hippocampal hypoxic-ischemic lesions.⁹⁷ Damage to the endothelial glycocalyx has been linked with long-term cognitive impairment in a preclinical model and humans with sepsis.⁹⁸ Although hippocampal ischemic injury may be an important contributory cause of cognitive impairment, animal studies suggest that cytokine-mediated injury from mechanical ventilation may also play a central role. In a porcine model of ARDS, cytokine-mediated brain damage from lung injury was found to be the major pathophysiological contributor to hippocampal damage, rather than hypoxemia.⁹⁹ This finding was supported by a pig model of mechanical ventilation-induced ARDS that found cognitive impairment was greater in the lung injury group (with evidence of more inflammation) compared with the hypoxia-only group.¹⁰⁰ Mechanical ventilation has also been shown to trigger hippocampal apoptosis in mechanically ventilated mice.¹⁰¹

Damage to the blood-brain barrier and amyloid- β clearance have also been proposed as potential mechanisms for the cognitive impairment seen following ARDS. Similarities between the pathophysiology of Alzheimer's disease (primarily accumulation of amyloid- β) and the acute sequelae of high-tidal volume mechanical ventilation in mice suggest that there may be a mechanistic link between delirium, Alzheimer's disease, and the underlying cognitive damage reported following ARDS.^{102,103} Chronic accumulation of amyloid- β contributes to baseline blood-brain barrier weakening, which, in turn, may result in an increased susceptibility to hippocampal exposure to cytokines and cytokine-mediated damage in patients with underlying cognitive impairment and Alzheimer's disease. Finally, emerging data suggest that bacterial translocation to the brain in sepsis may contribute to delirium and cognitive impairment.¹⁰⁴ Although the causal mechanisms are likely complex, it is clear that there is a link between the lung and brain injury seen in ARDS.

Mental health

Mental health symptoms have been described in a significant proportion of ARDS survivors. Among 629 patients enrolled in 3 ARDSnet trials with at least one psychiatric measure, two-thirds had substantial symptoms in one or more domain during 1-year follow-up.¹⁰⁵ At 6 months, prevalence of substantial symptoms of depression, anxiety, and posttraumatic stress disorder (PTSD) was 36%, 42%, and 24%, respectively. Most survivors (63%) with any psychiatric morbidity had substantial symptoms in 2 or more domains suggesting that co-occurrence of mental health symptoms is common. In this study, severity of illness, mechanical ventilation duration, and ICU length of stay were not associated with worse psychiatric symptoms; younger age, female sex, baseline unemployment, alcohol misuse, and greater in-ICU opioid use were associated with post-ICU psychiatric symptoms. In a systematic review by Davydow and colleagues,¹⁰⁶ the median point prevalence of

depression, PTSD, and nonspecific anxiety were similar at 28%, 28%, and 24%, respectively. In a longitudinal cohort of ARDS survivors with 5 year follow-up, 71 of 186 (38%) had a prolonged course (defined as continuous or recurring symptoms) of anxiety; 39 (32%) and 43 (23%) had a prolonged course of depression and PTSD, respectively.¹⁰⁵ Pre-ARDS mental health disorders were strongly and consistently associated with prolonged psychiatric morbidity after ARDS in this cohort as well suggesting that prior psychiatric history is an important risk factor for post-ARDS mental health symptoms.

Quality of life

ARDS survivors have been shown to have reduced post-hospitalization quality of life compared with the US general population.^{83,107,108} Although this finding has been consistent, baseline quality of life before the acute illness was not known in these cohort studies. In a prospective, population-based study, decreased quality of life and functional status postdischarge were largely explained by reduced baseline quality of life and functional status before critical illness.¹⁰⁹ In qualitative work with ARDS survivors and their families, ARDS has been described as a life-altering event often resulting in pervasive, persistent disability. It is clear that the recovery process following ARDS is complex and may not be fully captured by general health-related quality of life measures. For example, in this study, patients frequently described delusional traumatic ICU memories that disrupted their families and, at times, led to life-changing repercussions.¹¹⁰ Predominant memories were related to physical restraints, endotracheal tube suctioning, tracheostomies, and an inability to communicate.

ARDS influences long-term health domains beyond physical and mental health for both patients and families. A multicenter study in the United States found that nearly half of previously employed ARDS survivors were jobless at 12 months following their illness.¹¹¹ Those who return to work often experience job loss, occupation change, or worse employment status.¹¹² Noted barriers to returning to work include persistent fatigue and weakness, poor functional status, work-related stress, and the need for job retraining. Studies have uncovered significant financial burdens on ARDS survivors. One study of survivors found that average costs per patient from years 3 through 5 ranged from \$5000 to \$6000, close to costs incurred by patients with chronic disease.¹¹³ Cumulative costs were associated with increased coexisting illness at ICU admission. In another cohort of acute respiratory failure survivors, a significant proportion of patients and their family members reported financial stress after discharge; when present, financial stress was associated with symptoms of anxiety and depression and decreased global mental health.¹¹³ In another study following ARDS survivors participating in ARDS Network studies, 40% of patients reported at least one postdischarge hospitalization, with median estimated hospital costs of nearly \$19,000.¹¹⁴

More than 50% of patients who receive prolonged mechanical ventilation are dependent on caregiver assistance at 1 year follow-up.¹¹⁵ In a study looking at 1-year outcomes of the caregivers of critically ill patients, caregivers are at higher risk for clinical depression and poorer psychological well-being.¹¹⁶ In qualitative work with ARDS survivors and their caregivers, the caregivers have endorsed distress by patients' fluctuation in cognition and mental status.¹¹⁰ The caregivers also describe a lack of support after hospital discharge and significant strain both emotionally and financially with often a new caregiving role. Emerging data suggest that ARDS has a substantial impact on the long-term outcomes of both patients and their families.

One overarching problem with the long-term outcomes field has been a lack of standardization of the assessment tools across different research studies. There has been

an attempt to standardize the tools that clinical researchers use to measure long-term outcomes, to bring uniformity to this issue.¹¹⁷ Investigators designing studies should use these core outcome measures, which can also be found on <https://www.improvelto.com/coms/>

Clinical Evaluation of the Patient Post–Acute Respiratory Distress Syndrome

Detailed and comprehensive prospective observational studies have greatly impacted critical care and established the basic epidemiology and many of the risk factors for persistent impairments following ARDS.¹¹⁸ Through the work of a 3-round modified Delphi process, a core set of outcomes now exists for clinical research of acute respiratory failure,¹¹⁷ which will allow even greater comparison across cohort studies and the incorporation of these important outcomes in ICU and post-ICU clinical trials. Although there is growing consensus around the recommended evaluation of long-term outcomes following ARDS in clinical research, much less is known about the optimal evaluation of patients post-ARDS as part of routine clinical care.

To increase the awareness of long-term consequences of critical illness, the term “post-intensive care syndrome” (PICS) has been used to refer to the physical, cognitive, and/or mental health complications following an ICU stay.²⁰ The Society of Critical Care Medicine (SCCM) recently published recommendations related to screening tools and timing of assessments to identify long-term impairments after critical illness consistent with PICS that would apply to survivors of ARDS.⁹⁴ The recommendations by the SCCM include screening high-risk individuals early and serially for long-term impairments in cognition, mental health, and physical function using a standardized set of tools—the Montreal Cognitive Assessment (MoCA or MoCA-BLIND),¹¹⁹ the Hospital Anxiety and Depression Scale (HADS),¹²⁰ and the 6-minute walk test and/or the EuroQol-5D-5L.¹²¹ The initial assessment is recommended to occur within 2 to 4 weeks of hospital discharge and again with important life or health changes. Although the impact of screening ARDS survivors with these particular tools on longer-term outcomes (such as subsequent mortality or improvements in persistent impairments) has not been studied, we agree that these tools serve as a good place to start in the post-ICU evaluation of ARDS survivors. For those patients with subjective complaints of muscle weakness, a global assessment of muscle strength using the MRC scale or handheld dynamometers can also be useful, particularly if following patients longitudinally. Although not included in the SCCM recommendation, the short physical performance battery (SPPB), a tool extensively validated in the geriatric population and with increased use in the post-ICU population, may be a useful adjuvant. The SPPB evaluates lower extremity strength, balance, and gait speed and can be completed in 5 minutes.¹²² The SPPB may compliment the 6-minute walk test and provide insight into balance and lower extremity strength, which are key for maintaining functional independence.

Although most patients will have improvement in physical function in the weeks and months following hospital discharge, there will be some who report a persistent impairment in exercise tolerance.⁶⁵ In those patients, pulmonary function testing, chest imaging with CT, and echocardiography might be helpful to assess for post-ARDS pulmonary and cardiac injury. Patients who complain of impaired exercise tolerance without a clear cause from this initial evaluation may benefit from a cardiopulmonary exercise test. Finally, physical and mental health impairments have been found to be closely associated with each other in ARDS survivors, and an evaluation of persistent limitations in physical function should also include an assessment of mental health symptoms.¹²³

One important point to emphasize in the clinical evaluation of patients with ARDS is the need for standardized assessments, for both cognitive and physical function. In qualitative work, performance-based cognitive tests of memory and attention were not associated with cognitive impairments reported by patients with acute respiratory failure.¹²⁴ Patients did not report experiencing cognitive impairment when interviewed but did have memory impairment when compared with population norms, suggesting that patients may not be aware of their deficits, particularly in the domains of memory and executive function. Assessment of physical function through standardized tests such as the SPPB or 6-minute walk distance may assist in guiding a tailored approach to assess deficits in balance, strength, or endurance. Repeat functional testing over time can be useful to gauge recovery or lack thereof over time.

There has been a growing attention to the assessment of long-term outcomes following COVID-19 in patients both with and without ARDS. An International Task Force sponsored by the American Thoracic Society and the European Respiratory Society has suggested that obtaining pulmonary function testing and chest CT scans as well as a transthoracic echo may be useful in the evaluation of patients with post-COVID ARDS and should be obtained for those with persistent symptoms, but there is no evidence at present to support widespread screening with these tests in all patients recovering from COVID-19 or even COVID-19 ARDS.¹²⁵ In a more recent publication, the International Task Force recommends rehabilitation for those with persistent limitations and suggests pulmonary rehabilitation as a useful framework.¹²⁶ Based on what is known regarding long-term outcomes following ARDS, they also recommend a formal assessment of physical and emotional functioning at 6 to 8 weeks to identify unmet rehabilitation needs.¹²⁶ We anticipate that our understanding of the clinical evaluation of patients with ARDS will deepen as we learn from patients recovering from COVID-19 in the coming months.

SUMMARY

Long-term impairments in physical function, cognitive function, mental health, and other domains are common after ARDS. In the pre-COVID-19 era, long-term outcomes from ARDS became apparent as mortality from ARDS decreased. In the post-COVID-19 era, long-term outcomes will become a significant problem owing to the massive increase in ARDS associated with the pandemic. This lasting effect of the COVID-19 pandemic will persist long after the acute illness diminishes. Providers should be prepared to care for the myriad of problems that are of significant importance to patients and families experiencing ARDS.

CLINICS CARE POINTS

- In most patients with ARDS, lung function improves after discharge and returns to normal; deficits in physical and cognitive function are more common.
- Impairments in many organ systems can be seen post-ARDS, and mental health symptoms may present as functional limitations.
- Evaluation of ARDS survivors in the outpatient setting should include standardized assessments, be comprehensive, and include an evaluation of pre-ARDS function when possible.
- Communication between ICU and outpatient providers will be critical to supporting patients and their families as they transition from the ICU back into their communities.

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