Intensive Care Med (2016) 42:725–738
DOI 10.1007/s00134-016-4321-8

REVIEW

Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers

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Abstract

Outcomes after acute respiratory distress syndrome (ARDS) are similar to those of other survivors of critical illness and largely affect the nerve, muscle, and central nervous system but also include a constellation of varied physical devastations ranging from contractures and frozen joints to tooth loss and cosmesis. Compromised quality of life is related to a spectrum of impairment of physical, social, emotional, and neurocognitive function and to a much lesser extent discrete pulmonary disability. Intensive care unit-acquired weakness (ICUAW) is ubiquitous and includes contributions from both critical illness polyneuropathy and myopathy, and recovery from these lesions may be incomplete at 5 years after ICU discharge. Cognitive impairment in ARDS survivors ranges from 70 to 100 % at hospital discharge, 46 to 80 % at 1 year, and 20 % at 5 years, and mood disorders including depression and post-traumatic stress disorder (PTSD) are also sustained and prevalent. Robust multidisciplinary and longitudinal interventions that improve these outcomes are still uncertain and data in our literature are conflicting. Studies are needed in family members of ARDS survivors to better understand long-term outcomes of the post-ICU family syndrome and to evaluate how it affects patient recovery.

Keywords: Acute respiratory distress syndrome (ARDS), Outcome, ICU acquired weakness, Healthcare utilization, Cost, Neuropsychological

Introduction

The original description of acute respiratory distress syndrome (ARDS) in 1967 made the seminal observation that there was a unifying process of severe lung injury among a disparate grouping of clinical diagnoses [1]. The discovery of this syndrome promoted the characterization of its effect on pulmonary physiology function and quality of life. The observations that muscle wasting and weakness and central nervous system injury were common and consequential outcomes after an episode of ARDS stimulated a new body of work to understand if these sequelae extended to other groups of intensive care unit (ICU) survivors. What began as a study of lung inflammation has extended to a comprehensive understanding of those eloquent organ systems of nerve, muscle, and brain which are damaged during critical illness and largely determine our ability to function, to think, and to feel that our lives are worthwhile.

Outcome measures and morbidity after ARDS

ARDS survivors are a heterogeneous group precisely because they are unified through their predilection for important lung injury from a variety of inciting conditions [1]. They may spend weeks in the ICU and therefore are vulnerable to the cumulative insults of ICU care in the context of catabolism and systemic inflammation.

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Estimates suggest that acute lung injury (ALI)/ARDS affects 190,600 people per year in the USA and results in 74,500 deaths and 3.6 million hospital days [2]. Over 100,000 patients will survive ALI/ARDS each year and, with its attendant morbidity, this represents a public health priority [2].

Pulmonary function

Following the *Lancet* description of ARDS [1], there were many published case series which reported good lung recovery with either mild restrictive or obstructive patterns and a mild to moderate reduction in diffusion capacity [3, 4]. Early reports noted a correlation between severity of lung injury, subsequent lung volume impairment, and quality of life captured as the sickness impact profile [5], short-form 36 (SF-36) [6–8], and quality of well-being [9]. Most early studies reported that the degree of pulmonary dysfunction did not explain the observed functional limitation and that patients reporting compromised physical function did not attribute their poor quality of life to breathing difficulties.

Pulmonary function outcomes may be heterogeneous after an episode of ARDS, but most patients without prior lung disease return to normal or near-normal physiology with a persistent mild reduction in diffusion capacity. Lung function appears to be stable up to 5 years after an initial episode of severe ARDS [10].

There have been several imaging studies to date and the most comprehensive show that fibrotic changes after ARDS occur in the non-dependent lung zones and reflect ventilator-induced lung injury [11–13] (Fig. 1). The severity of scarring, bronchiectasis, and reticular change may be associated with duration of mechanical ventilation and extracorporeal life support (ECLS).

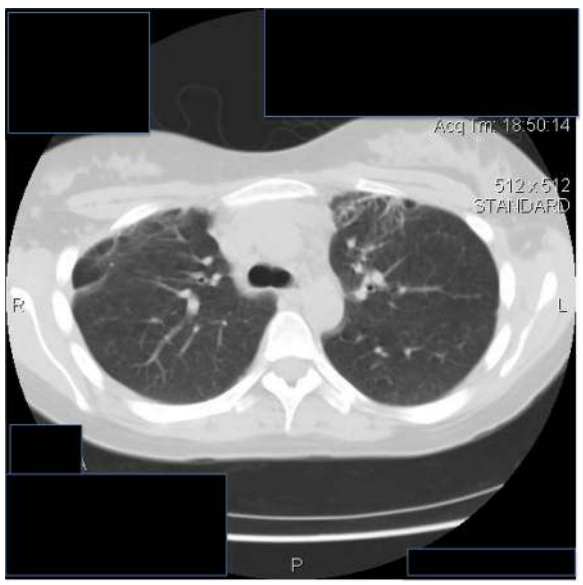

Fig. 1 CT scan of patient 1 year after severe ARDS. This shows the presence of fibrosis in the non-dependent 'baby lung'

Health-related quality of life (HRQL) and functional disability

HRQL is an important patient-centered metric of recovery from critical illness and how its sequelae relates to physical, social, emotional, and neurocognitive function.

Table 1 provides an overview of the emergence of the ARDS HRQL literature and how we have progressed from a sole focus on pulmonary function and its relationship to HRQL to extend our understanding to a spectrum of functional outcome measures that have disclosed ICU-acquired weakness (ICUAW) as a major determinant of poor long-term functional status and subsequent cost and healthcare utilization [5, 6, 8–10, 14–22].

The Toronto ARDS Outcomes study group measured multiple simultaneous outcomes to elucidate the relationships among lung injury and ICU exposures and subsequent pulmonary, exercise, quality of life, and healthcare utilization outcomes to understand the determinants of long-term disability. In-person interview and examination coupled with the 6 min walk test (6MWD) and the SF-36 generic quality of life measure showed that patients had important impairment of exercise capacity in the context of relatively preserved pulmonary function and exhibited marked and persistent muscle wasting and weakness on examination at 1 year [16] and which persisted to 5 years after ICU discharge [10] (Fig. 2).

ICUAW was described initially as a muscle wasting and weakness phenomenon [16] in this cohort of uniformly severe ARDS patients (median lung injury severity score of 3.7/4.0, median 25 days of mechanical ventilation, and 40 % ICU mortality) and the determinants of functional status captured as distance walked in 6 min included female sex, exposure to any systemic corticosteroids, burden of comorbid illness, and the rate of improvement of lung injury during the ICU stay. These same determinants of weakness and disability have been confirmed subsequently by the ICAP cohort and a study led by Fan and coworkers [15] and Needham and investigators in their ALTOS multicenter study of ARDS outcomes from ARDSNet ALTA and EDEN/OMEGA trials [23]. They further expanded the battery of outcome tests to include arm muscle area, muscle strength using the Medical Research Council (MRC) sum score, hand grip strength, maximum inspiratory pressure, and 4 m timed walking speed. The observation that ICUAW is likely ubiquitous after critical illness and contributes to functional disability in all patients and not solely those with ARDS has

Table 1 Physical, functional, and quality of life impairments in ARDS survivors

ARDS cohort	Outcome measures
McHugh et al. [5] *n* = 52	1-year outcome measures: pulmonary function, sickness impact profile Pulmonary function and self-perceived health scores improved the most in the first 3 months after extubation with minor further improvement to 6 months. Patients with the worst lung injury had the poorest pulmonary function. Health scores were not specifically related to pulmonary symptoms
Weinert et al. [18] *n* = 24	Outcome measures: pulmonary function, SF-36, qualitative evaluation using focus group methodology. Concerns with amnesia, depressed mood, avoidance behaviors, prolonged recovery. Reports of significant functional limitation, and important respiratory and psychologic symptoms
Davidson et al. [6] *n* = 73 pairs of ARDS and severity of illness-matched controls	1-year outcome measures: SF-36 and St. George's respiratory questionnaire (SGRQ) Largest decrements in quality of life seen in physical function domains of the SF-36 and pulmonary symptoms and limitations. Of the SGRQ and inferred that there is an ARDS-specific decrement in functional outcome
Schelling et al. [20] *n* = 50	5.5-year outcome measures: pulmonary function, SF-36 Long-term survivors have important pulmonary function impairments and these are associated with decrements in physical quality of life
Angus et al. [14] *n* = 200	1-year outcomes: quality of well-being/QALYs in ARDS compared to 2 control groups (cystic fibrosis patients and general population cohort). The mean QWB scores for the ARDS cohort at 6 and 12 months were significantly lower than patients with cystic fibrosis. The symptom component scores of the QWB accounted for 70 % of the decrement in perfect health and the most common complaints were musculoskeletal and constitutional
Orme et al. [8] *n* = 66	1-year outcome measures: pulmonary function, sickness impact profile, SF-36, Beck depression inventory, Beck anxiety inventory Pulmonary function was abnormal and not related to high tidal volume vs low tidal volume ventilation strategy but correlated with physical function domains of the HRQL measures
Toronto ARDS Outcome study Herridge et al. [10, 16]; Cheung et al. [19] *n* = 109	1-, 2-, and 5-year outcome measures: in person history and physical exam, weight/BMI, pulmonary function, 6MWT with oximetry, SF-36, and healthcare utilization and cost Exercise limitation persisted to 5 years and was related to muscle wasting and weakness. Corticosteroid exposure and severity of lung injury were associated with 6MWD. Pulmonary function was normal to near normal in this younger previously healthy study sample. Disability was persistent and associated with an increase in healthcare utilization and cost to 5 years after ICU discharge
ICAP study Fan et al. [15] *n* = 186	2-year outcome measures: evaluation of extremity, hand grip, respiratory muscle strength (maximum inspiratory pressure), anthropometrics, 6MWD, SF-36 Weakness is common and usually recovers within 12 months and is associated with impairments in physical function and quality of life that continue beyond 24 months
ALTOS Needham et al. [23] *n* = 203	Outcome measures: manual muscle testing, 6MWD, SF-36 PF domain (primary measures); arm muscle area, hand grip strength, maximum inspiratory pressure Important association between mean daily dose of systemic corticosteroid and ICU length of stay and impairments in functional outcome

QALY quality-adjusted life year, *QWB* quality of well-being, *BMI* body mass index, *6MWD* 6 min walk test

continued to gain momentum as has the concern that some patients will have an irreversible decrement in their functional status.

An excellent recent review of ICUAW by Hall and Kress [24] outlined the pathophysiology of ICUAW and also highlighted both nonmodifiable risk factors including multiple organ failure and severity of illness and modifiable factors such as muscle immobilization, hyperglycemia, corticosteroid and neuromuscular blocker use that contribute to this muscle and nerve injury. The following section briefly outlines the muscle and nerve injury relevant to survivors of ARDS and which contributes to their disability.

Critical illness polyneuropathy (CIP)

Bolton and coworkers first reported on CIP in 1984 [25] and described a small sample of critically ill patients who were unable to wean from mechanical ventilation and exhibited a primary axonopathy that manifested as a mixed sensorimotor neuropathy. Since this description, it is purported that CIP is common but determination of its true incidence is complicated by lack of consensus on surveillance, timing and nature of testing, and formal diagnostic criteria. Studies have reported an incidence of 25–36 % [26, 27] in those patients with demonstrable clinical weakness. A systematic review of 1421 critically ill patients reported an incidence of ICUAW of 46 %

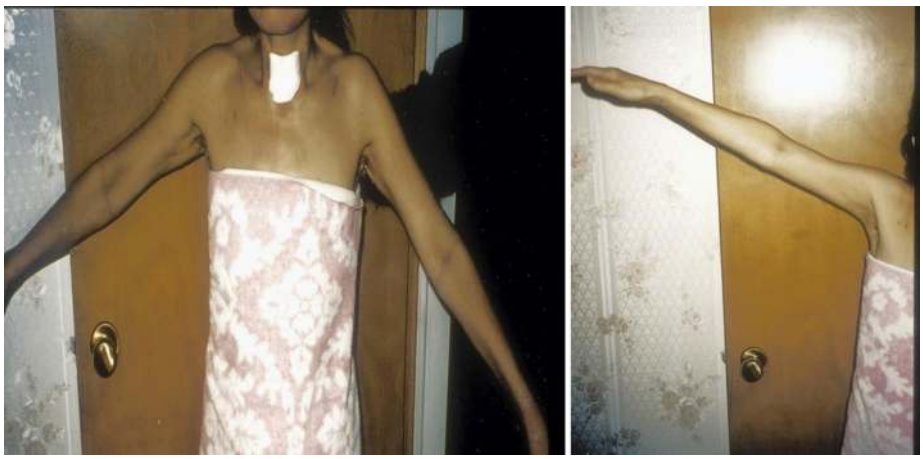

Fig. 2 A 46-year-old woman after severe ARDS secondary to community-acquired pneumonia from the Toronto ARDS Outcomes study (10, 16, 19). These photos show her significant weight loss and muscle wasting and her inability to abduct her arm at a 3-month follow-up visit in her home

(95 % confidence interval 43–49 %) [28] when patients were defined as having ICUAW using diagnostic tests alone (nerve conduction velocities, needle electromyography, direct muscle stimulation, histopathology of muscle or nerve tissue) or a combination of these in the context of muscle weakness, decreased or absent deep tendon reflexes, and/or inability to wean from mechanical ventilation. Weakness can initially be absent but later demonstrate axonal degeneration of the motor neurons with subsequent injury to the sensory neural fibers which coincides with acute and chronic changes of denervation noted on muscle biopsies in affected patients [29].

Critical illness myopathy (CIM)

CIM includes critical illness myopathy, acute quadriplegic myopathy, thick filament myopathy, and necrotizing myopathy and has a variable incidence of 48–96 % in prospective studies that have included muscle biopsy [30]. CIM is typically a non-necrotizing diffuse myopathy with associated fatty degeneration of muscle fibers, fiber atrophy, and fibrosis [31]. This has been described in patients exposed to systemic corticosteroids, paralytics, and also in the context of sepsis and clinical features may be identical to those of CIP where only muscle biopsy facilitates differentiation between these lesions. A case series of muscle biopsies from ARDS survivors showed chronic myopathic changes up to 2 years after the episode of critical illness suggesting that residual muscle injury may correlate with functional disability observed in these patients [32].

Thick filament myopathy shows a selective loss of myosin filaments in association with immobility and paralytic or corticosteroid exposure [33], and it may represent an antecedent to acute necrotizing myopathy. This is distinguished by extensive myonecrosis with vacuolization and phagocytosis of muscle fibers and is linked to multiple organ dysfunction [34]. The functional disabilities reported in ARDS, sepsis, and chronic critical illness have been inferred to be a consequence of ICU-acquired muscle wasting and weakness syndrome [21, 22].

Additional physical morbidities

Many physical sequelae also influence functional outcomes, HRQL, healthcare utilization and cost and have been catalogued in detail in recent ARDS publications [10]. These include tracheal stenosis, heterotopic ossification, contractures, frozen shoulders, hoarseness and voice changes, tooth loss, sensorineural hearing loss, and tinnitus (Fig. 3). Entrapment neuropathy (peroneal and ulnar) has also been noted with a 6 % prevalence at 1-year follow-up in the Toronto ARDS Outcomes study [16]. A 5 % prevalence of large joint heterotopic ossification, the deposition of para-articular ectopic bone, in association with polytrauma, burns, and pancreatitis [35] has been reported in ARDS survivors [16]. The physical devastation of ARDS leaves a lasting legacy and recent 5-year data describe ongoing concerns about cosmesis from scars related to laparotomy, chest tube, central line, arterial line and tracheostomy insertion, burns, striae from volume overload, and facial scars from prolonged non-invasive mask ventilation. Patients reported that cosmetic concerns contributed to emotional outcomes, social isolation, and sexual dysfunction.

Reports of functional limitation extend across cohorts of ARDS to sepsis and prolonged mechanical ventilation and reinforce the ubiquitous nature of these functional consequences of critical illness. In an older patient sample (median age 77), Iwashyna and colleagues [21]

Fig. 3 Photographs taken from the RECOVER program follow-up clinic showing bilateral frozen shoulders (**a**) and a chronic and complicated occipital head wound 1 year after ICU discharge (**b**) Herridge et al. [16]

reported persistent reduction in functional status up to 8 years after sepsis and critical illness and a high rate of new functional limitations in those who had no limitations prior to their episode of sepsis (mean 1.57 new limitations 95 % CI 0.99–2.15). In a report on outcomes in chronically critically ill patients, Unroe and colleagues [22] evaluated the trajectories of care and resource utilization for 126 patients with a median age of 55. At 1 year, only 11 patients (9 % of the cohort) were alive and without functional dependency and total cost for this cohort was US$38.1 million, for an estimated US$3.5 million per independently functioning survivor at 1 year [22].

ARDS and cognitive impairment

Cognitive impairments (prevalence, severity, domains)

A particularly devastating post-ICU morbidity for patients and families is cognitive impairment [36]. Cognitive impairments occur in patients of all ages and across ICU etiologies as over half of all survivors develop cognitive impairments and in some subgroups such as ARDS it may be higher [37]. Cognitive outcome studies conducted to date found that the prevalence of cognitive impairment in ARDS survivors ranges from 70 to 100 % at hospital discharge, 46–80 % at 1 year, 20–47 % at 2 years, and 20 % at 5 years (Table 2) [36]. The cognitive impairments may be severe and are reported to be below the 6th percentile of the normal distribution of cognitive functioning for some ARDS patients [38]. A study in a retrospective ARDS cohort found that cognitive impairment on a brief test of attention and memory was 9 % at 8 years [39] and a second retrospective study found 24 % of ARDS survivors had cognitive impairment after 6 years or more [40]. Cognitive impairment may affect a wide variety of cognitive domains including attention, visual-spatial abilities, declarative memory, and executive function [10, 38, 41–44]. A prospective multicenter study in 174 ARDS patients found that 36 % at 6 months and 25 % at 12 months had significant cognitive impairments in executive function, memory, attention, and working memory and their test performance was consistently below predicated values [42]. Memory assessment in 82 ARDS survivors using the Memory Assessment Clinics Self-Rating Scale showed 20 % scores more than 1 standard deviation below population normative data at 22 months and 15.2 % at 5 years [45, 46].

Although most studies exclude those patients with prior neurocognitive impairments it remains unclear if cognitive dysfunction is due to critical illness and its treatment or related to comorbid conditions. Differences in the prevalence of cognitive impairments across studies are due in part to the type of test used, e.g., the Mini Mental Status Examination has a lower sensitivity to detect impairments compared with comprehensive neuropsychological test batteries [47, 48]. A cross-sectional study that included data from two prospective randomized trials [ARDSNet Long Term Outcomes Study (ALTOS) and Awakening and Breathing Controlled Trial (ABC)] found that the sensitivity of the Mini Mental status Screening Test to detect cognitive impairment in ARDS survivors was 19–37 % which is substantially lower than a comprehensive neuropsychological test battery [47]. A recent study from China study used the Montreal Cognitive

Table 2 Cognitive impairments in ARDS survivors

Study	Study design	Instruments	Significant findings
Hopkins et al. [142] $n = 106$; 62 reached 1-year follow-up	Prospective cohort	Neuropsychological test battery including intelligence, attention, concentration, memory, processing speed, and language	78 % cognitive impairment at 1 year Partial pressure of oxygen at enrollment was associated with cognitive impairment
Rothenhausler et al. [40] $n = 46$	Retrospective cohort 6-year follow-up	Syndrom–Kurz test—assess for attention, concentration, and memory	23.9 % had cognitive impairment Cognitive impairment was associated with lack of employment and reduced quality of life
Kapfhammer et al. [39] $n = 46$ enrolled from 2001 Rothenhausler study	Retrospective cohort 8-year follow-up	Syndrom–Kurz test—assess for attention, concentration, and memory	10 % had mild or moderately severe cognitive impairment No association between PTSD and cognitive impairment
Hopkins et al. [38] $n = 120$	Prospective cohort 2-year follow-up	Comprehensive neuropsychological test battery including intelligence, attention, concentration, memory, processing speed, and language	70 % cognitive impairment at hospital discharge 46 % cognitive impairment at 1 year 47 % cognitive impairment at 2 years Duration of hypoxemia was associated with impaired attention, memory, and executive function at hospital discharge but not 1 or 2 years
Mikkelsen et al. [143] $n = 79$ self-selected via Internet-based support site	Cross-sectional cohort	Battery of neuropsychological tests that assessed orientation, attention, working memory, short-term memory, reasoning, and executive function	56 % had cognitive impairment in at least 1 domain 29 % impaired executive function 24 % impaired memory
Jackson et al. [144] $n = 1$ case report	Case study 8-month and 3.5-year follow-up	Pre-ARDS IQ tests Post-ARDS battery of neuropsychological tests	Decline in intellectual function from the 99th to the 61st percentile after critical illness
Adhikari et al. [45] $n = 82$ from 109 Herridge et al. [16]	Prospective cohort 2-year follow-up	Memory Assessment Clinics Self-rating Scale (MAC-S)	8 % were >2 SD 16 % > 1.5 SD below age-adjusted normative data for memory ability scale Symptoms of depression were associated with memory impairments
Adhikari et al. [46] $n = 74$ from 109 Herridge et al. [16]	Prospective cohort 41-month follow-up	Memory Assessment Clinics Self-rating Scale (MAC-S)	4.3 % were >2 SD 8.7 % > 1.5 SD below age-adjusted normative data for memory ability scale Depressive symptoms and reduced quality of life were associated with memory impairments
Mikkelsen et al. [50] $n = 102$ tested at 12 months	Prospective multicenter cohort Survivors of ARDSNet fluid and catheter treatment trial 12-month follow-up	Battery of neuropsychological tests that assessed orientation, attention, working memory, short-term memory, reasoning, and executive function	55 % cognitive impairment 13 % impaired memory 16 % impaired verbal fluency 49 % impaired executive function Cognitive impairment associated with anxiety and conservative fluid-management strategy
Needham et al. [42] $n = 525$ and 510 enrolled in ALTOS at 6 and 12 months	Longitudinal outcome study NHLBI ARDSNet EDEN trial 6- and 12-month follow-up	Mini Mental State Examination Telephone Version	25 % cognitive impairment at 6 months; 21 % cognitive impairment at 12 months No difference between initial trophic and full feeding for cognitive performance

Table 2 continued

Study	Study design	Instruments	Significant findings
Needham et al. [43] *n* = 174 enrolled and 163 and 149 tested at 6 and 12 months	Prospective longitudinal outcome study NHLBI ARDSNet EDEN trial 6- and 12-month follow-up	Battery of neuropsychological tests that assessed executive function, language, memory, verbal reasoning and concept formation, attention, and working memory	36 % cognitive impairment at 6 months; 25 % cognitive impairment at 12 months There was no difference between initial trophic and full feeding for cognitive impairment
Needham et al. [54] *n* = 130 and 149 tested at 6 and 12 months	Longitudinal outcome study NHLBI ARDSNet SAILS trial 6- and 12-month follow-up	Battery of neuropsychological tests that assessed executive function, language, memory, verbal reasoning and concept formation, attention, and working memory	37 % cognitive impairment at 6 months 29 % cognitive impairment at 12 months No difference between rosuvastatin and placebo for cognitive impairment Assignment to rosuvastatin was associated with worse delayed memory

Assessment (MoCA) test to assess cognitive function and found that the rate of cognitive impairment was 52 % in a mixed group of ICU survivors [49]. The MoCA has not been evaluated in ARDS populations.

The mechanism of cognitive impairments in ARDS is likely multifactorial and current data do not support an association with illness severity scores or older age. A single-center cohort study in ARDS survivors found that a longer duration of hypoxemia was associated with cognitive impairment [38]. This association was also noted in a prospective multicenter study [50]. Hypoxia has been linked to brain atrophy, lateral ventricle enlargement, and concomitant impairments in memory [51]. Duration of hypotension, lower central venous pressure, hyperglycemia, and blood glucose variability have all been associated with cognitive impairment at 12-month follow-up [38, 50, 52]. Cognitive outcome trajectories are unclear. A 2-year outcome study in ARDS survivors found improvement in cognitive function from hospital discharge to 1 year but there was no change in the rate of cognitive impairments at 2 years [38]. There is almost no data pertaining to longitudinal functioning over time periods longer than 2 years and there are likely multiple recovery trajectories of cognitive functioning after ARDS.

There is limited data regarding whether ICU interventions can prevent or improve long-term cognitive impairments in ARDS survivors. Several studies have evaluated outcomes of the Acute Respiratory Distress Syndrome Clinical Trials Network (ARDS Network) of the National Heart, Lung, and Blood Institute (NHLBI) studies. The ARDS Cognitive Outcomes Study (ACOS) that assessed cognitive outcomes of the Fluid and Catheter Treatment Trial (FACTT) study found that cognitive impairment was present in 55 % of patients at 12 months and was associated with enrollment in the conservative fluid management strategy [53]. This study had a number of limitations including a young sample with few comorbidities and substantial loss to follow-up from the FACTT study. ALTOS assessed cognitive outcome in the EDEN trial and found that 36 % at 6 months and 25 % at 12 months had cognitive impairments, but there was no effect of initial trophic versus full enteral feeding on cognitive outcomes at 6- or 12-month outcome [42]. ALTOS was also an ancillary multicenter study to the Statins for Acutely Injured Lungs from Sepsis (SAILS) NHLBI study that assessed mortality and ventilator-free days for rosuvastatin compared to placebo for sepsis-associated ARDS [54]. The study assessed 272 patients from 35 hospitals for delirium and cognitive outcome. The patients in both groups experienced delirium on approximately 32 % of ICU days and overall cognitive impairment occurred in 37 % of ARDS survivors at 6 months and 29 % at 12 months. There was no difference in the rate of overall

Table 3 Highlights of recent cohort studies addressing mood disturbances in ARDS survivors

Study	Highlights
Toronto ARDS cohort Herridge et al. [10]; Cheung et al. [19] $n = 61$	41 and 19 % had moderate-to-severe depressive symptoms at about 2- and 5-year follow-up, respectively Depressive symptoms were associated with worse subjective memory function and not returning to work
ICAP Fan et al. [15] $n = 186$	Over 2-year follow-up, point prevalences of substantial PTSD, depression, and general anxiety symptoms were 22–24, 26–33, and 38–44 % Co-occurrence was frequent, remission infrequent, over 2-year follow-up (assessments at 3, 6, 12, and 24 months) Critical illness-related PTSD symptoms occurred in 33 %; of these, 40 % saw a psychiatrist, and 50 % took a psychiatric medication Onset of depression symptoms occurred in 40 %; prior depression was associated with incident impaired physical function General anxiety symptoms were associated with worse physical functioning and health-related quality of life
ACOS Mikkelsen et al. [50] $n = 122$	Substantial PTSD, depression, and non-specific anxiety symptoms occurred in 39, 36, and 62 %, respectively Risk factors for substantial psychiatric symptoms included lower partial pressure of oxygen
ALTOS Needham et al. [23] $n = 698$	66 % had substantial symptoms in at least 1 domain (24 %, PTSD; 36 %, depression; 42 %, general anxiety), frequent co-occurrence Risk factors included baseline younger age, female sex, unemployment, and alcohol use; and greater in-ICU opioid sedation

ICAP Improving Care of Acute lung injury Patients study, *ACOS* ARDS Cognitive Outcomes Study, *ALTOS* ARDSNet Long-Term Outcomes Study

cognitive impairment for the rosuvastatin group compared to the placebo group at either 6 or 12 months [54].

Mood disturbances in ARDS survivors

Patients with ARDS and other critical illnesses face numerous unforeseen physical and psychic stressors, including hypoxia and respiratory failure, painful life-saving procedures, systemic inflammation, hypothalamic–pituitary–adrenal axis and sympathetic nervous system hyperactivity, acute brain dysfunction that prevents normal processing of events, and complete dependence on others with whom they have difficulty communicating [55, 56]. In addition, survivors often have long recovery periods, with physical weakness, cognitive impairments, and strained families [57, 58]. Thus, it should not be surprising that survivors often have high levels of psychological distress [59–61], especially ARDS survivors [62], whose critical illnesses tend to be prolonged and complex [63] (Table 3).

In the late 1990s, clinical researchers in Europe and the USA began investigating the correlates of diminished health-related quality of life in ARDS survivors [18, 64], including mood disturbances like post-traumatic stress disorder (PTSD), depressive, and non-specific anxiety phenomena [18, 39, 65, 66]. For example, Schelling and colleagues noted that patients who survived ARDS, while grateful to be alive, often had substantial residual angst, with vivid and distorted frightening memories of what they had experienced even after their acute brain dysfunction had resolved [67]. At the last follow-up a median of 8 years after ARDS, the authors noted that, while the prevalence of PTSD declined over time, about one in four survivors still had PTSD; in addition, PTSD was associated with non-specific somatic concerns [39]. In 2007, Davydow and colleagues systematically reviewed the literature on psychiatric morbidity in ARDS survivors [60]; ten articles [18, 38, 39, 64–66, 68–71] describing six unique cohorts were included (total $n = 331$). The median study prevalence of PTSD, depression, and non-specific anxiety symptoms was 28, 28, and 24 %, respectively. Since 2007, clinical researchers have conducted a number of additional relevant studies [16, 43, 45, 46, 50, 72–82]. These include four additional observational cohort studies, with longitudinal psychiatric measures on an additional 978 ARDS survivors: the Toronto study [45, 46, 83], the Improving Care of Acute lung injury Patients (ICAP) study [72, 73, 75–77, 80–82], ACOS [50], and ALTOS [42, 79]. Highlights from these studies are summarized in Table 3. As in the general psychiatric literature, prior psychiatric illness is a potent risk factor for psychiatric morbidity after ARDS. As in the broader critical illness literature, in-ICU sedative doses are, if anything, positively associated with post-ICU psychiatric morbidity, while in-ICU corticosteroids may prevent post-ICU PTSD.

Clinical researchers are investigating a range of in-ICU and post-ICU interventions to prevent long-term psychiatric morbidity in survivors of ARDS and encouraging examples include ICU diaries, written by clinicians and family members *to* critically ill patients [84–87], in-ICU psychological interventions, and post-ICU coping skills training [88, 89].

ICU interventions associated with ARDS outcome

There has been focused interest on improving the common and devastating long-term cognitive dysfunction and ICUAW in survivors of ARDS [10, 15, 23]. Cohort studies demonstrate an independent association with both onset and duration of ICU delirium and long-term cognitive impairment [44, 90, 91] and, while interventions for prevention or treatment are lacking, pharmacologic agents such as haloperidol or atypical antipsychotics may prevent or attenuate ICU delirium and improve long-term cognition of ICU survivors [92, 93]. Non-pharmacologic interventions directed at reduction of sedatives may also improve long-term cognition both by decreasing the duration of mechanical ventilation and reducing the direct toxicity of sedatives themselves [94–96].

Fluid management strategies may be associated with long-term cognitive function. Although limited by small size and loss to follow-up, a post hoc study of select survivors enrolled in the ARDS Network FACTT suggested that conservative fluid management may be associated with long-term neuropsychological impairment [50]. Other data suggest that PTSD may be causally related to high systemic norepinephrine levels [97] and beta-blockers may offset these effects on the basis of observations from a modest study of cardiac surgery patients [98].

Critical care nutrition is an intervention that has received interest since increased caloric intake has been associated with both improved mortality and physical function outcomes in observational cohorts with critical illness [99]. However, a large multicenter randomized controlled trial in ARDS patients (EDEN trial) failed to demonstrate any significant short-term or long-term benefit from targeting caloric intake goals compared to trophic enteral feeds during the first 6 days [100]. Although a single-center phase II study of similar design suggested more discharges home compared to rehab with full calorie feeds [101], 12-month post-ICU follow-up failed to demonstrate improved physical or cognitive function in the larger multicenter EDEN trial [43]. While this dampens enthusiasm for optimizing caloric intake, administering supplemental protein to patients with ARDS early in the acute illness may provide the needed building blocks to maintain muscle [43] and combining this supplementation with mobility, cycling in-bed, or electrical muscle stimulation may further attenuate the catabolism of critical illness [102, 103]. Whether the addition of anabolic agents like oxandrolone [104] will improve long-term physical function remains unknown.

Tight glycemic control may also improve long-term physical function. Maintaining normal or near-normal blood glucose levels in critical illness has been shown to be associated with less critical illness neuropathy [29]. Maintaining euglycemia should be done carefully since hypoglycemia during critical illness may be associated with subsequent symptoms of depression and other mood disorders [77].

Although initially reported to be a risk factor for development of neuromuscular weakness post critical illness [77], the effect of paralytics or neuromuscular blockade on long-term outcomes remains unknown. A large randomized controlled trial showed reduction in mortality and duration of mechanical ventilation with cisatracurium for the initial 48 h of ARDS, without any increase in short-term neuromuscular weakness [105]. However, neuromuscular weakness was assessed using an insensitive measure and long-term weakness was not evaluated.

Healthcare utilization during and after ARDS and critical illness

As a result of the need for invasive monitoring, prolonged mechanical ventilation, and extended ICU and hospital lengths of stay, acute hospitalizations for ARDS patients are costly. In a prospective cohort of 109 ARDS survivors, average total hospital costs were $128,860 (in 2002 Canadian dollars), with the vast majority due to ICU care ($97,810) [10, 16, 19, 106]. Over 75 % of these ICU costs were related to nursing care. These total hospital costs for ARDS patients are consistent with the care of other similarly ill patients such as those with septic shock or acute exacerbations of COPD [106–110].

After the acute care hospitalization, ARDS survivors also utilize a significant amount of healthcare resources. At 2 years after acute hospital discharge, 39 % of ARDS survivors required at least one readmission, and overall 20 % of these patients were readmitted more than once. Post-acute care hospital costs were $28,350 by year 2 (2002 Can$) and totaled $49,572 by year 5 (2009 Can$) [10, 16, 19, 106]. The majority of these post-acute care hospitalization costs were related to subsequent hospitalizations and inpatient rehabilitation. Home care (primarily due to nursing expenses), outpatient pharmacy, and physician expenses accounted for most of the remaining healthcare utilization and costs. Post-discharge costs varied significantly depending on the number of coexisting illnesses. Patients with no more than one coexisting illness incurred less than Can$40,000 by year 5, whereas those with more than two coexisting illnesses incurred costs of over Can$80,000 [10].

Additional insights regarding post-discharge healthcare utilization can also be derived from other critically ill patients such as those who require prolonged mechanical ventilation. During the first year after hospitalization, patients who received prolonged ventilation (defined as $\geq$4 days with tracheostomy placement or ventilation for $\geq$21 days without tracheostomy) spent an average of 74 %

of all days alive either in a hospital, post-acute care facility, or receiving home healthcare [22]. In the subgroup of these patients who survived their acute hospitalization, 67 % of them required at least one repeat hospitalization, with an average of 2.2 readmissions. Overall, 65 % of the readmissions occurred within the first 3 months and nearly half were related to the development of sepsis. The highest mean post-acute care costs were accumulated in those patients receiving long-term acute care (US$91,277), followed by those receiving care in a skilled nursing facility ($31,892), care in an inpatient rehabilitation facility (US$21,244), and home health service care (US$6669). Of interest, annual transportation costs exceeded US$10,000 per patient. Using Medicare claims data linked to a prospective cohort study of older Americans, Prescott and colleagues examined 1-year healthcare utilization in severe sepsis survivors [111]. Overall, 27 % of these patients were readmitted within 30 days of hospital discharge, and a total of 63 % were readmitted at some point during the first year. Of their days alive in the year after discharge, severe sepsis survivors spent a median of 16 days (9.6 %) in an inpatient healthcare facility.

Rehabilitation during and after mechanical ventilation

Bedrest is associated with muscle atrophy, weakness, and increased inflammation [112]. Increasing physical activity during and after critical illness has been a key target for interventions designed to improve physical function. In a landmark study, Bailey and colleagues demonstrated that a progressive activity protocol for mechanically ventilated patients in the ICU was safe and feasible [113]. At ICU discharge, 85 patients survived and 77 % were able to walk. This report led to a paradigm shift in critical care and was followed with brisk clinical and research activity. Morris and colleagues demonstrated the safety and feasibility of truly early activity in the ICU, beginning at admission of medical ICU patients on mechanical ventilation, in a quasi-experimental design using an ICU mobility team. This approach to early activity was not associated with increased complications, but was significantly associated with reductions in ICU and hospital length of stay, and with reduced hospital readmissions and mortality in the first year after discharge [114, 115].

In order to prove that early activity casually improved patient outcomes, Schweickert and colleagues randomized medical ICU patients receiving mechanical ventilation to early physical and occupational therapy versus standard care [116]. More patients in the intervention group achieved independent functional status by hospital discharge (59 vs. 35 %, $p = 0.02$) as well as decreased median duration of delirium (2 vs. 4 days) and mechanical ventilation (3.4 vs. 6.1 days). Early activity protocols with bedside ergometry may improve hospital outcomes (6 min walk distance at hospital discharge) [117], but recent evidence suggests that intensive versus standard early activity with physical therapy does not improve longer-term physical function [118].

There is also great interest in improving longer-term outcomes through the provision of therapy after ICU and hospital discharge. In important foundational work published in 2003, Jones and colleagues demonstrated with a randomized trial that post-ICU provision of a self-help rehabilitation manual was associated with a significant and clinically important decrease in physical impairment at 8 weeks and 6 months [119]. This early success was followed by four subsequent randomized trials of intensive follow-up programs (nurse or therapist-directed) designed to improve functional outcome and quality of life after critical illness, but none has shown benefit [120–123].

The current lack of evidence of outcome benefit of post-ICU programs highlights the importance of reducing immobility and promoting activity beginning early during critical illness. However, recent point prevalence studies have shown that early activity has not been incorporated into practice, as most mechanically ventilated patients may receive no out of bed activity at all [124]. Future work is essential to identify patients with highest potential benefit, to tailor rehabilitation programs' timing and content within the heterogeneous and growing population of survivors of critical illness, and to promote widespread implementation.

Caregiver and family burden in ARDS and critical illness

An emerging priority is the effect of critical illness on the family unit. Relatives may present with an ICU and a post-ICU syndrome from having a critically ill loved one and experiencing difficult stressors [125] concurrent with the need to manage uncertainty and fatigue in the complex ICU environment [126–128]. Families need to adapt while not having their needs fully met [126], lack a complete understanding of what is happening to their loved one [129–131], and suffer with important symptoms of anxiety and depression from day 3 of ICU admission [132]. Although studies have shown that these symptoms improve over time, anxiety, depression, and PTSD may persist up to 1 year in a significant number of relatives [127, 133]. These symptoms tend to decrease after the first year, but no follow up studies are currently available to properly report on long-term outcomes. The impact of caregivers' burden has been evaluated in stroke and elderly care-giving literature, suggesting that those who are challenged in these roles may compromise rehabilitation for survivors [134] or

the ability to sustain care in the home [135, 136]. Fifty-seven percent of ICU survivors who received long-term mechanical ventilation still required the assistance of a family caregiver 1 year after their critical illness [137] and this may have a deleterious impact on caregivers and compromise their health-related quality of life [138]. Ref. [139] concluded that caregivers experience burden due to the challenges of managing complex care in the home, lifestyle disruption, and providing high levels of care [130, 138, 140]. Further studies on caregivers of ARDS survivors are warranted since several questions remain unanswered. For instance, are families able and willing to provide complex care at home? [141]. Identifying specific needs of these caregiving relatives is warranted to establish the framework of a multidisciplinary follow-up program. Also, studies surveying patients and relatives at the same time are needed to understand the dynamic over time of the experience of the patient–relative dyad and to help define the type of support that is needed for each of them [133, 141]. Last, preliminary programs that train and educate family members during the physical and neurocognitive rehabilitation of ARDS survivors are being developed and will need further evaluation.

Summary

ARDS patients are heterogeneous and their disability is similar to other survivors of critical illness whose outcome is dependent on underlying premorbid health status, ICU length of stay, and treatment. The morbidities of ICUAW and neuropsychological dysfunction are prevalent and debilitating and require concerted translational research efforts to elucidate their mechanism and clinical correlates to inform future interventions. The family caregivers have a parallel traumatic life event and need to be integrated into a multidisciplinary and multimodality longitudinal follow-up program.

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Compliance with ethical standards

Conflicts of interest
The authors have nothing to disclose.

Received: 1 March 2016 Accepted: 9 March 2016
Published online: 30 March 2016

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