Lung function and quality of life in survivors of the acute respiratory distress syndrome (ARDS)

M. Elizabeth Wilcox¹, Margaret S. Herridge²

1. University of Toronto, Toronto Western Hospital, Division of Pulmonary and Critical Care Medicine, Toronto, Ontario, Canada
2. University of Toronto, Toronto General Hospital, Division of Pulmonary and Critical Care Medicine, Toronto, Ontario, Canada

Correspondence:
M. Elizabeth Wilcox, Toronto Western Hospital, Division of Pulmonary and Critical Care Medicine, McLaughlin Wing 2-411P, 399, Bathurst Street, Toronto, Ontario, M5T 2S8 Canada. elizabeth.wilcox@utoronto.ca

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Summary

Recent studies have begun to describe the long-term outcomes of acute respiratory distress syndrome (ARDS) survivors. These patients experience a number of physical, mental and psychological morbidities that significantly impair their health-related quality of life (HRQL). The trajectory of pulmonary recovery in survivors of ARDS, as it relates to lung function, structure and health-related quality of life (HRQL), is predictable and often persists years after hospital discharge. True pulmonary parenchymal morbidity is uncommon and when present, persistent restrictive disease is likely related to diaphragmatic weakness with a mild reduction in diffusion capacity (DLCO). Future research should focus on identifying patients at risk for long-term functional limitations and the design of rehabilitation interventions tailored to individual patient needs.

Acute lung injury (ALI)/ARDS is an important public health problem with an estimated 190,600 cases and 74,500 deaths per year in the United States [1,2]. The incidence of lung injury increases with age, peaking at 306 cases per 100,000 person years in those aged 75 to 84 years [2]. Milberg et al. first described declining fatality rates from acute respiratory distress syndrome (ARDS) from 1983 to 1993 [3]. This trend has continued, and it is estimated that mortality rates from ARDS are decreasing at a rate of 1.1% per year [4]. As a result, more people are surviving their critical illness, but often at the cost of surviving with significant morbidity [5–11].

The burden of critical illness includes reduced exercise capacity, cognitive dysfunction, and significant cognitive sequelae such as depression, anxiety disorder, and post-traumatic stress syndromes (PTSS/PTSD) [5,7–10]. Pulmonary dysfunction is typically considered a minor morbidity, as clinical symptoms are less likely to be derived from underlying lung pathology and more likely to be secondary to extrapulmonary respiratory muscle weakness and diaphragmatic atrophy [12].
This article reviews the trajectory of pulmonary recovery in survivors of ALI/ARDS as it relates to lung function, structure and health-related quality of life (HRQL). It will review both disease- and ventilation strategy-specific outcomes.

Health-related quality of life

Health-related quality of life (HRQL) is a self-reported measure of one’s own physical, mental, and social well-being [13,14]. It has become an important gauge of recovery and outcome after critical illness and captures resultant physical, cognitive, emotional, and/or social functioning from the cause of the critical illness, underlying co-morbidities, and therapies. The most commonly used and best-validated tool to measure HRQL is the Short Form-36 (SF-36) health survey. The SF-36 is a questionnaire describing HRQL over eight domains: four of which (physical functioning, role physical, general health, bodily pain) are combined into a physical component score, and four of which (vitality, social functioning, emotion role, mental health index) can be combined into a mental component summary score [15]. Other measures of HRQL include the Sickness Impact Profile (SIP), Nottingham Health Profile (NHP) and EuroQol (EQ-5D) questionnaire. The St George’s Respiratory questionnaire (SGRQ) is also a standardized self-completed assessment. It measures impaired health and perceived well-being specific to chronic airways diseases [16].

Lung function and quality of life

ARDS was first described in 1967 as a syndrome characterized by severe dyspnea, tachypnea, hypoxemia, loss of pulmonary compliance, and diffuse alveolar infiltrates on chest radiograph in association with a spectrum of clinical conditions [17]. Risk factors associated with ARDS in the original publication included multiple trauma, acute pancreatitis, pneumonia, and aspiration of gastric contents. Since its initial description, ARDS has been recognized as a distinct clinical syndrome of severe lung injury characterized by acute onset, PaO₂/FiO₂ ≤ 200 mmHg, diffuse bilateral pulmonary infiltrates and a pulmonary capillary wedge pressure ≤ 18 mmHg in the context of an identifiable risk factor [17].

McHugh et al. were the first to conduct a prospective cohort study of 52 ARDS survivors to evaluate pulmonary function and self-perceived health 1 year after surviving their ICU stay [18]. Pulmonary function and SIP tests were performed at 3, 6 and 12 months. Data from this study suggested that ARDS patients did not attribute their health problems to breathing difficulties. Hugh’s study however had incomplete follow-up (> 75% patients lost to follow-up) and lacked measures of functional outcome to capture their patients’ exercise capacity. Weinert et al. subsequently published contradictory results, when they evaluated 24 survivors of ARDS and found long-term ARDS-associated pulmonary sequelae had previously been underestimated [14]. Thirty-six percent of ARDS survivors in their study reported moderately severe exertional dyspnea and only 25% of patients returned to work [18]. There were large decrements in all domains of the SF-36 in this group compared to a normal population and lower mental health and social functioning scores than a sample of chronically ill cardiac or diabetic patients [14]. Although these results were very striking, it was unclear how reduced quality of life measures related to functional capacity and chronic health care needs. Further, it was unclear whether the extent of pulmonary recovery determined exercise capacity. Pulmonary function testing has been used as the important clinical outcome measure in the majority of studies [14,18–22]. Early results showed only minor changes in pulmonary function and this was inconsistent with the poor exercise capacity observed in these patients [23].

With improved survival, a new body of literature studying the HRQL of ARDS survivors began to emerge (table 1). Initially, reductions in HRQL were thought to be a specific result of ARDS as pronounced reductions in physical functioning and pulmonary disease-specific domains were seen [24]. Further study would determine the concomitant role of musculoskeletal dysfunction in clinical symptoms and functional limitation, suggesting the role for global assessment in determining possible contributors to HRQL decrements [6].

Lung function

Survivors of ARDS may have abnormalities in pulmonary function and exercise endurance, which, although usually mild, can persist up to 5 years following an acute illness (figure 1) [7,10,25–29]. The Toronto ARDS outcomes study group evaluated both exercise capacity (distance walked in 6 minutes...
with continuous oximetry (6MWD) and pulmonary function, and found that patients showed mild restrictive disease and decreased diffusion capacity at 3 months post-discharge [7,10]. By 6 and 12 months, lung volume and spirometric measures were nearly normal with persistently mild reduction in diffusion capacity [7,10]. In observing this patient cohort at 2 years, median lung volumes and spirometry remained within the predicted normal range (Forced vital capacity (FVC) 86% predicted [Interquartile range (IQR) 71–100%] and forced expiration volume in 1 second (FEV1) 87% predicted [IQR 75–99%] [10]. There was no significant change in 6MWD at year 2 as compared to the first 12 months (median 416 metres) [7].

Looking at the physical domains of the SF-36 for HRQL, the cohort scored below that of the normal population although

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<td>Summary of investigations into long-term outcomes of acute respiratory distress syndrome (ARDS) survivors specific to pulmonary function and health-related quality of life (HRQL)</td>
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<tr>
<th>Authors</th>
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<tr>
<td>Heyland et al. [23]</td>
<td>73</td>
<td>3, 6 and 12 months</td>
<td>PFTs, SF-36, St. George’s Respiratory Questionnaire (SGRQ), Zubrod Scale</td>
<td>PFTs correlated with measures of physical function in SF-36. Worst lung function had highest SGRQ and worse HRQL. Most notable improvement over 1st 6 months was the SF-36 domain of physical function.</td>
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<tr>
<td>Herridge et al. [7]</td>
<td>104</td>
<td>3, 6 and 12 months</td>
<td>PFTs, 6MWD, SF-36</td>
<td>80% spirometry within predicted values at 6 months. 6MWD improved over first year post-ICU discharge. All domains of SF-36 improved from 3 to 12 months (physical role and physical functioning domains showed greatest improvement). At 1 year all domains except emotional role were reduced compared to general population.</td>
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<td>Orme et al. [19]</td>
<td>66</td>
<td>1 year</td>
<td>Spirometry, ABG, SF-36, Sickness Impact Profile (SIP), Beck’s Depression Inventory (BDI), Beck’s Anxiety Inventory (BAI)</td>
<td>Reduced pulmonary function in both groups (no significant difference between HTV and LTV). No significant difference in HRQL and ventilation strategy. Reduced scores in all domains of SF-36 except social functioning. Moderate symptoms of anxiety and depression.</td>
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<td>Cheung et al. [10]</td>
<td>86 at 1 year; 78 at 2 years</td>
<td>1 and 2 years</td>
<td>PFTs, 6MWD, SF-36</td>
<td>No improvement in 6MWD between 1st and 2nd year. HRQL domains below normal in all except emotional role and mental health at 1 year. Trend towards improved physical functioning, general health and social function.</td>
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<td>Cooper et al. [24]</td>
<td>20</td>
<td>1–2 years</td>
<td>PFTs, ABGs, 6MWD, Spitzer’s Quality of Life Index, Chronic Respiratory Questionnaire (CRQ)</td>
<td>Reduced diffusing capacity and normal volumes, flows and ABGs (no significant difference between HTV and LTV). Exercise tolerance comparable to patients with chronic respiratory diseases. No between group differences in Spitzer QOL index and comparable CRQ to patients with chronic disease.</td>
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<tr>
<td>Schelling et al. [18]</td>
<td>50</td>
<td>4 and 5.5 years</td>
<td>PFTs, ABG, SF-36</td>
<td>54% survivors had normal lung function at 5.5 years. Impairment of all domains SF-36 (25% reduction in physical functioning and physical role function).</td>
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over time there was a trend towards improvement in absolute median scores for both physical functioning (median 70, 80% predicted) and general health (median 62, 79% predicted) which was not reflected in an improvement in exercise capacity [7,10]. Schelling et al. have demonstrated that as the number of impairments in pulmonary function increase, HRQL scores resultanty decrease [25]. Patients with multiple (> 1) impairments reported lower physical and mental component scores, scoring lower in all categories of the SF-36 except pain and physical or emotional role function ($P > 0.077$) [25]. In addition, they are less likely to return to work [25]. Among the measured pulmonary function parameters, DLCO was the only one that was found to correlate with HRQL scores ($P < 0.031$) [25]. Low tidal volume ventilation strategies have been shown to improve survival in patients with ARDS, but as yet no correlation has been demonstrated between ventilatory strategies and long-term pulmonary function or HRQL. Two studies published concomitantly with the ARDSnet Low Tidal Volumes Trial [30].
showed pulmonary function to be consistently reduced in patients receiving either higher (HTV) or lower tidal volume (LTV) ventilation strategies at one to 2 years follow-up [26,31]. In a study by Cooper et al., 65% of patients had mild pulmonary function impairments. In this twenty patient cohort, FEV1 was reported to be 109 and 111% predicted (P-value 0.74) with FVC measured at 111 and 110% predicted (P-value 0.82) in the HTV (median 10.4 ± 2.5 mL/kg) and LTV (median 7.5 ± 1.1 mL/kg) groups respectively [31]. In a larger cohort study (n = 66), again pulmonary function was reduced in both HTV and LTV groups [26]. Approximately 10% of patients had a mild to moderate reduction in DLCO [26]. Neither study showed a significant difference on any category of the SF-36 between HTV and LTV groups [26]. These studies however were underpowered to be able to ascertain any difference. The majority of survivors have normal or near normal lung function, so it may be very difficult to associate any degree of minor pulmonary disability to a functional QOL measure. However, a study by Heyland et al. [29] did suggest that the physical function domain of the SF-36 correlates with FEV1. In this cohort, 64.9% had a reduction of less than 80% predicted, in measured FEV1 [29]. At 3, 6 and 12 months, FEV1 was 75, 80, 89% predicted respectively, correlating with physical function domain mean scores (PCS mean; normal value 50.5) of 40, 49 and 55 [29]. In evaluating physical performance by the Zubrod scale at 12 months, an increased number of patients were able to be able to perform daily activities [29]. The majority of survivors have normal or near normal lung function, so it may be very difficult to associate any degree of minor pulmonary disability to a functional QOL measure. However, a study by Heyland et al. [29] did suggest that the physical function domain of the SF-36 correlates with FEV1. In this cohort, 64.9% had a reduction of less than 80% predicted, in measured FEV1 [29]. At 3, 6 and 12 months, FEV1 was 75, 80, 89% predicted respectively, correlating with physical function domain mean scores (PCS mean; normal value 50.5) of 40, 49 and 55 [29].

Pulmonary structure

Few studies have evaluated the long-term structural changes and their functional sequelae in survivors of ALI/ARDS. Studies are limited by the lack of a validated radiographic scoring system specific to ALI/ARDS [35–37]. Methods have been adapted from the chronic respiratory disease literature for such diseases as acute/usual interstitial pneumonia [38,39] and non-cystic fibrosis bronchiectasis [40]. Nobauer-Huhmann et al. were first to radiographically evaluate patients at 6 to 10 months follow-up [41]. In this small case series (n = 15), 87% of patients demonstrated localized parenchymal changes in a primarily ventral distribution (P < 0.01) [41]. High-resolution computed tomography (HRCT) findings were found to correlate with both the severity of ALI, defined as a FiO2 peak > 70% (P < 0.05) and a peak pressure over 30 mmHg (P < 0.05), as well as the duration of mechanical ventilation (MV) [41]. Approximately two thirds of patients had either a mild restrictive or obstructive disordered pattern on lung spirometry testing [41]. No data on HRQL was reported. At 3 years follow-up, Desai et al. reported the CT findings of 27 survivors of ARDS [36]. Eighty-five percent of patients were found to have coarse reticular patterning, with an extensive anterior predilection (P < 0.01) [36]. Although reticular changes were the most common finding, ground-glass opacification (GGO) and areas of decreased attenuation were also seen, again predominantly in anterior lung zones (P = 0.01 and P = 0.05, respectively) [36]. Duration of MV was independently associated with the extent of reticular patterning (P = 0.02) [36], suggesting that anterior scarring of lung parenchyma is a result of ventilator-induced injury.

Two independent cohorts have had radiographic follow-up to five years after surviving critical illness: the Toronto ARDS Outcomes cohort [n = 25] [7,42] and Linden et al. [n = 21]. The majority of patients had persistent respiratory symptoms, all however had evidence of radiographic abnormality to some degree [42]. These findings were typically minor, such as nondependent areas of pulmonary fibrosis (96% of patients) [42]. Greater than one third of patients, in addition to minor abnormalities, had significant bronchiectasis and/or de novo pulmonary fibrosis [42]. HRCT findings were associated with dyspnea, sputum production and reduced spirometry at this stage of illness [42]. However, no clear predictors for persistent pulmonary symptoms and persistent lung injury were identified [42]. In Linden’s cohort, patients required extracorporeal rescue therapy (ECMO) due to the severity of their ARDS [43]. At follow-up, the most common finding (76%) was a reticular pattern of parenchymal distortion likely representing of interstitial fibrosis [43]. The total extent of pathological parenchyma was limited in distribution, with a mean involvement of 10% of lung zones (range 0-35%) [43]. In this case series, no significant difference in ventrodorsal distribution was observed [43]. The length of time on ECMO was found to correlate with the degree of HRCT changes suggestive of fibrosis (P < 0.01) [43]. Mean values of all lung spirometry measures were within lower normal, although increased ECMO dependence was associated with reduced TLC (P < 0.05). The mean scores on the SGRQ were higher than normal values in all domains, indicating subjective respiratory problems impacting daily life [43]. As this instrument was validated in those with known structural lung disease, the domains of the SGRQ are very specific in terms of implicating the lungs causally in decrements of HRQL [16].
When survivors of critical illness report dyspnea, although it was initially inferred that they had pulmonary specific issues, their symptoms are most likely from resultant diaphragmatic dysfunction and therefore the SGRQ is insensitive in this patient population.

The use of HRCT in tracking pulmonary sequelae is likely limited in a comprehensive approach to long-term follow-up in survivors of ALI/ARDS. Follow-up studies in larger cohorts for longer duration may allow subgroups of patients with significant respiratory symptoms to identify themselves as requiring further investigation.

**Musculoskeletal causes of weakness, dyspnea and fatigue**

Subjective respiratory symptoms such as dyspnea and exercise tolerance are often intimately tied with overall musculoskeletal (MSK) function, not just with pulmonary reserve. A brief overview of MSK outcomes in ARDS survivors would thus be useful in our understanding of longer-term respiratory outcomes.

The Toronto ARDS Outcomes study observed that patients on average lost 18% of their body weight while in the ICU [7]. ARDS survivors were found to have persistent and profound muscle weakness and wasting and at 1 year could only achieve 66% of their predicted exercise capacity [7]. Disability in function was reflected in low SF-36 scores in both physical function and role-physical domains [7]. The precise determinants of observed wasting and weakness were unclear in this study but impaired exercise capacity was related to co-morbid disease burden, exposure to systemic corticosteroids during ICU stay, and rapidity of resolution of lung injury and its associated multi-organ dysfunction [7].

A key contributor to post-ICU observed weakness is critical illness polyneuropathy (CIPN) and/or myopathy. The reported prevalence rate of CIPN is 70% in survivor populations with sepsis, multiple organ dysfunction, and ARDS [44]. The precise etiology of this complex process of primary motor and sensory axonal degeneration is unknown, but may represent ischemic nerve injury secondary to a disturbance in the microcirculation [45,46]. CIPN may persist for years after ICU discharge and be one of the major contributors to long-term physical limitations in function [47].

The incidence of an ICU-acquired myopathy and its impact on disability and prolonged rehabilitation in the post-ICU period is also uncertain. A recent report described a 25% incidence of ICU-acquired paresis in patients remaining on the mechanical ventilator for greater than 7 days [48]. Myopathic changes have been documented both in the presence and the absence of corticosteroids and neuromuscular blockade use [49,50]. Four patients from the Toronto ARDS Outcomes study underwent open muscle biopsy at a median time of 1-year post-ICU discharge and all patients had histopathological evidence of a chronic myopathic process [51]. Muscle injury may occur very early in the course of critical illness. A recent study demonstrated that muscle atrophy occurs within hours of the onset of mechanical ventilation [12]. These investigators evaluated biopsy samples taken from diaphragms of organ donors (n = 14) and compared them to intraoperative samples (n = 8) ventilated for 18 to 69 hours and 2–3 hours respectively [12]. Specimens from the organ donor population were shown to be atrophied and had significantly decreased cross sectional areas of both slow-twitch and fast-twitch fibers, in the absence of inflammatory cell infiltrate [12]. Muscle injury, exemplified by diaphragmatic atrophy, is likely multifactorial and may be an important determinant of long-term respiratory function impairment.

**Special case: severe acute respiratory distress syndrome**

SARS presented an exceptional opportunity to use modern methods to study long-term outcomes in a narrowly defined cohort who suffered ARDS. Emerging on the global stage in 2003, a total of 8096 cases with 774 deaths have been reported by the World Health Organization (WHO) [52]. SARS cohorts have been studied at variable times of long-term follow-up; 2-year follow-up data has most recently become available [53]. What is different in the SARS cohort, in comparison to a group of ALI/ARDS patients or generally critically ill, is that the majority of patients did not require advanced support such as mechanical ventilation [54]. ICU length of stay was on average 10 days and 62% of patients received systemic corticosteroids [54]. This presents a unique opportunity to study the contributions of extrapulmonary injury on physical morbidity such as myopathy from viral infection and/or other factors related to the morbidity of critical illness.

The first information published on survivors of SARS was from Hsu et al. Their 52-patient cohort with a mean age 42.5 years, were seen at 1-month follow-up. Thirty-seven percent of patients complained of significant clinical symptoms at this time [55]. Pulmonary function tests had variable results but were found to correlate with radiographic abnormality [55]. All symptomatic patients had changes on HRCT; 36.8% had GGO and 63.2% had fibrosis in addition to GGO. Only 16% of patients had a zonal predominance on imaging [55]. HRCT scores correlated with dyspnea scores (r = 0.78, P < 0.01) and reduced DLCO (r = 0.0923, P < 0.001). Patients with GGO and fibrosis had significantly lower spirometry (FEV1: 64.7 ± 87.1%, predicted, FVC 62.3 ± 81.9% predicted and DLCO 53 ± 73% predicted) when compared to those with GGO only [55].

These results are supplemented by those recently published by Ngai et al., in which 97 patients were seen at 3, 6, 12 and 24 months [53]. Pulmonary function was within low normal limits, and remained relatively unchanged over time [55]. Mean 6MWD increased significantly from 3 to 6 months (439 metres to 460.1 metres) and then stayed steady [53]. Similar results for functional recovery were seen in the
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110-patient cohort of Hui et al. [56]. In correlating functional outcomes and HRQL, a positive correlation was found between lung function (FVC (r = 0.363, P < 0.01) and FEV1 (r = 0.3, P < 0.05)) and the domain of physical functioning [56]. In addition, 6MWD was found to correlate with all SF-36 domains except emotional role and mental health [53]. No significant association has been found between parameters of pulmonary function and BMI, steroid use, length of stay, admission to ICU, baseline LDH, peak LDH, baseline CRP or peak CRP [53]. Decrements in all SF-36 domains persist at 24 months, except in the domains of role emotional and mental health [53].

Both Ong et al. [n = 94] and Tansey et al. [n = 107] have followed SARS survivors out to 1 year. Again, these cohorts were predominantly young, health care workers with little co-morbidity prior to critical illness [54]. The median length of stay in the ICU was 10 days (IQR 7–19 days) and less than 10% of patients required mechanical ventilation [54]. In the Ong cohort, the group means for FEV, FVC, DLCO were within normal limits (> 80% predicted) at 1 year [57]. Only 35 patients (37%) had impairments in a pulmonary function parameter [57]. SGRQ scores (total, symptoms, activity and impacts) were worse than population norms but the decrements were unlikely related to specific intrinsic pulmonary dysfunction but instead reflected weakness secondary to muscle wasting and critical illness deconditioning [57]. Reported symptoms of fatigue, difficulty sleeping, and dyspnea were reported by 45%, 60%, 44% and 45% of patients, respectively in the Tansey group [54]. Only 13% of survivors of SARS were asymptomatic at 1 year [54]. Chest radiographs were normal or returned to pre-SARS baseline in all patients by 1 year, with the exception of one long-stay ICU survivor whose chest radiograph showed small lung volumes, fibrosis, and GGO beyond 1 year [54]. SF-36 domains were typically 0.3–1.0 SD below normal [54]. SGRQ total and domain scores also were indicative of decreased HRQL, a finding that was persistent at 1 year [54].

Significant morbidity prevents survivors of critical illness from returning to work. At 3 months, approximately 36% of survivors had not returned to previous levels of employment although there was a trend towards improvement over time, as 78% of patients had returned to work by 24 months [54,57]. Of all survivors of SARS in a Toronto cohort, 17% had not returned to work, while another 9% had not returned to their previous level of employment prior to their critical illness at 1 year [48]. Significantly more non-health care workers than health care workers returned to the workplace (70.4 vs. 92.9% respectively) [54]. This is more likely to be related to psychological and cognitive consequences of SARS than physical morbidity. Persistence of symptoms and perception of physical limitations were reflected in QOL measures [53–57]. Reductions in self-reported physical health may be reflective of subtle degrees of respiratory muscle weakness secondary to viral-myositis (at initial presentation or chronic), muscle wasting and deconditioning due to bed rest, steroid-induced myopathy and/or CIPN, suggesting again the extrapulmonary contribution to persistent symptoms of shortness of breath and fatigue in survivors of ALI.

Rehabilitation and follow-up clinic

After surviving critical illness and the inpatient setting, patients are discharged with persistent physical morbidity [11,58–65]. Activities related to mobility, autonomy, and quality of life remain restricted at 24 months. In light of the recent research suggesting that critically ill patients have both initial and persistent debilitating limitations in physical function, early intervention strategies to prevent or ameliorate physical morbidity may prove important for treating survivors of critical illness. This is because impaired HRQL has little to do with pulmonary function per se, as symptoms are a result of impaired recovery of strength, immobilization, critically illness polyneuropathy, and entrapment neuropathies. A study by Cuthbertson et al. evaluated the effect of a nurse-led intensive care follow-up program on the HRQL of ARDS survivors (n = 192) and found no impact on patient SF-36 physical or mental component scores at 12 months post-discharge. This program was significantly more costly than standard care [66]. Recently, Iwashyna et al. published the results of a study looking at new functional restrictions following admission for sepsis, reporting 1.57 new deficits per admission, and an ongoing risk of further limitations at a rate of 0.51 per year [67]. Declines in physical function persisted at 8 years [67]. Further studies are needed to identify patients and their family members at risk for long-term sequelae and tailor therapeutic interventions in a timely and targeted manner.

Future research

Our understanding of ALI/ARDS and its long-term consequences has increased substantially over the past few decades, and with it, we have seen advances in supportive care for survivors of critical illness. Many improvements, however, remain to be made. High priority research areas include exploring the mechanisms of muscle and nerve injury, reliably cataloguing the rehabilitative needs of patients across their illness trajectory and obtaining direct utility measurements of HRQL to improve cost-effectiveness analyses. For now, the low HRQL experienced in the ALI/ARDS survivor population highlights immediate opportunities to improve patient care. Multidisciplinary rehabilitation and behavioral therapy has been successful in improving HRQL in other chronic diseases and may prove beneficial in ARDS. Descriptive data from longitudinal cohort studies may help to inform clinicians of late pulmonary prognosis after severe lung injury.

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