# What's Next After ARDS: Long-Term Outcomes

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**ARDS is a life-threatening organ failure due to several pulmonary and extrapulmonary injuries with an incidence between 5 and 60 cases/100,000 persons/y. Patients with ARDS have non-cardiogenic pulmonary edema and dyspnea often requiring invasive mechanical ventilation and intensive care admission. Although the short-term mortality rate has significantly decreased in the last decade, mainly due to the widespread application of lung-protective ventilation and better general support, long-term outcomes are still unsatisfactory. Besides simply evaluating the outcome at hospital discharge, several recent studies have assessed the health-related quality of life, neuropsychological disability, radiological findings, and pulmonary dysfunction up to 5 y. This paper reviews the literature regarding the long-term outcomes in patients with ARDS.** *Key words: ARDS; long-term outcomes; health-related quality of life; neuropsychological disability; pulmonary function; lung imaging.* [Respir Care 2016;61(5):689–699. © 2016 Daedalus Enterprises]

## Introduction

ARDS is an acute respiratory failure with bilateral opacities, pulmonary edema not fully explained by cardiac failure or fluid overload, and hypoxemia with $P_{aO_2}/F_{IO_2} < 300$ with $\geq 5$ cm $H_2O$ PEEP.[1] It can arise in response to different pathological insults, such as sepsis, trauma, pneumonia, massive transfusion, and surgical conditions.[2] Due to hypoxemia, patients with ARDS often require a variety of supportive care, such as protective mechanical ventilation, inhaled nitric oxide, ventilation in prone position, high-frequency oscillatory ventilation, or extracorporeal membrane oxygenation (ECMO).[3-5]

Thanks to these strategies[4,6-8] and improvements in ICU supportive care,[9] several studies have reported a decrease in the short-term mortality rate.[10-12] However, patients who survive ARDS remain at risk for mortality and may have persistent morbidity.[13-18] This article will review the long-term outcomes after ARDS, focusing on mortality, health-related quality of life (HRQOL), neuropsychological disability, radiological findings, and pulmonary dysfunction (Table 1).

## Long-Term Mortality

Hospital mortality has been reported to decrease from 50% in the years 1988–1992 to 33% between 2006 and 2010.[17] Despite this improvement, however, data indicate broad differences between survival at hospital discharge

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The authors have disclosed no conflicts of interest.

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DOI: 10.4187/respcare.04644

Table 1. Clinical Studies Investigating the Long-Term Outcomes After ARDS

| First Author (Year) | Outcomes | Timing | Main Results |
|---|---|---|---|
| Studies investigating the long-term outcomes within 1 y after ARDS | | | |
| Weinert (1997)[14] | HRQOL: SF-36 | 6–41 mo (median 15 mo) after diagnosis | HRQOL: all domains were below those of general population with similar physical difficulties to out-patients with chronic medical condition, but more deficits in social and mental domains |
| Desai (1999)[19] | Radiological findings | 110–267 d (mean 196.2 d) | CT scan: reticular pattern with anterior distribution was the most frequent abnormality (85% of subjects), related to duration of ventilation |
| Angus (2001)[16] | Survival | 6–12 mo | 55.7 ± 3.7% at 6 with no change at 12 mo |
| | Neuropsychological disability | | Depression, anxiety, or insomnia in 46% of subjects; cognitive impairment in 21% |
| Nöbauer-Huhmann (2001)[20] | Pulmonary function | 6–10 mo | PFT: mild restrictive pattern (33% of subjects), mild obstructive pattern (33% of subjects) |
| | Radiological findings | | CT scan: lung fibrosis in 87% of subjects; lesions were more represented in non-dependent lung regions |
| Herridge (2003)[21] | Survival | 3, 6, and 12 mo after ICU discharge | 1-y mortality 11% |
| | HRQOL: SF-36 | | HRQOL: all domains improved from 3 to 12 mo, but all were below those of control population |
| | Pulmonary function | | PFT: spirometric measures were within 80% of predicted values |
| | Radiological findings | | Chest radiograph: normal in 80% of subjects, minor changes in 20% of subjects |
| Kim (2004)[22] | Pulmonary function | 6 mo | $D_{LCO}$ impairment (59.2% of subjects) |
| | Radiological findings | | CT scan: the extent of lung lesions was 15.3% of total lung volume; lesions were more extensive in pulmonary than in extrapulmonary ARDS |
| Heyland (2005)[23] | HRQOL: SF-36 | 3, 6, and 12 mo | HRQOL: all domains were below those of control population, with an improvement over first 12 mo in physical function; PFT were correlated with physical function in SF-36 at 1 y |
| | Pulmonary function | | PFT: mild abnormalities of $FEV_1$ (64.4% of subjects) and of FVC (49.2% of subjects) stable over time |
| Mikkelsen (2011)[24] | Neuropsychological disability | 12 mo post-H discharge | Psychiatric impairment: depression 36%, PTSD 39%, anxiety 62%; cognitive impairment in 55% of survivors |
| Chiumello (2012)[25] | Survival | 12 mo | 1-y survival: 40% |
| | HRQOL: SF-36 | | HRQOL: all domains were similar to those of healthy population |
| | Pulmonary function | | PFT: within normal or near normal values |
| | Radiological findings | | Quantitative CT analysis was identical to healthy subjects |
| Masclans (2011)[26] | Pulmonary function | 6 mo | PFT: abnormality in 67% of subjects, restrictive pattern in 58% of subjects; $D_{LCO}$ mild-moderate impairment; 6MWT; 60–65% of predicted distance |
| | Radiological findings | | CT scan: the extent of lung lesion was <25% of total lung volume in non-dependent regions |

(*continued*)

Table 1. Continued

| First Author (Year) | Outcomes | Timing | Main Results |
|---|---|---|---|
| Luyt (2012)[27] | HRQOL: SF-36 | 1 y after ICU discharge in H1N1 influenza subjects treated with or without ECMO | HRQOL: all domains were below those of control population in both groups |
| | Neuropsychological disability | | Anxiety (50–56%), depression (28%), and PTSD (41–44%) |
| | Pulmonary function | | PFT: near normal in both groups; $D_{LCO}$ impairment in in both groups |
| | Radiological findings | | CT scan: minor abnormal findings in both groups |
| Wang (2014)[28] | Survival | 1 y | 1-y mortality: 41%, higher than H mortality |
| Studies investigating the long-term outcomes between 1 and 2 y after ARDS | | | |
| Davidson (1999)[15] | Survival | 8–1,503 d (median 753 d) | ARDS does not increase the risk of death in sepsis or trauma subjects survived to H discharge |
| Cooper (1999)[29] | Pulmonary function | 1–2 y | PFT: obstructive pattern (30% of subjects), restrictive pattern (15% of subjects); $D_{LCO}$ impairment (50% of subjects); protective ventilation did not improve pulmonary function outcome |
| Hopkins (2005)[30] | HRQOL: SF-36 | 1–2 y after H discharge | HRQOL: decreased SF-36 score at 1 y with an improvement in physical domain but no additional improvement at 2 y and with mental health domain at 2 y similar to the H discharge level |
| | Neuropsychological disability | | Anxiety at 1–2 y 24% and 23%; neurocognitive impairment at 1–2 y 46% and 47% |
| Cheung (2006)[31] | Survival | 1–2 y | Survival at 2 y: 85% |
| | HRQOL: SF-36 | | HRQOL: all domains below those of control population |
| | Pulmonary function | | PFT: no significant changes between 1 and 2 y and within the normal range; 6MWT: lower than normal at 2 y |
| Deja (2006)[32] | HRQOL: SF-36 | >1 y post-ICU discharge | HRQOL: all domains were below those of control population |
| | Neuropsychological disability | | 29% of subjects were at increased risk of PTSD and had higher impairment in mental health domains of SF-36 |
| Linden (2009)[33] | HRQOL: respiratory questionnaire | ≥1 y in ECMO-treated ARDS subjects | HRQOL: reduction due to subjective respiratory problems compared with normal values |
| | Pulmonary function | | PFT: mild obstructive pattern (43% of subjects); $D_{LCO}$ impairment in 65% of subjects; exercise test: below normal values in 43% of subjects |
| | Radiological findings | | CT scan: the extent of lung lesion was 10% of total lung volume; reticular pattern was present in 76% of subjects |
| Ngai (2010)[34] | Pulmonary function | 3, 6, 12, 18, and 24 mo | $D_{LCO}$ impairment at 2 y |

(*continued*)

Table 1. Continued

| First Author (Year) | Outcomes | Timing | Main Results |
|---|---|---|---|
| Schmidt (2013)[35] | Survival | 11–28 mo (median 17 mo) after ICU discharge in ECMO-treated ARDS subjects | Survival: 60% |
| | HRQOL: SF-36 | | HRQOL: physical domains were lower, psychological domains were similar compared with those of control population |
| | Neuropsychological disability | | Anxiety 34%, depression 25%, risk for PTSD 16% |
| Studies investigating the long-term outcomes >2 y after ARDS | | | |
| Schelling (1998)[36] | HRQOL: SF-36 | 5 y after ICU discharge | HRQOL: median reduction 21.3% in all domains |
| | Neuropsychological disability | | 28% of survivors had PTSD |
| Schelling (2000)[13] | HRQOL: SF-36 | 5.5 y (median) after ICU discharge | HRQOL: impairment in all domains: 25% reduction physical function and physical role function, 17.5% impairment in general health |
| Kapfhammer (2004)[37] | Neuropsychological disability | 8 y (range 3–13) after ICU discharge | 43.5% of survivors had PTSD at H discharge, 23.9% at 8 y; PTSD was associated with impairment in general health, social function, and mental health of SF-36 |
| Herridge (2011)[38] | Survival | 1, 2, 3, 4, and 5 y after ICU discharge | Survival from 1 to 5 y: 86, 85, 90, 82, and 86% |
| | HRQOL: SF-36 | | HRQOL: all domains below those of control population; 6MWT correlated with physical domain of SF-36 |
| | Pulmonary function | | PFT was near normal at 5 y; 6MWT: normal in 39% of subjects |
| | Radiological findings | | CT scan: minor, non-dependent lung fibrotic changes |
| Khandelwal (2011)[39] | Survival | 3 y | Survival of patients treated with rescue therapies was 65% at 3 y after H discharge, comparable with survival of conventionally treated subjects |
| Wilcox (2013)[40] | Pulmonary function | 5 y | PFT: near normal; $D_{LCO}$ impairment; 6MWT: mild-moderate impairment |
| | Radiological findings | | CT scan: the extent of lung lesion was 10% of total lung volume; mainly reticular pattern in non-dependent lung regions |

Shown are a selection of clinical studies from the literature over the last 20 y. Their main results are summarized according to the investigated items of interest. Studies are presented according to follow-up period.
HRQOL = health-related quality of life
SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey, Standard Form
CT = computed tomography
PFT = pulmonary function test
$D_{LCO}$ = diffusing capacity of the lungs for carbon monoxide
H = hospital
PTSD = posttraumatic stress disorder
ECMO = extracorporeal membrane oxygenation
6MWT = 6-min walk test

and long-term follow-up characterized by a high mortality rate.[18]

To quantify this survival gap, Wang et al[28] compared short- and long-term mortality in subjects with ARDS. Hospital mortality was significantly lower (24%) than 1-y mortality after hospital discharge (41%) regardless of the etiology of ARDS.[28] Both the severity and the presence of ARDS did not increase the risk of mortality during a median follow-up time of 2 y in sepsis or trauma subjects with ARDS compared with equally ill subjects without ARDS (sepsis-ARDS subjects [59%] vs sepsis controls [72%]; trauma-ARDS subjects [12%] vs trauma controls

[13%]).[15] Age and comorbidities, in addition to the sepsis, strongly influenced the late mortality.

The Canadian Critical Care Trials Group, following ARDS survivors up to 5 y from ICU discharge, found a 1-y mortality rate of 11%.[38] Moreover, 76% of survivors at 1 y were still alive at 5 y. The better reported outcomes compared with other studies could be due to the therapeutic effect of the relationship between the study team, the subjects and their caregiver helped to ensure an excellent follow-up.

A 3-y survival probability post-hospital discharge of 85% was also found by Khandelwal et al[39] It was comparable between subjects treated with rescue therapies (prone position ventilation or inhalation of nitric oxide) and with standard treatment, although the former had higher in-hospital mortality, 47% versus 32%.

To investigate the influence of rescue therapies on 1-y mortality, Chiumello et al[25] compared ARDS subjects ventilated in prone or supine position without finding any difference, although they reported an overall high mortality rate (60%). They could not establish whether this high rate was mainly due to respiratory function impairment or extrapulmonary complications.

Still taking into account rescue therapies, little is known about the long-term survival of ARDS patients treated with ECMO. A follow-up study reported only the 6-month mortality rate, which was 40% and comparable with that of the ECMO arm of the CESAR trial.[35] Older age, comorbidity status, higher pre-ECMO airway plateau pressure, lower PEEP level, the absence of prone positioning, and the number of days receiving mechanical ventilation before ECMO were identified as factors independently associated with mortality.

Long-term mortality in patients with ARDS can be significantly higher than expected and mainly depends on non-modifiable factors, including previous comorbidities and age, but not on severity of acute illness, which, instead, is a strong predictor of hospital mortality. In other words, the treatment of ARDS does not resolve the underlying diseases, and the survivors mainly die from their underlying or original diseases.

### Health-Related Quality of Life

Although the long-term HRQOL of ARDS survivors has gained more attention, it is hard to define precisely because of the small samples of subjects enrolled in the studies, the large losses during follow-up, and the different scales used to quantify it.[41] The most common scale used to measure the HRQOL of survivors of critical illness is the Medical Outcomes Study 36-Item Short Form Health Survey, Standard Form (SF-36).[42] This questionnaire consists of 36 items, which measure both physical health (physical function, physical role function, bodily pain, and general health) and mental health (vitality, social function, emotional function, and mental health). However, it has not been validated specifically for ARDS patients. On the contrary, several HRQOL scales have been used in ARDS patients, making a quantitative synthesis of different studies results difficult. In fact, Dowdy et al,[41] who performed a meta-analysis to summarize the HRQOL of ARDS survivors, could use only 5 of 13 selected studies due to the different scales used to measure HRQOL. Significant HRQOL decrements compared with the general population were found, especially with higher decrements in the physical domains compared with the mental domains 6 months after ICU discharge. Although a significant improvement in physical role and physical functioning during the first year of follow-up was demonstrated by the Toronto ARDS Outcomes Study Group,[21] the scores for all domains, except emotional role, remained below those of an age- and sex-matched control population.

Interestingly, from hospital discharge up to 2 y after, ARDS survivors can present 3 distinct evolving patterns for SF-36 domains: (1) improvements in physical, social functioning, and vitality domains during the first year with no additional improvement at 2 y; (2) small changes in emotional role, pain, and general health domains; and (3) a slight improvement in mental status, with a subsequent return to hospital discharge level at 2 y.[30] At 5 y after discharge from ICU, ARDS survivors have impairment in all SF-36 health dimensions, with reductions of 25% in physical function and physical role function, 17.5% in general health, and a smaller but statistically significant decrease in psychosocial functioning compared with the general population.[13] Similarly, at 5 y, Herridge et al[38] reported that even relatively young subjects with few coexisting illnesses who survived ARDS had a persistently reduced physical HRQOL in terms of SF-36 score, although those who were younger than 52 y showed a significant improvement in the physical component score from discharge to 5 y, when compared with subjects older than 52 y.

To clarify the specific contribution of ARDS to long-term outcomes, several studies have compared HRQOL in ARDS survivors versus ICU survivors without ARDS, without finding any differences in HRQOL beyond 6 months after discharge.[43-45] However, we know that there is a correlation between pulmonary dysfunction and long-term HRQOL, as indicated in several reports.[13,15,16,23]

The severity of the initial acute lung injury/ARDS and the rapidity of its resolution seem to correlate significantly with long-term (1-y) physical function, although the inability to exercise in terms of muscle wasting and weakness has a multifactorial etiology and can be due to extrapulmonary disease.[21] Similarly, ARDS subjects treated with ECMO suffered a loss of HRQOL because of pulmonary sequelae at 1 y after ECMO.[33] However, the re-

duced HRQOL does not seem to be related only to pulmonary dysfunction. The regression model developed by Heyland et al[23] demonstrated that subjects with a high comorbidity score had a lower SF-36 score at 12 months, supporting the conclusion of Garland et al[46] that most of the decline in functional status was attributable to preexisting comorbidities.

The literature in the last decade has shown that ARDS survivors suffer substantial loss of their HRQOL compared with the general population due to their preexisting comorbidities and subsequent pulmonary sequelae. Nevertheless, these results should be interpreted cautiously, considering the heterogeneity of acute lung disease encompassed by the definition of ARDS over the years and by the different baseline characteristics of each enrolled population in terms of age, preexisting pulmonary disease, and comorbidities.

### Neuropsychological Disability

Neuropsychological disability after ARDS includes psychiatric dysfunction and neurocognitive impairment. Psychiatric dysfunction involves posttraumatic stress disorder and depression. In fact, it has been demonstrated that after recovery in the ICU, a higher number of patients reported symptoms, such as anxiety, pain, and nightmares, that can turn into chronic psychiatric disorders and depression. In 1998, Schelling et al[36] found an incidence of posttraumatic stress disorder of 28% in survivors of ALI/ARDS after 5 y. In general, the prevalence of posttraumatic stress disorder changes depending on the time of assessment, and it was found to be higher at ICU discharge. Kapfhammer et al[37] found that 43.5% of long-term survivors of ARDS had posttraumatic stress disorder at the time of hospital discharge, but only 23.9% had posttraumatic stress disorder at 8 y. Subjects with posttraumatic stress disorder had a greater tendency to somatization and anxiety and a major impairment in some dimensions of HRQOL (general health, social function, and mental health) compared with subjects without posttraumatic stress disorder, who, on the contrary, had SF-36 scores within the range for the general population. To assess the influence of posttraumatic stress disorder on HRQOL, Deja et al[32] followed 65 ARDS subjects for >1 y from ICU discharge and showed that subjects with high risk for posttraumatic stress disorder (29% at 1 y) reported an associated impairment in the mental component and mental health domains of the SF-36 compared with low-risk subjects for posttraumatic stress disorder who were similar to healthy controls in the mental component. A significant positive correlation was also found between the number of traumatic memories and the experience of anxiety with the severity of posttraumatic stress disorder, whereas social support from family or caregivers during ICU stay and rehabilitation was demonstrated to prevent posttraumatic stress disorder symptoms. The duration of sedation, mechanical ventilation, and ICU stay are considered as predictors of later symptoms of posttraumatic stress disorder.[14,37,47]

The incidence of depression is much higher than posttraumatic stress disorder. Angus et al[16] found that 50% of ARDS survivors were depressed 1 y after treatment, and according to the Toronto ARDS outcomes group,[31] 58% of ARDS survivors suffered symptoms of depression 2 y after discharge. The social impact of depression is substantial; in fact, subjects with moderate to severe symptoms have more difficulties in returning to work than those with mild to moderate symptoms.[48]

The etiology of ARDS-associated psychological disorders is unknown.[49,50] However, the severity of ARDS, defined as requiring extracorporeal lung assist, does not seem to influence the psychological impairment at 1 y in terms of symptoms of anxiety, depression, and risk of posttraumatic stress disorder.[27] Most of the literature concludes that physiopathological alterations related to the critical illness (hypoxemia, activation of the hypothalamic-pituitary axis, elevated cytokines, organ dysfunction) and medications (epinephrine or norepinephrine, sedatives) contribute all together to the long-term psychological disorders. Little is also known about the pathophysiology of the neurocognitive impairment after ARDS. However, ARDS survivors can show long-term cognitive dysfunction in terms of attention, memory, mental processing speed, and executive function.[24,51] In 1999, Hopkins et al[51] found marked cognitive impairment in all 55 ARDS subjects within their cohort at hospital discharge; at 2 y, 47% of survivors showed persistent neurocognitive impairment with no improvement from 1 to 2 y. More recently, Mikkelsen et al[24] confirmed that long-term cognitive impairment, especially in executive dysfunction, was present in 55% of survivors at 1 y. Cognitive impairment was significantly associated with lower oxygenation at 1 y and with psychiatric disorder, particularly anxiety. However, HRQOL was low in the overall population but significantly worse in the subgroup of survivors with psychiatric disorders.

It is likely that different mechanisms contribute to the development of neurocognitive dysfunction, such as hypoxia, delirium, glucose dysregulation, the effects of sedatives, preexisting cognitive impairment and many others. Investigation of these risk factors and the development of preventive strategies represent an evolving field of research.

### Radiological Findings

In clinical practice, radiological investigation in ARDS patients includes chest radiography and computed tomography (CT). Since 1980, CT has been used to study the inhomogeneous pattern of lung lesions in ARDS.[52] Since CT study of the lung parenchyma has led to major

findings in ARDS comprehension, in this review, we reported data from follow-up CT scan studies. Four CT abnormalities were found in ARDS subjects, based on the Fleischner Society Glossary: (1) ground glass opacity (defined by a hazy increase in lung attenuation with preservation of bronchial and vascular margins); (2) consolidation or intense parenchymal opacification in the previously published glossary of the society (defined by a homogeneous increase in pulmonary parenchyma attenuation that obscures the margins of vessels and the airway wall); (3) reticular pattern (defined by a collection of innumerable small linear opacities, constituted by interlobular septal thickening, intralobular lines, or the cyst walls of honeycombing); and (4) decreased attenuation (which includes emphysema and small airways disease).[53] In the acute phase of ARDS, the classical morphological CT description is the result of a combination of alveolar flooding (edema), interstitial inflammation, and compression atelectasis, which are associated with overall disease severity and mortality.[54]

The first observations regarding changes in lung morphology after ARDS resolution were published in 1999 by Desai et al.[19] CT scan morphologic abnormalities were analyzed in a sample of 27 subjects in the acute phase of disease (7.7 ± 6.2 d after intubation) (early phase) and after a median time of 5 months (196.2 ± 41.3 d) (late phase) after ARDS resolution. In the early phase, ground glass opacity and consolidation were seen in all subjects; however, ground glass opacity was more prevalent in non-dependent regions, whereas consolidation was more prevalent in the dependent ones. In the late phase, the reticular pattern was the single most frequent pattern (85% of subjects) and was more represented in the non-dependent regions. Analyzing the relationship between the early and the late CT scan, the reticular pattern in the late CT scan was more represented, but in the early phase, ground glass opacity was more represented, and consolidation was less represented. Interestingly, reticular pattern was related to the duration of mechanical ventilation: the more time spent receiving mechanical ventilation, the more reticular pattern in the late phase. These observations were confirmed in 2001, when Nöbauer-Huhmann et al[20] performed a high-resolution CT in a group of survivors at 6–10 months after ARDS due to polytrauma. Pulmonary fibrosis was identified in 87% of 15 subjects. Parenchymal changes, such as thickened interlobular septa, non-septal lines, parenchymal bands, and cystis, were more frequent and pronounced in the non-dependent lung regions compared with the dependent lung regions, and the most severe type of alterations, such as honeycombing and subpleural cystis, were found exclusively in the non-dependent regions. Also, in this study, a clear relationship between extent of lung alteration at follow-up CT scan and the duration of high pressure ventilation (peak pressure >30 cm $H_2O$) was found.

Regarding lung insult mechanisms, ARDS can be classified as pulmonary or extrapulmonary.[55] In 2004, Kim et al[22] investigated possible differences between pulmonary and extrapulmonary ARDS over 6 months after diagnosis. In lung CT scans performed at 20.2 ± 11.9 months, lesions were significantly more extensive in pulmonary ARDS than in the extrapulmonary ARDS group, although the mean proportion of lesions in all subjects was 15.3 ± 11.1% of total lung volume. In particular, ground glass opacity and the reticular pattern were more represented than consolidation and decreased attenuation, which were similar in both groups. The total ventilation time and the duration of ICU stay were longer in pulmonary than extrapulmonary ARDS. These findings suggested that pulmonary ARDS may be more vulnerable to ventilator-induced lung injury, leading to more severe sequelae after long-term recovery. However, independent of the etiology, lung abnormalities seem to involve only a small fraction of parenchyma.

This consideration was also confirmed in a group of 21 survivors of severe ARDS treated with ECMO support.[33] The most common residual pathological finding in CT scan at 26 (interquartile range 12–50) months was the reticular pattern (76% of subjects), whereas ground glass opacity was found in 24% of subjects 1 y after ARDS. Of note, also in these severe ARDS subjects at this time point, the total extent of pathological parenchyma was only 10% (range 0–35%) of the total volume. Furthermore, there was not the typical distribution of lesions in non-dependent region found in subjects managed with standard ventilation (high volume, high pressure). The duration of ECMO treatment was related to the extent of fibrosis.

The results of the small single-center studies previously cited were confirmed in a multi-center prospective study in 2011: 6 months from ARDS after onset, the most common lesion on CT scan was the reticular pattern, which involved <25% of the lung parenchyma, followed by ground glass opacity.[26] These alterations were most frequently distributed in the non-dependent regions.

In addition to the classical morphological evaluation, several studies have employed a quantitative lung analysis of CT scan to quantify lung alterations, especially during the acute phase of ARDS.[56] Chiumello et al[25] investigated a group of ARDS subjects managed with protective ventilation previously enrolled in a randomized multi-center trial to test the long-term outcomes of patients receiving prone compared with supine positioning. The mean extent of reticular pattern was <10–15% of total lung volume 1 y after ARDS in both supine and prone groups, and there were also no differences in the amount of collapsed (8.1 ± 3.1% vs 7.3 ± 3.4%), poorly aerated (15.3 ± 3.6% vs 17.1 ± 4.9%), and well aerated (64.0 ± 8.4% vs

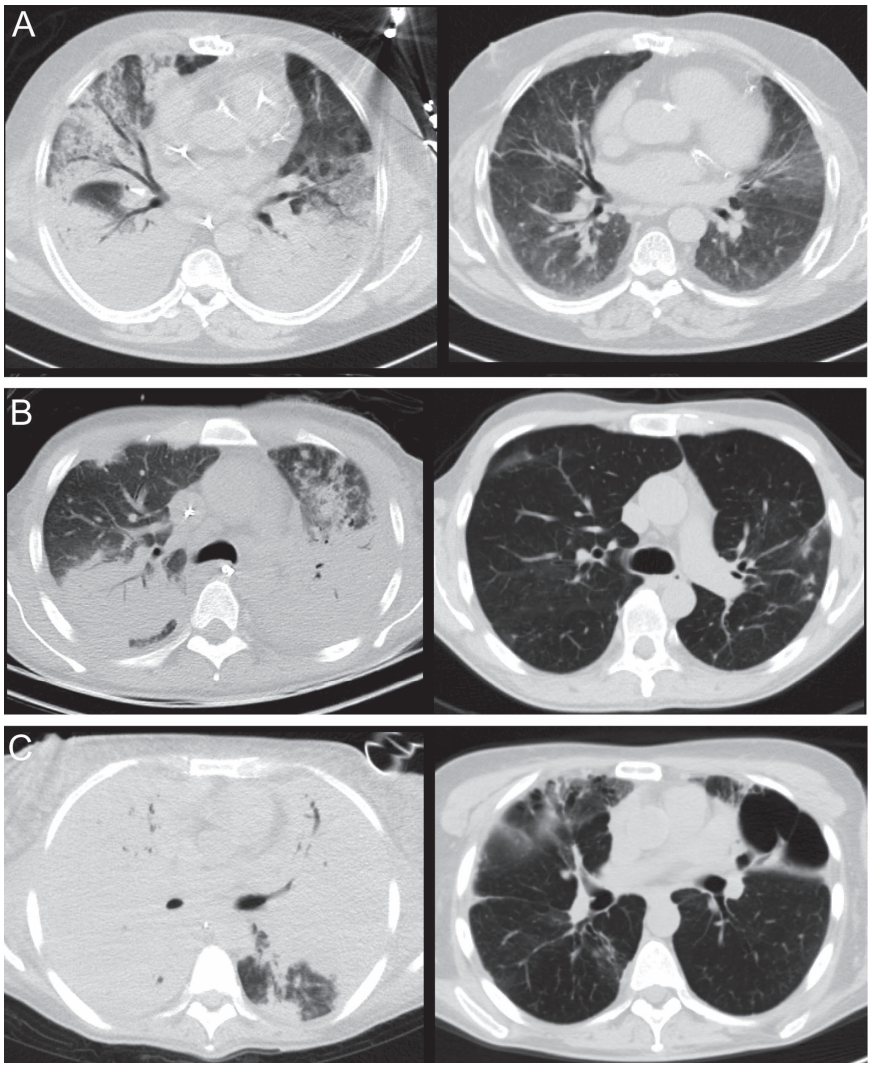


Fig. 1. Each panel corresponds to one patient; in the left column images of the acute phase of ARDS are shown, whereas on the right images taken after 6 months are shown. As shown, consolidation completely recovered in all patients. The first patient recovered with ground-glass opacity in the left lung (A). The second patient completely recovered (B). The third patient recovered with some bullae of different dimensions in the non-dependent regions of lung parenchyma (C).

70.2 ± 8.4%) tissue between the 2 groups. The only significant difference was found in the amount of overinflated tissue: 12.5 ± 6.5% versus 5.3 ± 5.5% in the prone and supine group, respectively. Of note, in the follow-up CT scan, poorly aerated tissue was equivalent to ground glass opacity and reticular pattern.

The Toronto ARDS Outcomes Study Group investigated the CT scan at 5 y after severe ARDS of subjects enrolled between May 1998 and May 2001.[40] During this period, mechanical ventilation was used in a conventional manner (high volume, high pressure), but 11 subjects (46%) received non-conventional modes of mechanical ventilation (high frequency oscillation, high frequency jet ventilation). Almost one-third of the subjects required rescue therapies, such as prone positioning, inhaled nitric oxide, and/or recruitment maneuvers. The mean extent of lung parenchyma abnormalities was 8.5%. Pulmonary abnormalities were found in 75% of subjects; however, they were minor and located in the non-dependent lung regions (56%). The main abnormality at 5 y was the reticular pattern (59%), followed by ground glass opacity (42%). Decreased attenuation was seen in 38% of subjects, whereas no subjects presented intense opacification. The radiological distribution of the lung abnormalities in the anterior non-dependent regions, when reported in the different studies, suggested that these lesions may be sequelae to ventilator-induced lung injury.

In summary, the long-term radiological findings of ARDS are the reticular pattern, followed by ground glass

opacity. Less than 10% of total lung parenchyma had any abnormality 1 y after ARDS, and it was distributed in the non-dependent lung regions (Fig. 1).

### Pulmonary Dysfunction

Although a protective ventilation strategy can improve short-term survival in ARDS subjects,[4] no difference in pulmonary function was found compared with standard ventilation treatment up to 2 y after the acute-phase resolution.[29,57]

The outcome of pulmonary function has been evaluated in various ways, for instance by spirometry, plethysmography, diffusing capacity of the lung for carbon monoxide, maximal oxygen consumption, blood gas analysis at rest and during maximal exercise, and 6-min walk test.[58] In this review, we considered data regarding 3 main evaluations: spirometry, in order to assess static and dynamic lung volumes; diffusing capacity, in order to assess the capacity of gas exchange across the alveolar barrier; and 6-min walk test, a standardized method to globally evaluate cardiopulmonary function. These methods are the most cited in the literature, and, taken together, they give a global and almost complete evaluation of pulmonary function.

Herridge et al[21] reported that lung volumes at 3 and 6 months returned to normal values. However, the overall evaluation of spirometry has shown a wide range of percentages of subjects affected with an obstructive and restrictive pattern, ranging from 6%[26] to 43%[33] for an obstructive pattern and from 15%[29] to 58%[26] for a restrictive pattern, within the first year after ARDS. Of note, the restrictive pattern could be due both to lung fibrosis and to weakness of respiratory muscles. In ARDS survivors, spirometric tests showed no differences between pulmonary and extrapulmonary ARDS[22] and between subjects treated with prone or supine positioning[25] at 6 months.

The diffusing capacity is the single functional variable most compromised in all studies we analyzed. It improved during the first year after ARDS, from 62–63% to 72–77% of predicted value, and then it remained at the lower limit or slightly under the lower limit of normality.[21,38]

The 6-min walk test assessed global physical function. In particular, the distance covered depends on the lung and the cardiac function of patients as well as on the muscle strength. The distance increased quickly in the first year after ICU discharge from 49% to 66–75% of predicted, and then this value remained nearly constant, at a value that was below the lower limit of normality.[21,25,34,38] Whether this inability to exercise is due to dyspnea or to muscle weakness is unknown; probably, it is multifactorial. In fact, no correlation was found in the literature between parenchymal abnormalities, detected with follow-up CT scan, respiratory symptoms, pulmonary function tests, and 6-min walk tests.[40] However, even if spirometry indicates a good recovery in terms of lung volumes within 6 months after ARDS, diffusing capacity and 6-min walk test highlighted a reduction of function that persisted up to 5 y after ARDS.

### Summary

In follow-up studies of ARDS survivors, long-term mortality has been reported to range between 11 and 60%, not dependent on the severity of ARDS but mainly on age and comorbidities. Because of the decrease in short-term mortality and the wide range of long-term mortality, in recent years, the mechanisms of ARDS sequelae have been studied but not fully understood. In fact, although patients who survived ARDS show mild radiological pulmonary abnormalities and a recovery of pulmonary function, they continue to present a reduced quality of life characterized by persistent exercise limitations and neuropsychological disorders up to 5 y after their critical illness. Further research to understand the mechanisms and causes of long-term ARDS consequences could provide new preventive and therapeutic strategies.

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