EDITORIAL

The Burden of Functional Recovery from ARDS

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The acute respiratory distress syndrome (ARDS) is commonly a cause for admission to the intensive care unit (ICU) and for mechanical ventilation. Within the past decade, research has shown not only that the need for acute supportive care is extensive and protracted, but also that the arc of recovery can be long, and the burden for survivors of ARDS is actually psychological and neuromuscular dysfunction.[1,2] Ironically, the respiratory system seems to respond with a relatively rapid and complete recovery. A groundbreaking paper by Herridge and colleagues in the *Journal* nearly 8 years ago described the physical and psychological disabilities of 83 patients with ARDS who survived for 1 year after their illness.[2] Our current knowledge about the persistent problems faced by these ICU survivors — deconditioning, neuromuscular weakness, and psychological maladjustment — derives from the pioneering work done by this group. The implication of their findings for the ongoing function of this population remains of great interest to the medical community.

In this issue of the *Journal*, Herridge et al. describe the 5-year postdischarge follow-up of this same cohort of patients with ARDS (now reduced to 64 survivors as a result of death and loss to follow-up).[3] This study is unique in terms of its long follow-up time, the broad range of end points measured, and the low percentage of patients lost to follow-up. The high degree of granularity of this information makes this a unique description of the aftermath of critical illness.

Near-normal lung function noted at 1 year persisted without deterioration at the 5-year mark. It seems safe to conclude that near-complete recovery of lung function can be expected relatively early in the average ARDS survivor, with no evidence of subsequent deterioration.

Similarly, quality-of-life assessments made with the use of the mental component score of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) appeared to approach near-normal. However, in sharp contrast, the SF-36 physical component scores plateaued at the 2-year mark and never reached the levels seen in a normal population. This finding coincided with results on 6-minute walk tests that were substandard and remained so throughout the 5 years of follow-up. In spite of these persistent physical limitations, 78% of these patients were able to return to work by 1 year after ICU discharge; this percentage rose to 94% by the 5-year mark.

This study raises several important points. First, the fact that lung recovery was sustained for 5 years in these ARDS survivors is both remarkable and encouraging to those who care for these patients. The lung's ability to return to near-normal function after a life-threatening injury is a testament to the body's resilience. Research to discover therapies to prevent lung injury and to accelerate healing during the acute phase of the illness is still needed,[4] since the scourge of critical illness on other body functions may be related to the time the patient spends on mechanical ventilation in the ICU.

Second, functional limitations — particularly those of a physical sort — appear to be the greatest long-term burden in ARDS survivors. Although preventing neuromuscular dysfunction in ICU survivors would likely be an arduous task, some evidence suggests that it is possible. Reducing bed rest with early mobilization while the patient is in the ICU is a reasonable starting

point, with recent evidence supporting this approach.[5] Other methods, such as electrical muscle stimulation, are promising but less fully tested.[6] With improvements in survival after ARDS,[7] and as aging of the population brings more of these patients to the ICU, strategies to prevent or reduce ICU-acquired weakness are needed. Outcomes among those requiring prolonged mechanical ventilation are poor,[8] and neuromuscular weakness is a common reason for the need for long-term ventilation. It is interesting that real-time ICU interventions for both physical and psychological[9] impairments appear to provide better results than do post hoc therapies.[10] This finding suggests that early rather than delayed attention to the disabilities described by Herridge et al. may result in better outcomes. Clearly, further research is needed in this area.

Lastly, the fact that virtually all survivors were able to return to work despite their physical limitations suggests that adaptation to a new handicap was an important part of the recovery process in these patients. Although not described in detail, these findings suggest that rehabilitative services that focus on occupational as well as physical function are important as survivors of ARDS move back into the mainstream of society.

As the authors correctly note, recovery from other types of critical illness may not follow the same pattern as that observed in the patients in their study, so it is important not to extrapolate their findings to other post-ICU situations.[3] Studies of long-term outcomes among survivors of other types of critical illness will be needed to allow comparisons with this benchmark report. In addition, this work sets the stage for future investigations regarding the management of ARDS. With the problems faced by ARDS survivors now more clearly described, we can better focus our strategies on their prevention and treatment.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Functional Disability 5 Years after Acute Respiratory Distress Syndrome

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ABSTRACT

BACKGROUND

There have been few detailed, in-person interviews and examinations to obtain follow-up data on 5-year outcomes among survivors of the acute respiratory distress syndrome (ARDS).

METHODS

We evaluated 109 survivors of ARDS at 3, 6, and 12 months and at 2, 3, 4, and 5 years after discharge from the intensive care unit. At each visit, patients were interviewed and examined; underwent pulmonary-function tests, the 6-minute walk test, resting and exercise oximetry, chest imaging, and a quality-of-life evaluation; and reported their use of health care services.

RESULTS

At 5 years, the median 6-minute walk distance was 436 m (76% of predicted distance) and the Physical Component Score on the Medical Outcomes Study 36-Item Short-Form Health Survey was 41 (mean norm score matched for age and sex, 50). With respect to this score, younger patients had a greater rate of recovery than older patients, but neither group returned to normal predicted levels of physical function at 5 years. Pulmonary function was normal to near-normal. A constellation of other physical and psychological problems developed or persisted in patients and family caregivers for up to 5 years. Patients with more coexisting illnesses incurred greater 5-year costs.

CONCLUSIONS

Exercise limitation, physical and psychological sequelae, decreased physical quality of life, and increased costs and use of health care services are important legacies of severe lung injury.

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The acute respiratory distress syndrome (ARDS) represents an important and costly public health problem.[1] Prospective systematic evaluation of long-term outcomes among survivors of ARDS has been limited to 2 years of follow-up.[2-11] Few comprehensive, longitudinal data have been obtained from survivors of critical illness with regard to 5-year pulmonary, functional, and health-related quality-of-life outcomes or health care utilization and costs. The Toronto ARDS follow-up study began in 1998 and enrolled relatively young patients with very severe lung injury and few coexisting illnesses.[10] The primary goal of this 5-year follow-up study was to catalogue, quantify, and describe the extent of physical, mental, and quality-of-life impairments after ARDS and to determine factors associated with poor outcomes and increased health care utilization.

Methods

Study Design

We conducted a prospective, longitudinal cohort study of 109 patients with ARDS who survived until they were discharged from the intensive care unit (ICU). The patients were recruited from four academic medical–surgical ICUs in Toronto between May 1998 and May 2001. Inclusion and exclusion criteria have been described previously.[10] At the end of 1 year, written informed consent was obtained from all patients to permit another 4 years of follow-up. The study was approved by the research ethics boards at all participating hospitals.

Characteristics of Patients and ICU Course

At the time of the onset of ARDS, the median age of the patients was 44 years (interquartile range, 35 to 57); 83% had no or one coexisting condition, and 83% were working full time. Pneumonia and sepsis were the most common risk factors for ARDS in this cohort. We collected data on baseline demographic characteristics and measures of severity of illness in the ICU daily during the first week and twice weekly thereafter.[10] These measures included the Acute Physiology and Chronic Health Evaluation II (APACHE II) (range of scores, 0 to 71, with higher scores indicating greater severity of illness),[12] the Multiple Organ Dysfunction Score (range, 0 to 24, with higher scores indicating more severe organ dysfunction),[13] and the modified Lung Injury Score (range, 0 to 4, with higher scores indicating more severe lung injury).[14] Other characteristics of the patients during their stay in the ICU are listed in Table 1.

Follow-up Protocol

We evaluated survivors of ARDS in an ambulatory clinic or in their homes at 3, 6, 12, and 24 months and then yearly for up to 5 years after they were discharged from the ICU. At each visit, patients underwent a detailed interview, physical examination (including muscle-strength measurements), pulmonary-function testing, chest radiography, and the 6-minute-walk test[15] with continuous oximetry. They also completed the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) (scores range from 0 to 100, with higher scores indicating better health status).[16] Family caregivers were also interviewed. A description of the follow-up visits can be found in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Health Care Utilization and Cost Data

We prospectively collected data on health care utilization from hospital and outpatient clinical records, patients' monthly diaries, and self-reports at scheduled study visits. This approach provided patient-specific and activity-based resource-use data after hospital discharge. For health care costs, we took the perspective of a third-party payer (Ontario Ministry of Health) to estimate direct medical charges, which we equated with costs that included hospitalization, emergency room and outpatient visits, professional fees, drugs, laboratory and radiology tests and procedures, outpatient and inpatient rehabilitation, home care, and services provided in a long-term care facility. We excluded indirect medical costs and direct nonmedical costs. Costs were adjusted for inflation rates with the use of the health care component of the Canadian Consumer Price Index[17] and were expressed in 2009 Canadian dollars. Our methods for determining health care use and costs are detailed in the Supplementary Appendix.

Statistical Analysis

Continuous variables were summarized with the use of medians and the 25th and 75th percentiles (the interquartile range). Categorical variables were summarized with the use of proportions and

95% confidence intervals. Reported costs for patients who died before the 5-year period ended are complete costs. To avoid bias in our cost analyses because of incomplete cost data, we used the partitioned estimator of Bang and Tsiatis to estimate mean total costs to 5 years and costs accrued in each year.[18] In addition, we used the regression method of Lin to estimate the dependence of total costs on patient-level covariates.[19] Details of modeling and further analyses are included in the Supplementary Appendix. All analyses were preplanned.

RESULTS

BASELINE CHARACTERISTICS AND FOLLOW-UP ASSESSMENTS

Of the 109 patients included in the follow-up, 83 reconsented at 1 year to an additional 4 years of follow-up. The proportions of surviving patients who were included in the follow-up during the 1-year to 5-year periods, respectively, were 86%, 85%, 90%, 82%, and 86% (Fig. 1).

GLOBAL ASSESSMENT

At 5 years after ICU discharge, no patient had demonstrable weakness on examination, but all commented on having varying degrees of perceived weakness and stated that their ability to do vigorous exercise was reduced, as compared with their ability before their critical illness. Patients' weight remained stable between 1 and 5 years after ICU discharge.

At 5 years, the median distance walked in 6 minutes was 436 m (interquartile range, 324 to 512) (76% of the distance in an age-matched and sex-matched control population), which was consistent with a persistent reduction in ability to exercise (Fig. 2). Distance walked in 6 minutes was significantly correlated with the physical-component score of the SF-36 at 3, 6, and 12 months and at 2, 3, 4, and 5 years ($P<0.01$). The patient and ICU characteristics originally evaluated as part of the 1-year ARDS outcomes analyses are shown in Table 1. None of these characteristics were significantly associated with the 6-minute walk distance at 5 years. However, patients for whom the rate of change in the Lung Injury Score was above the median, indicating faster resolution of lung injury during the ICU stay, had a longer median 6-minute walk distance at the 5-year follow-up than did those with a rate of change below the median, indicating slower resolution of lung injury during the ICU stay (454 m vs. 427 m, $P=0.09$). This was also true for the rate of change in the Multiple Organ Dysfunction Score during the ICU stay ($P=0.09$).

Thirty-nine percent of patients achieved a 6-minute walk distance of 80% or more of the predicted distance at 5 years. When we looked at whether age, coexisting illness, or rate of resolution in the Lung Injury Score during the ICU stay was associated with a better functional outcome, we found a very small effect of age, with greater odds of a walk distance above 80% of the predicted distance with increasing age (odds ratio, 1.46 per decade [1.04 per year]; $P=0.06$). Coexisting illness had a greater effect, with a lower chance of being above 80% of the predicted distance with each additional illness (odds ratio, 0.48 per illness; $P=0.06$). There was no association with the rate of resolution in the Lung Injury Score during the ICU stay ($P=0.54$).

The mean score on the physical component of the SF-36 at 5 years remained approximately 1 SD below the mean score for an age-matched and sex-matched control population. Age was significantly associated with the slope of the physical-component score over the 5-year period after discharge from the ICU. In post hoc analyses in which patients were divided into thirds according to age (<38, 38 to 52, and >52 years), those in the two younger groups had a significantly steeper slope in improvement in the physical-component score from discharge to 5 years, as compared with those who were older than 52 years of age ($P=0.002$) (see the Supplementary Appendix). The estimated mean increases in physical-component score were 11.7 and 9.2 points greater in the two younger age groups, respectively, than the corresponding increase in the oldest age group, but none of the three groups had a score as high as the predicted score at 5 years.

SPECTRUM OF IMPAIRMENTS 5 YEARS AFTER ARDS

The patients with ARDS had new or continued impairments related to a variety of physical and neuropsychological disorders between 2 and 5 years of follow-up. These included new tracheal stenosis requiring surgical resection and dilation and rehospitalizations (in 2 patients) and complicated by a major depressive disorder in 1 patient; ongoing disability from heterotopic ossification involving the knees and elbows (in

4 patients); frozen shoulders (in 2 patients); vocal-cord dysfunction and voice changes (in 1 patient); new or recurrent reactive airways disease (in 4 patients); and dental implants for ICU-acquired tooth damage (in 1 patient). There were ongoing concerns about cosmesis in 10 patients; these were related to procedures (e.g., laparotomy; tracheostomy or tracheostomy revision; insertion of a chest tube, a central line, or an arterial line; and burns, striae, and facial scars from prolonged noninvasive mask ventilation). Patients reported that these concerns contributed to social isolation and sexual dysfunction. Other causes of disability included bilateral forefoot amputations due to necrosis from vasopressor use (in 1 patient) and new sensorineural hearing loss and tinnitus attributed to ototoxic ICU medications (in 2 patients). Fifty-one percent of patients reported at least one episode of physician-diagnosed depression, anxiety, or both between 2 and 5 years of follow-up; several patients had substantial mental health challenges, including an acute psychotic episode due to post-traumatic stress disorder (in 1 patient) and severe agitated depression and agoraphobia (in 2 patients). Family mental health problems, including anxiety, depression, or post-traumatic stress disorder, as reported by patients or family members, occurred in 27% of cases over the same time period. Other problems, such as social isolation, sexual dysfunction, job loss, and disputes over disability and insurance claims, were also qualitatively discussed during the study interviews.

Table 1. Characteristics of Patients with the Acute Respiratory Distress Syndrome (ARDS) at 1 Year and 5 Years after Discharge from the Intensive Care Unit (ICU).

Characteristic	At 1 Year (N=83)	At 5 Years (N=64)
Age at enrollment — yr		
Median	45	44
Interquartile range	36–56	35–57
Male sex — no. (%)	46 (55)	33 (52)
Coexisting illness — no. (%)*		
None	34 (41)	26 (41)
1	31 (37)	27 (42)
2 or more	18 (22)	11 (17)
Preexisting pulmonary disease — no. (%)	8 (10)	6 (9)
Working full time before ARDS — no. (%)	64 (77)	53 (83)
Education — yr		
Median	13	13
Interquartile range	9–16	12–16
Ever smoked — no. (%)	43 (52)	30 (47)
Presence of informal caregiver — no. (%)	73 (88)	58 (91)
Body-mass index ≥30 before ARDS — no. (%)†	27 (32)	21 (33)
APACHE II score‡		
Median	23	23
Interquartile range	17–27	16–28
Maximal Lung Injury Score§		
Median	3.7	3.7
Interquartile range	3.3–4.0	3.3–4.0
Maximal Multiple Organ Dysfunction Score¶		
Median	11	11
Interquartile range	10–13	10–13

Table 1. (Continued.)

Characteristic	At 1 Year (N=83)	At 5 Years (N=64)
Risk factor for ARDS — no. (%)‖		
Pneumonia	44 (53)	32 (50)
Sepsis	33 (40)	25 (39)
Trauma or burn	19 (23)	15 (23)
Pancreatitis	8 (10)	6 (9)
Other	25 (30)	20 (31)
Any renal-replacement therapy — no. (%)	11 (13)	9 (14)
Any paralytic agent — no. (%)	50 (60)	41 (64)
Any systemic glucocorticoid therapy — no. (%)	30 (36)	23 (36)
Tracheostomy — no. (%)	43 (52)	32 (50)
Ventilator use — days		
Median	21	24
Interquartile range	12–40	12–41
Length of stay in ICU — days		
Median	25	26
Interquartile range	14–47	16–49
Length of hospitalization — days		
Median	47	49
Interquartile range	26–73	29–72

* Coexisting illnesses were defined on the basis of documented clinical diagnostic categories. These included neurologic, cardiac, gastrointestinal, respiratory, renal, liver, hematologic, and vascular disease; compromised immune system; diabetes; a history of cancer within the previous 5 years; active cancer at the time of ICU admission; and prior receipt of organ or bone marrow transplant.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Scores on the Acute Physiology and Chronic Health Evaluation II (APACHE II) can range from 0 to 71, with higher scores indicating more severe illness.
§ Static lung compliance was not measured. The Lung Injury Score can range from 0 to 4, with higher scores indicating more severe lung injury. The cumulative score is the sum of the scores for chest radiography, hypoxemia, and positive end-expiratory pressure.
¶ The Multiple Organ Dysfunction Score can range from 0 to 24, with higher scores indicating more severe dysfunction.
‖ The percentages for risk factors do not add up to 100% because some patients had more than one risk factor; 47% of patients had two or more risk factors, and 42% had both direct and indirect risk factors. For example, a patient with pneumonia (direct) and sepsis (indirect) would be counted as having two risk factors for ARDS.

PULMONARY-FUNCTION TESTING AND CHEST RADIOGRAPHY

Patients had normal or near-normal volumetric and spirometric test results between 3 and 5 years (Table 2). Forty percent of the participants were seen at a home visit, during which pulmonary assessment was limited to spirometry. After ICU discharge, 25 patients underwent computed tomography (CT) of the chest at least once between the 2-year and 5-year follow-up visits. The most common finding was minor, nondependent pulmonary fibrotic changes that were consistent with ventilator-induced lung injury. Less common findings included bronchiectasis, bullae, pleural thickening, and pulmonary fibrosis. Only patients with bronchiectasis, pulmonary fibrosis, or both on CT imaging had clinically important pulmonary symptoms, including cough, sputum production, and exertional dyspnea.

SURVIVAL AND RETURN TO WORK

A Kaplan–Meier 5-year survival curve is shown in Figure 2. During the first year of follow-up, 12 patients died,[10] and 9 died over the next 4 years (Fig. 1). Causes of death in these 9 patients are listed in the Supplementary Appendix.

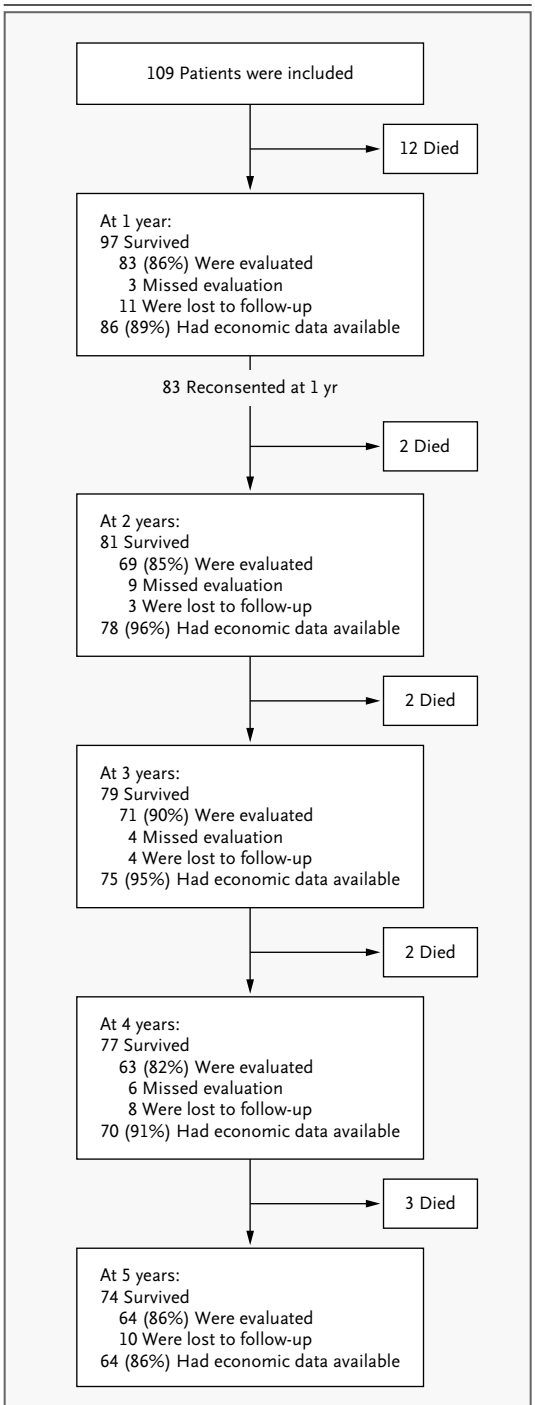


Figure 1. Follow-up Status of Patients with Acute Respiratory Distress Syndrome from 1 Year to 5 Years.

The number of patients designated as lost to follow-up varies between yearly visits because some patients returned after missing one or more visits over the 5-year course of the study.

Eighty-three percent of the patients who were followed up for 5 years were working full time before their critical illness (Table 1); 77% of these patients were working for a salary outside the home, 6% were students attending college or university, and 17% were women doing unpaid work within the home. At the 5-year follow-up, 77% of patients had returned to work, and 94% of these patients returned to their original work. Two patients reached retirement age and did not return to work. The majority of patients who returned to work did so by 2 years after ICU discharge; five patients returned to work between 3 and 5 years after discharge, but not all of the five remained in the work force (Table 2). Patients often required a gradual transition to work, a modified work schedule, or job retraining in collaboration with third-party private insurers, with supporting justification and documentation from our ARDS research group.

HEALTH CARE UTILIZATION AND COSTS OVER 5 YEARS

Average costs per patient per year from years 3 through 5 ranged from $5,000 to $6,000 (Table 2). Medication costs increased to year 3 and then remained constant in years 4 and 5. Rehospitalization costs decreased up to 3 years of follow-up and then remained stable in years 4 and 5, and outpatient costs declined each year throughout the 5 years. Rehospitalizations were related to ICU-acquired complications, complications of preexisting illnesses, or the development of new medical problems. Cumulative postdischarge costs per patient were associated with the number of coexisting illnesses at the time of ICU admission (≤1 vs. ≥2 coexisting illnesses) (Fig. 3). Only the presence of coexisting disease was significantly associated with costs incurred over the 5-year follow-up period in regression modeling (data not shown).

DISCUSSION

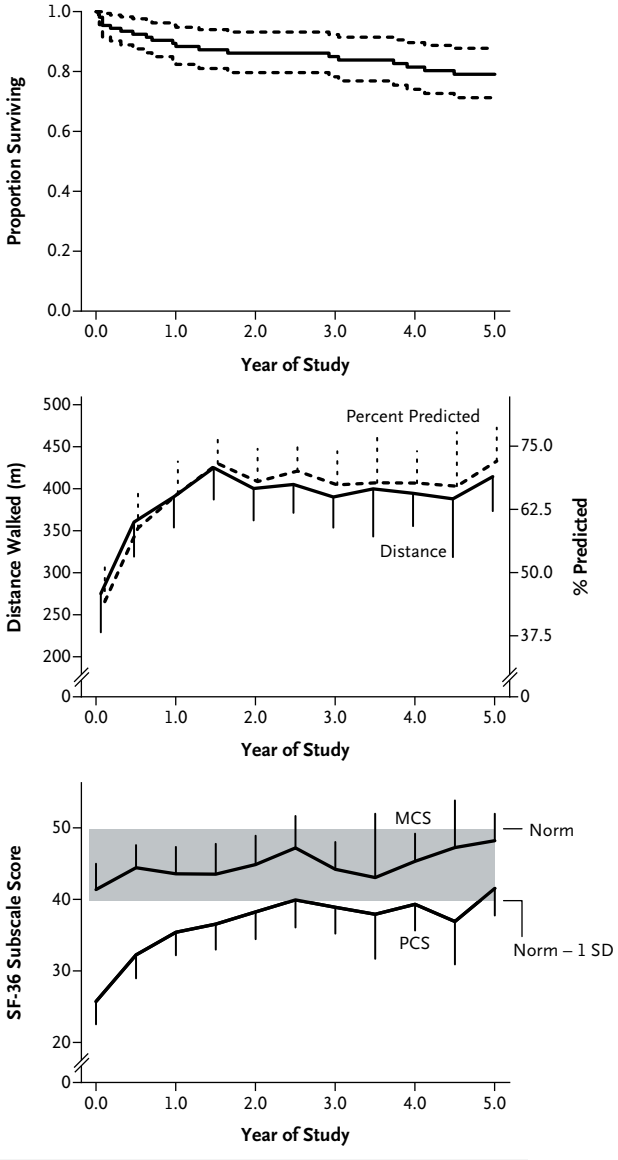
We found that relatively young patients who survived ARDS had persistent exercise limitations and a reduced physical quality of life 5 years after their critical illness. Pulmonary function was near-normal to normal at 5 years. The decrements in quality of life and exercise capacity may have resulted from persistent weakness, as well as a

spectrum of physical and neuropsychological impairments that were also documented during follow-up. These patients had modest preexisting illnesses, and most were working before their illness yet they incurred health care costs at a greater rate over time than did age-matched and sex-matched healthy persons.

We also found that the cumulative costs after hospitalization were associated with the burden of coexisting illnesses at the time of ICU admission. This observation is consistent with other reports that link coexisting illness with poor clinical outcomes after ICU discharge and increased costs over time.[20-22] The incremental cumulative health care costs of an ARDS episode are difficult to determine without a control group. However, the costs reported for the patients with ARDS in our study are higher than those incurred by healthy workers ($1,100 to $3,200 per year)[23,24] and are closer to the low end of the range of costs among patients with chronic disease.[24,25] One may view survivors of severe ARDS as having a burden of chronic disease related to a decrement in coexisting organ dysfunction or the development of new disability. The finding that relatively young, previously working persons with modest coexisting disorders do not return to baseline levels of health care utilization after an episode of critical illness may have important public health ramifications.

ICU-acquired weakness may continue to be an important contributor to long-term function and quality-of-life outcomes in survivors of ARDS.[23-33] The spectrum of physical and neuropsychological impairments that compound such weakness may also contribute to these outcomes. These data are consistent with other reports of long-term sequelae in survivors of critical illness.[7,34-52] However, our study shows that such dysfunction persists over a period of 5 years and that heterogeneous issues contribute to this reported disability over time. Our study also shows that psychological and emotional dysfunction persists in both patients and caregivers for up to 5 years after discharge from the ICU.

The decrements in the 6-minute walk distance and the score on the physical component of the SF-36 at 5 years may suggest that previously working, relatively young patients may have an irreversible decrease in function after critical illness, although this decrease is less marked than the



No. at Risk	109	92	86	79	77	74	69	64
No. for 6-Min Walk	80	78	81	60	64	64	57	54
No. for SF-36	67	74	74	56	57	57	49	50

Figure 2. Survival Rates, 6-Minute Walk Distance, and Quality of Life for 5 Years after Discharge from the Intensive Care Unit.

Exact survival times were used for these analyses. In the top graph, the solid line is the Kaplan–Meier survival curve from 0 to 5 years; dashed lines represent the 95% confidence interval. The middle graph shows the distance walked in 6 minutes in meters (solid line) and the percent of the predicted distance (dashed line). The bottom graph shows the physical-component score (PCS) and the mental-component score (MCS) on the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36); scores range from 0 to 100, with higher scores indicating better health status. Vertical bars in the middle and bottom graphs represent half 95% confidence intervals.

decrements recently described in older patients with more coexisting disorders.[22,53] Early mobility and rehabilitation are promising interventions for ameliorating such impairments, but the ability to stratify risks and tailor programs to individual needs requires further study.[54-65] Recent work highlights the need to balance the potential risk of ICU-acquired weakness with the potential benefit of neuromuscular blockers and systemic glucocorticoids in severely lung-injured patients.[66-68] In addition, ICU-based interventions may play a role in reducing longer-term neuropsychological disorders in ICU survivors (e.g., ICU diaries to help reduce post-traumatic stress disorder[69,70]). These data underscore both the important effect that the process of ICU treatment may have on longer-term outcomes and the need for ongoing study in this area.[66-70]

Through in-person follow-up we came to understand the burden on caregivers associated with the recovery of patients with lung injury. There is an emerging literature on morbidity among caregivers and the important psychological impairments sustained by family members for prolonged periods after the initial episode of critical illness.[71-76] Dysfunction in these family members may also have an important negative effect on patients' recovery and rehabilitative potential.

Table 2. Clinical Outcomes from 1 Year to 5 Years in Survivors of ARDS.

Clinical Outcomes	At 1 Year (N=83)	At 2 Years (N=69)	At 3 Years (N=71)	At 4 Years (N=63)	At 5 Years (N=64)
Site of visit — no. of patients (%)					
Clinic	60 (72)	44 (64)	42 (59)	36 (57)	35 (55)
Home	23 (28)	25 (36)	29 (41)	27 (43)	29 (45)
Returned to work — no. of patients (%)*	40 (48)	45 (65)	50 (70)	46 (73)	49 (77)
Returned to original work — no. of patients/total no. (%)	31/40 (78)	36/45 (80)	46/50 (92)	41/46 (89)	46/49 (94)
Pulmonary function — % of predicted†					
Forced vital capacity					
Median	85	86	76	84	84
Interquartile range	71–98	71–100	67–98	70–100	72–101
Forced expiratory volume in 1 sec					
Median	86	87	79	85	83
Interquartile range	74–100	75–99	66–97	68–98	69–98
Total lung capacity‡					
Median	95	94	93	92	94
Interquartile range	81–103	84–108	78–107	79–104	78–105
Residual volume‡					
Median	105	96	101	96	96
Interquartile range	90–116	78–118	80–116	80–110	73–108
Carbon monoxide diffusion capacity‡					
Median	72	78	77	82	80
Interquartile range	61–86	63–89	63–93	68–94	70–86
Distance walked in 6 min§					
Median — m	422	416	418	406	436
Interquartile range	277–510	285–496	311–474	314–488	324–512
Percent of predicted¶	66	68	67	71	76
Oxygen saturation <88% — no. of patients/total no. (%)	5/81 (6)	7/64 (11)	6/64 (9)	5/57 (8)	8/54 (15)
Change in weight from pre–ICU stay — %	–2	1	2	2	3

Table 2. (Continued.)

Clinical Outcomes	At 1 Year (N=83)	At 2 Years (N=69)	At 3 Years (N=71)	At 4 Years (N=63)	At 5 Years (N=64)
Median SF-36 score‖					
Physical functioning	60	70	70	75	75
Role, physical	25	50	100	75	88
Bodily pain	62	62	72	74	74
General health	52	62	55	59	62
Vitality	55	55	50	50	55
Social functioning	63	75	75	69	75
Role, emotional	100	100	100	100	100
Mental health	72	76	72	76	76
Mean costs after initial hospitalization — Canadian $**					
Medication costs	1,441	1,652	2,288	2,713	2,152
Rehospitalization costs	11,875	3,727	2,217	1,945	2,700
Outpatient costs	8,993	4,506	1,558	1,091	714
Total	22,309	9,885	6,063	5,749	5,566

* This category includes return to school, home duties, volunteer work, or paid employment; information was missing for one patient at 1 year. ICU denotes intensive care unit.

† At 1 year, two patients were cognitively unable to complete the testing and one was not evaluated; at 2 years, there were two spirometer malfunctions during home visits and one patient was cognitively unable to complete the testing; at 3 years, two patients declined testing, one patient was cognitively unable to complete the testing, and one was not evaluated; at 4 years, there were two spirometer malfunctions during home visits, one patient was cognitively unable to complete the testing, and one did not take the test because of recent surgery; at 5 years, two patients were cognitively unable to complete the testing.

‡ This test could not be performed during home visits.

§ At 1 year, one patient did not walk and for another the distance walked was not recorded; at 2 years, two patients declined to walk, one patient was missed, one was not tested owing to low oxygen saturation, and one was unable to walk owing to fatigue; at 3 years, three patients declined to walk, the distance walked was not recorded for two patients, one patient's record was lost, and one patient was unable to walk owing to hip pain; at 4 years, two patients were missed, one patient was ill, one patient had a broken foot, one patient was unable to walk owing to shortness of breath, and one patient declined to walk; at 5 years, four patients were missed, three patients declined to walk, one patient assessment was done by mail, one patient was unable to walk owing to dizziness, and one had a torn muscle.

¶ Normal values were calculated in an age-matched and sex-matched population according to the regression method of Enright and Sherrill.[15]

‖ For the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), scores range from 0 to 100, with higher scores indicating better health status; 80 questionnaires were returned at 1 year, 62 at 2 years, 59 at 3 years, 50 at 4 years, and 55 at 5 years.

** Costs (in 2009 Canadian dollars) are for subsequent hospitalizations, inpatient rehabilitation, outpatient rehabilitation, home care, physician costs (for both primary and subspecialty care), diagnostic testing, and medications.

The strengths of our study are the well-defined multisite inception cohort, detailed characterization of the patients, and longitudinal design, with high rates of follow-up to 5 years and comprehensive in-person evaluations. Our findings may help to inform patients, family caregivers, primary care physicians, and specialists about patterns of very-long-term outcomes after critical illness. A limitation of the study is the modest sample size. In addition, the patients were relatively young and they had severe lung injury, with few coexisting illnesses and minimal preexisting pulmonary disease. Therefore, these data cannot be generalized to all survivors of critical illness. Subtle impairments may be less evident in younger patients, and reported coexisting illness might be underestimated in this young patient population. We did not record standardized serial strength measurements or conduct a detailed neuromuscular assessment; however, the patients were examined and muscle power was formally evaluated during follow-up visits. The relationship be-

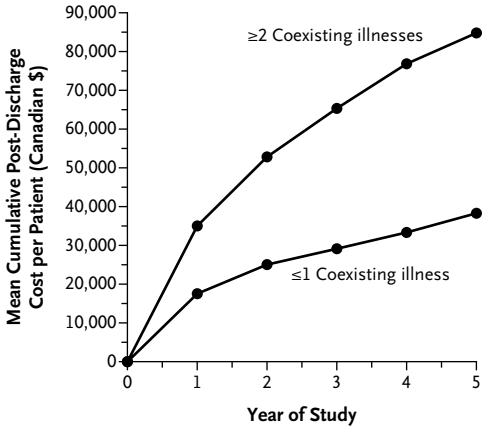


Figure 3. Cumulative Costs to 5 Years after Discharge from the Intensive Care Unit (ICU), Stratified According to Number of Coexisting Illnesses at Time of ICU Admission.

Costs are in 2009 Canadian dollars.

tween the study team and the patients and their caregivers helped to ensure excellent follow-up, but it may have had a therapeutic effect, thereby confounding the outcome measurements. Thus, the outcomes we report may be better-than-average outcomes for patients with ARDS, given the active surveillance and care administered. The data on cost and health care utilization consisted of information that was externally validated, either fully (ICU and inhospital data) or partially (hospital readmission [63%]), combined with self-reports (on outpatient care utilization and medication use); the latter may be limited by reporting or recall bias.

In summary, young, previously working patients with ARDS who have few coexisting illnesses may not recover completely and may have ongoing functional limitations after an episode of critical illness. This may be attributed to persistent ICU-acquired weakness, in addition to a variety of other physical and mental health impairments. Family members may also have psychological dysfunction, which may further compromise outcomes. The health burden of critical illness may be likened to that of chronic disease with similar health care utilization. Research priorities include a better understanding of the pathophysiology of ICU-acquired weakness and an evaluation of the effects of a customized, family-centered, rehabilitation program on long-term outcomes after a critical illness.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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