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One-Year Outcomes in Survivors of the Acute Respiratory Distress Syndrome

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ABSTRACT

BACKGROUND

As more patients survive the acute respiratory distress syndrome, an understanding of the long-term outcomes of this condition is needed.

METHODS

We evaluated 109 survivors of the acute respiratory distress syndrome 3, 6, and 12 months after discharge from the intensive care unit. At each visit, patients were interviewed and underwent a physical examination, pulmonary-function testing, a six-minute–walk test, and a quality-of-life evaluation.

RESULTS

Patients who survived the acute respiratory distress syndrome were young (median age, 45 years) and severely ill (median Acute Physiology, Age, and Chronic Health Evaluation score, 23) and had a long stay in the intensive care unit (median, 25 days). Patients had lost 18 percent of their base-line body weight by the time they were discharged from the intensive care unit and stated that muscle weakness and fatigue were the reasons for their functional limitation. Lung volume and spirometric measurements were normal by 6 months, but carbon monoxide diffusion capacity remained low throughout the 12-month follow-up. No patients required supplemental oxygen at 12 months, but 6 percent of patients had arterial oxygen saturation values below 88 percent during exercise. The median score for the physical role domain of the Medical Outcomes Study 36-item Short-Form General Health Survey (a health-related quality-of-life measure) increased from 0 at 3 months to 25 at 12 months (score in the normal population, 84). The distance walked in six minutes increased from a median of 281 m at 3 months to 422 m at 12 months; all values were lower than predicted. The absence of systemic corticosteroid treatment, the absence of illness acquired during the intensive care unit stay, and rapid resolution of lung injury and multiorgan dysfunction were associated with better functional status during the one-year follow-up.

CONCLUSIONS

Survivors of the acute respiratory distress syndrome have persistent functional disability one year after discharge from the intensive care unit. Most patients have extrapulmonary conditions, with muscle wasting and weakness being most prominent.

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THE ACUTE RESPIRATORY DISTRESS SYNdrome is characterized by bilateral pulmonary infiltrates on frontal chest radiography, a ratio of arterial oxygen tension (PaO_2) to the fraction of inspired oxygen (FiO_2) of 200 or less, and the absence of clinical evidence of left atrial hypertension.[1] As survival rates improve among patients with the acute respiratory distress syndrome,[2-5] there is a growing need to understand the long-term effects of this condition and its treatment.

Patients who survive the acute respiratory distress syndrome are at risk for physical and neuropsychological complications of the lung injury itself, associated multiorgan dysfunction, and their long stay in the intensive care unit (ICU). Several investigators have evaluated morbidity among survivors using pulmonary-function tests,[6-21] neuropsychological and cognitive assessments,[22-26] and quality-of-life measures,[27-31] and most have indicated that there is persistent morbidity after discharge from the ICU. However, no study has prospectively performed individualized assessments of physiological, functional, and quality-of-life measures during the year after discharge from the ICU to ascertain the main determinants of functional disability. Therefore, the goal of this study was to characterize long-term pulmonary and extrapulmonary function in a prospectively identified cohort of patients who survived the acute respiratory distress syndrome.

METHODS

STUDY DESIGN

This longitudinal study was conducted at four university-affiliated medical–surgical ICUs in Toronto from May 1998 to May 2002; the last patient completed his stay in the ICU in May 2001. We identified potential patients from a prospective, daily screening log. Patients were eligible for enrollment if they were at least 16 years of age, had a PaO_2:FiO_2 ratio of 200 or less while receiving mechanical ventilation with a positive end-expiratory pressure of at least 5 cm of water, evidence of air-space changes in all four quadrants on chest radiography, and an identifiable risk factor for the acute respiratory distress syndrome. Patients were excluded if they were immobile before being admitted to the ICU, had a history of pulmonary resection, or had a documented neurologic or psychiatric disease.

We obtained written informed consent from the surrogate decision maker near the time of the patient's admission to the ICU. Written consent for the one-year follow-up was obtained directly from the patient at the time of discharge from the ICU. This study was approved by the institutional ethics committee at each of the participating hospitals.

SEVERITY OF ILLNESS AND COURSE IN THE ICU

We used the Acute Physiology, Age, and Chronic Health Evaluation (APACHE II)[32] to determine the severity of illness within the first 24 hours after each patient was admitted to the ICU. Scores can range from 0 to 71, with higher scores indicating more severe illness. We also determined the Multiple Organ Dysfunction Score[33] and a modified Lung Injury Score[34] daily from day 0 (the day of eligibility) to day 7 and then twice per week for the duration of the stay in the ICU. The Lung Injury Score is an aggregate of the score for the chest radiograph, hypoxemia, positive end-expiratory pressure, and respiratory-system compliance. Since respiratory compliance was not measured as part of this study, a modified Lung Injury Score was used, which consisted of the sum of the first three components. The Multiple Organ Dysfunction Score can range from 0 to 24, with higher scores indicating more severe dysfunction. The Lung Injury Score can range from 0 to 4, with higher scores indicating more severe lung injury. Other characteristics of the patients during their stay in the ICU are outlined in Table 1.

FOLLOW-UP PROTOCOL

We evaluated patients in an ambulatory clinic 3, 6, and 12 months after they were discharged from the ICU. At each visit, the patient was interviewed; underwent a physical examination, pulmonary-function testing, posteroanterior and lateral chest radiography, resting oximetry, and a standardized six-minute–walk test[35] with continuous oximetry; and completed the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36), which measures the health-related quality of life.[36] The SF-36 includes eight multiple-item scales that assess physical functioning, social functioning, physical role, emotional role, mental health, pain, vitality, and general health. Scores for each aspect can range from 0 (worst) to 100 (best). When a follow-up appointment was missed, the patient was given an opportunity to reschedule or request a home visit. Home visits were limited to a round-trip travel time of 10 hours from the greater Toronto area (approximately 700 km). On home visits, pulmonary-function testing was limited to spirometry and no chest radiograph was obtained.

Table 1. Characteristics of Patients with the Acute Respiratory Distress Syndrome (ARDS) at Enrollment and in the ICU, According to Whether They Survived to Discharge.

Characteristic	Surviving Patients (N=117)	Patients Who Died (N=78)	P Value*
Age — yr			0.02
Median	45	50	
Interquartile range	36–58	39–68	
Male sex — no. (%)	66 (56)	48 (62)	0.55
Preexisting organ dysfunction — no. (%)†	72 (62)	69 (88)	<0.001
Preexisting pulmonary disease — no. (%)‡	13 (11)	16 (21)	0.12
APACHE II score§			<0.001
Median	23	28	
Interquartile range	17–27	22–33	
Maximal Lung Injury Score¶			0.002
Median	3.7	4.0	
Interquartile range	3.0–4.0	3.7–4.0	
Multiple Organ Dysfunction Score‖			
Day 0 (date of eligibility)			0.03
Median	9	10	
Interquartile range	7–11	8–12	
Day 3			<0.001
Median	9	11	
Interquartile range	7–12	9–13	
Day 7			<0.001
Median	8	11	
Interquartile range	7–10	9–13	
Day 14			0.02
Median	7	12	
Interquartile range	5–9	8–15	
Risk factor for ARDS — no. (%)**			
Pneumonia	62 (53)	50 (64)	0.12
Sepsis	48 (41)	46 (59)	0.01
Trauma or burns	26 (22)	3 (4)	<0.001
Pancreatitis	10 (9)	3 (4)	0.20
Other	40 (34)	16 (21)	0.04
Requirement for renal-replacement therapy — no. (%)	14 (12)	26 (33)	0.004
Tracheostomy — no. (%)	60 (51)	13 (17)	<0.001
Days of ventilator use			0.001
Median	21	13	
Interquartile range	12–40	8–27	
Length of stay in ICU — days			<0.001
Median	25	13	
Interquartile range	15–45	8–27	
Length of hospitalization — days			<0.001
Median	48	18	
Interquartile range	27–77	10–31	

* The Wilcoxon rank-sum test was used for continuous variables, and the Pearson chi-square test was used for categorical variables.

† Preexisting organ dysfunction was defined on the basis of documented clinical diagnostic categories that included the following: neurologic, cardiac, gastrointestinal, respiratory, renal, hematologic, liver, or vascular disease; immunocompromised host; diabetes; history of cancer (except nonmelanoma skin cancer) within the previous five years or active cancer at the time of ICU admission; and previous organ or bone marrow transplantation.

‡ Preexisting pulmonary disease was defined as follows: any obstructive lung disease (asthma, chronic bronchitis, emphysema, or bronchiectasis); any restrictive lung disease (any pulmonary parenchymal or extrapulmonary restrictive process); previously documented chronic hypoxemia, hypercapnia, or both; secondary polycythemia; or documented pulmonary hypertension.

§ Scores for the Acute Physiology, Age, and Chronic Health Evaluation (APACHE II) can range from 0 to 71; higher scores indicate more severe illness.

¶ The Lung Injury Score did not include measures of static compliance.[34] The cumulative score was the sum of the chest radiography, hypoxemia, and positive end-expiratory pressure scores. Scores can range from 0 to 4; higher scores indicate more severe lung injury.

‖ The Multiple Organ Dysfunction Score can range from 0 to 24; higher scores indicate more severe multiorgan dysfunction.

**Patients could have more than one risk factor; 47 percent of patients had two or more risk factors, and 42 percent had both direct (e.g., pneumonia) and indirect (e.g., sepsis) risk factors.

VALIDATION OF DATA

Inclusion and exclusion criteria were independently verified for each patient by a principal investigator and a coinvestigator at each ICU. Discrepancies were resolved by an ICU physician who was not involved in the study. We audited the data base by obtaining a random sample of 10 percent of all charts and abstracting and independently verifying all ICU variables.

STATISTICAL ANALYSIS

The primary outcome measure of the study was the distance walked in six minutes 3, 6, and 12 months after discharge from the ICU. This measure provides a standardized, objective, integrated assessment of the cardiopulmonary and musculoskeletal system that is relevant to daily activities.[35]

A sample of 100 patients was required to demonstrate a difference of 50 m in a six-minute–walk test at each follow-up between patients with moderate lung injury (Lung Injury Score, less than 3.0) and those with severe lung injury (Lung Injury Score, 3.0 or higher) with an alpha level of 0.05 and a statistical power of 80 percent. Since these outcomes have not been reported for survivors of the acute respiratory distress syndrome, we based our estimates on data from patients with chronic obstructive pulmonary disease. We used a difference of 50 m because this is validated as a minimal clinically important difference among patients with chronic lung disease.[37]

We summarized continuous variables with medians and the 25th and 75th percentiles (the interquartile range) and used the Wilcoxon rank-sum test for comparisons between survivors and those who died. We summarized categorical variables using proportions and 95 percent confidence intervals and used the Pearson chi-square test for comparisons between survivors and those who died. We used Fisher's exact test when appropriate.

We performed univariate analyses to evaluate the potential determinants of long-term function expressed as the distance walked in six minutes. Multiple independent variables were identified a priori. Variables significant in the univariate analyses ($P<0.2$) were considered for inclusion in the multivariable linear regression analysis. We included age and sex in the final multivariable models because they are independent determinants of the distance walked in six minutes.[38] We performed the multivariate analysis using a backward stepwise selection for each follow-up period (3, 6, and 12 months), and covariates remained in the multivariable model if the associated P value was less than 0.2. This was done to maximize the number of covariates in each model and increase the variance explained (R^2). SAS software (version 8, SAS Institute) was used for all statistical analyses.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Over the 36-month recruitment period, we enrolled 198 of 228 eligible patients. Reasons for exclusion are outlined in Figure 1. Two patients with prior

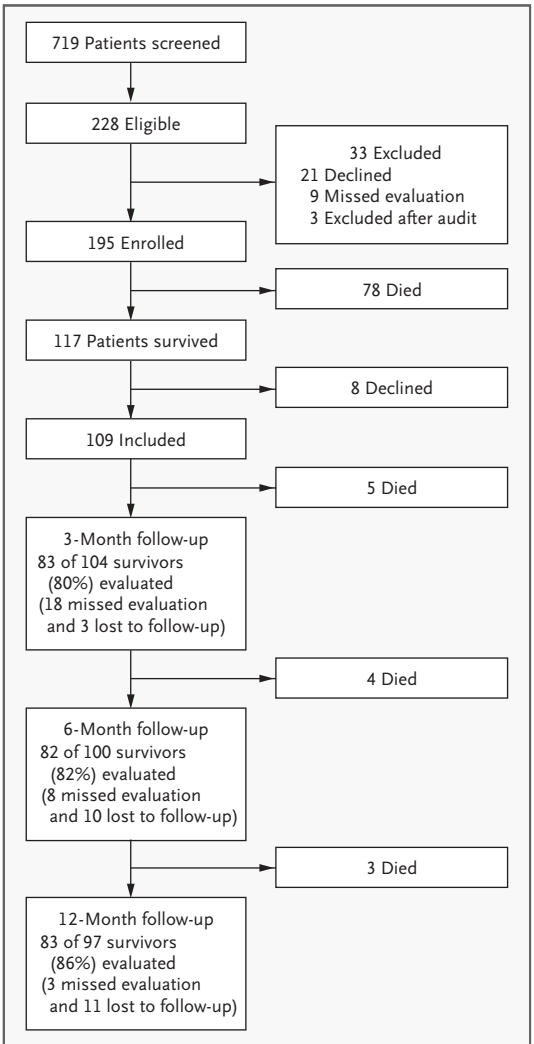

Figure 1. Enrollment of Patients with the Acute Respiratory Distress Syndrome and Follow-up for the First 12 Months after Discharge from the ICU.

pulmonary lobectomies and one patient with a history of psychiatric disease were excluded after the audit. Consent was obtained from 109 of 117 survivors, and these patients were included in the study (Fig. 1).

The actual median follow-up times for the visits at 3, 6, and 12 months were 2.0, 7.1, and 12.6 months, respectively. The rate of in-person follow-up at the three-month visit was 80 percent; 18 patients were not evaluated, because they were in a rehabilitation facility and inaccessible or because they declined a home visit. The rate of in-person follow-up at the 12-month visit was 86 percent. Forty-four percent of the patients received at least one home visit during the one-year follow-up period. Twelve patients died during the 12-month follow-up period, reflecting a 1-year mortality rate of 11 percent. Most deaths (9 of 12) occurred during the first six months after discharge from the ICU and were related to preexisting medical problems. Three patients died with multisystem organ failure, two died of hospital-acquired pneumonia, one died suddenly at home, one died of respiratory arrest, one of a pulmonary embolus, one of new-onset acute leukemia, one of hepatic failure, and two of unknown causes.

The median age of the patients with the acute respiratory distress syndrome who survived to be discharged from the ICU was 45 years, and 56 percent were male (66 of 117) (Table 1). The APACHE II score, Lung Injury Score, and Multiple Organ Dysfunction Score reflect the severity of illness in these patients. This group of patients spent a median of 25 days in the ICU and 48 days in the hospital. Twelve percent required renal-replacement therapy in the ICU. After discharge from the ICU, only one patient continued to undergo dialysis, and this patient had end-stage renal disease at admission.

GLOBAL ASSESSMENT

At the time of discharge from the ICU, patients who survived the acute respiratory distress syndrome were severely wasted and had lost 18 percent of their base-line body weight (Fig. 2). Seventy-one percent of patients (59 of 83) returned to their base-line weight by one year. All patients reported poor function and attributed this to the loss of muscle bulk, proximal weakness, and fatigue. Most patients had alopecia, which resolved by six months. Ten patients (12 percent) had marked and persistent pain at the sites of insertion of chest tubes at one year. Six patients (7 percent) had entrapment neuropathies.

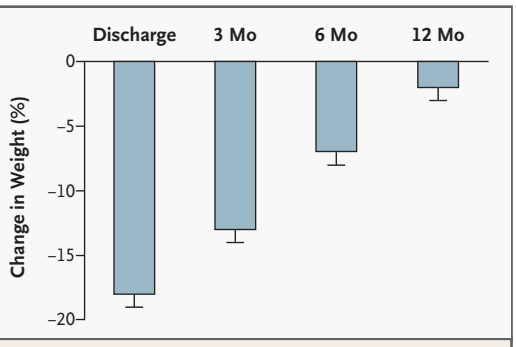

Figure 2. Mean (+SE) Change in Weight from Base Line among Patients with the Acute Respiratory Distress Syndrome at the Time of Discharge from the ICU and at 3, 6, and 12 Months.

Four (5 percent) had enlargement and immobility of large joints as a result of heterotopic ossification. Six (7 percent) were troubled by the appearance of their tracheostomy sites and had them surgically revised. Three patients (4 percent) had contractured fingers or frozen shoulders because of immobility during their stay in the ICU. Two patients (2 percent) underwent successful treatment of tracheal stenosis with laser excision of tissue.

PULMONARY-FUNCTION TESTING, CHEST RADIOGRAPHY, AND OXYGEN REQUIREMENTS

Patients had a mild restrictive pattern on lung-function testing, with a mild-to-moderate reduction in carbon monoxide diffusion capacity at three months (interquartile range, 54 to 77 percent of the predicted values) (Table 2). Median carbon monoxide diffusion capacity improved by 9 percentage points from month 3 to month 12 (from 63 percent to 72 percent of the predicted value). Median lung volume and spirometric measures were within 80 percent of the predicted values by six months. Because of weakness, six patients were unable to perform pulmonary-function tests at the three-month assessment. Chest radiographs were normal in 80 percent and revealed minor changes in 20 percent at one year. When present, radiologic changes included linear fibrosis, isolated areas of pleural thickening, and small, bullous cysts. None were receiving supplemental oxygen at the 12-month visit. Two patients were still receiving supplemental oxygen at the six-month visit: one died shortly thereafter, and the other no longer required oxygen at rest or on exertion after the six-month appointment.

Table 2. Recovery of Pulmonary Function among Patients with the Acute Respiratory Distress Syndrome during the First 12 Months after Discharge from the ICU.

Variable	3 Mo (N=71)*	6 Mo (N=77)†	12 Mo (N=80)‡
	median (interquartile range)		
Forced vital capacity (% of predicted)	72 (57–86)	80 (68–94)	85 (71–98)
Forced expiratory volume in one second (% of predicted)	75 (58–92)	85 (69–98)	86 (74–100)
Total lung capacity (% of predicted)§	92 (77–97)	92 (83–101)	95 (81–103)
Residual volume (% of predicted)§	107 (87–121)	97 (82–117)	105 (90–116)
Carbon monoxide diffusion capacity (% of predicted)§¶	63 (54–77)	70 (58–82)	72 (61–86)

* Ten patients were too sick to be evaluated at three months (six were too weak and unable to sit up, two were cognitively unable to be tested, and two were isolated because of an infection with methicillin-resistant *Staphylococcus aureus*), and two other patients were also not evaluated.
† Four patients were too sick to be evaluated at six months (two were cognitively unable to be tested, and two were isolated because of an infection with methicillin-resistant *S. aureus*), and one other patient was also not evaluated.
‡ Two patients were cognitively unable to complete testing at 12 months, and one other patient was also not evaluated.
§ This variable could not be assessed during home visits.
¶ Carbon monoxide diffusion capacity was not corrected for hemoglobin.

DISTANCE WALKED IN SIX MINUTES

The distance walked in six minutes improved over the 12 months after discharge from the ICU but still remained lower than the predicted value[38] (Table 3). The patients attributed exercise limitation to global muscle wasting and weakness, foot drop (as a result of nerve-entrapment syndromes that began in the ICU), immobility of large joints (heterotopic ossification[40,41]), and dyspnea. The proportion of patients whose arterial oxygen saturation fell below 88 percent during the six-minute–walk test (defined as "persistent pulmonary morbidity") was 10 percent at 3 months, 8 percent at 6 months, and 6 percent at 12 months.

RETURN TO WORK

One year after discharge from the ICU, 49 percent were working, and the majority of these patients had returned to their original position (Table 4). Reported reasons for not returning to work were as follows: persistent fatigue and weakness, poor functional status as a result of foot drop and immobility of large joints, work-related stress, voluntary retirement, and job retraining.

QUALITY OF LIFE

The scores for all domains of the SF-36 improved from 3 to 12 months after discharge from the ICU (Table 3). The scores for the physical role and physical functioning domains improved dramatically during the year, paralleling the incremental improvement in the distance walked in six minutes. At one year, scores for all domains except emotional role were below those of an age- and sex-matched control population.[39] At 3 months, 15 patients did not complete the SF-36 questionnaire, and 6 of those attributed this to fatigue or weakness. At 6 and 12 months, six and three patients, respectively, did not complete the questionnaire, and the reasons were not specified.

RELATION BETWEEN PATIENTS' CHARACTERISTICS AND DISTANCE WALKED IN SIX MINUTES

The results of univariate analyses are presented in Table 4. As compared with a Lung Injury Score of 3.0 or more, a score of less than 3.0 was significantly associated with a shorter distance walked in six minutes at 6 months ($P=0.009$) but not at 3 months ($P=0.98$) or 12 months ($P=0.82$). Treatment with any systemic corticosteroid during the admission to the ICU, the presence of illness acquired during the ICU stay, and the rate of resolution of the lung injury and multiorgan dysfunction during the ICU stay (as reflected by the slope of the Lung Injury Score and the Multiple Organ Dysfunction Score, respectively) were the most important determinants of the distance walked in six minutes during the first year of follow-up.

The results of multivariate analyses are also presented in Table 4. The slopes of the Lung Injury Score and the Multiple Organ Dysfunction Score were highly correlated; thus, only the slope of the Lung Injury Score was included in the final models. The APACHE II score and the presence of any illness acquired during the ICU stay were highly associated; the former was more informative at three months and the latter more informative at six months. The absence of systemic corticosteroid treatment during the stay in the intensive care unit had the strongest association with a longer distance walked in six minutes at three months ($R^2=0.31$). At six months, the absence of illness acquired during the ICU stay and a rapid resolution of lung injury (on the basis of the Lung Injury Score) during the ICU stay predicted a longer distance walked in six minutes ($R^2=0.37$). The only factor associated with a longer distance

walked in six minutes at 12 months was rapid resolution of lung injury during the ICU stay (R^2=0.10).

DISCUSSION

We found that patients who survived the acute respiratory distress syndrome have persistent functional limitation one year after being discharged from the ICU, largely as a result of muscle wasting and weakness and, to a lesser extent, to entrapment neuropathy, heterotopic ossification, and intrinsic pulmonary morbidity. Our results suggest that the inability to exercise is primarily due to extrapulmonary disease; our impression is that impaired muscle function had an important effect on the long-term outcomes in these patients.

We postulate that the observed muscle wasting and weakness in survivors of the acute respiratory distress syndrome is multifactorial and may be due in part to corticosteroid-induced and critical-illness–associated myopathy. The results of multivariate regression analysis support this hypothesis. At three months, we found that the use of any systemic corticosteroid treatment is the main determinant of the ability to exercise. At six months, the effect of the use of systemic corticosteroids is lost and the burden of illness acquired during the ICU stay and rate of resolution of illness (as reflected by the slopes of the Lung Injury Score and the Multiple Organ Dysfunction Score) become the important determinants of exercise capacity. A variety of changes in the nerves, muscles, or neuromuscular junctions may also explain our findings of muscle wasting and weakness, such as anterior-horn cell loss as a result of hypoxic myelopathy, the polyneuropathy of critical illness, atrophy or disuse myopathy resulting from prolonged use of sedation and paralytic agents, mitochondrial myopathy, and prolonged post-paralysis syndrome.[42]

The results of the six-minute–walk test and quality-of-life assessments are consistent with data published previously. Cooper and colleagues noted decreases in the distance walked in six minutes in a group of survivors of the acute respiratory distress syndrome who were evaluated one to two years after they participated in a trial of mechanical ventilation.[43] Davidson and colleagues found that survivors of the acute respiratory distress syndrome reported an important decrement in the physical functioning domain of the SF-36 23 months after discharge from the intensive care unit.[30] Angus et al. demonstrated that the quality of life of these pa-

Table 3. Ability to Exercise and Return to Work and Health-Related Quality of Life among Patients with the Acute Respiratory Distress Syndrome during the First 12 Months after Discharge from the ICU.

Outcome	3 Months	6 Months	12 Months
Distance walked in 6 min			
No. evaluated	80*	78†	81‡
Median — m	281	396	422
Interquartile range — m	55–454	244–500	277–510
Percentage of predicted value§	49	64	66
Returned to work — no./total no. (%)¶	13/83 (16)	26/82 (32)	40/82 (49)‖
Returned to original work — no./total no. (%)	10/13 (77)	23/26 (88)	31/40 (78)
SF-36 score**			
Physical functioning			
Median (normal value)	35 (90)	55 (89)	60 (89)
Interquartile range	15–58	30–75	35–85
Physical role			
Median (normal value)	0 (85)	0 (84)	25 (84)
Interquartile range	0–0	0–50	0–100
Pain			
Median (normal value)	42 (77)	53 (77)	62 (77)
Interquartile range	31–73	37–84	41–100
General health			
Median (normal value)	52 (78)	56 (77)	52 (77)
Interquartile range	35–67	36–74	35–77
Vitality			
Median (normal value)	45 (69)	55 (68)	55 (68)
Interquartile range	30–55	28–63	28–63
Social functioning			
Median (normal value)	38 (88)	63 (88)	63 (88)
Interquartile range	19–69	38–88	38–100
Emotional role			
Median (normal value)	33 (84)	67 (84)	100 (84)
Interquartile range	0–100	0–100	17–100
Mental health			
Median (normal value)	68 (78)	70 (78)	72 (78)
Interquartile range	54–80	54–88	52–88

* One patient was positive for methicillin-resistant *Staphylococcus aureus,* one was not evaluated, and one declined to be evaluated.

† Three patients were not evaluated, and one declined to be evaluated.

‡ One patient was not evaluated, and the distance walked was not recorded for one patient.

§ Normal values were calculated in an age- and sex-matched population according to the method of Enright and Sherrill.[38]

¶ This category includes return to school, home duties, volunteer work, or paid employment.

‖ Data on one patient were not recorded.

**The domains of the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) are defined as follows: physical functioning, the extent to which health limits physical activity; physical role, the extent to which physical health interferes with work or limits activity; pain, the intensity of pain and the effect of pain on patient's ability to work; general health, patient's own evaluation of his or her health or health outlook; vitality, the degree of energy the patient has; social functioning, the extent to which health or emotional problems interfere with social activities; emotional role, the extent to which emotional problems interfere with work or activities; and mental health, general mental health. Scores for each domain can range from 0 to 100; higher scores denote a better health-related quality of life. The normal Canadian values are from Hopman et al.[39] A total of 15 patients at three months, 6 patients at six months, and 3 patients at one year did not complete the questionnaires. The numbers evaluated were therefore 68 at three months, 76 at six months, and 80 at one year.

Table 4. Predictors of Distance Walked in Six Minutes during the First 12 Months after Discharge from the ICU.*

Variable	3 Months (N=83)		6 Months (N=82)		12 Months (N=83)	
	Univariate Analysis	Multivariate Analysis (R^2=0.31)	Univariate Analysis	Multivariate Analysis (R^2=0.37)	Univariate Analysis	Multivariate Analysis (R^2=0.10)
Age (in deciles)						
β coefficient	−30.2±14.1	−20.3±13.4	−15.4±13.1	−5.84±11.4	−0.4±12.6	−5.5±12.7
P value	0.04	0.14	0.24	0.61	0.98	0.67
Female sex						
β coefficient	−50.74±46.4	−18.55±41.9	−95.78±40.6	−111.5±37.5	−56.90±36.9	−52.0±38.3
P value	0.28	0.66	0.02	0.004	0.13	0.18
No systemic corticosteroid treatment						
β coefficient	178.18±43.7	127.0±47.5	116.16±41.1	61.0±40.5	72.70±37.8	55.7±38.9
P value	<0.001	0.009	0.006	0.14	0.06	0.16
Total days in ICU (increments of 7 days)						
β coefficient	−16.8±4.9	−8.0±5.2	−5.5±4.7	−6.5±4.6	−2.8±4.2	
P value	0.001	0.13	0.25	0.16	0.51	
Slope of Lung Injury Score†						
β coefficient	−529.4±180.4	−260.8±180.5	−591.33±156.6	−493.3±155.5	−277.6±146.8	−260.1±146.9
P value	0.004	0.15	<0.001	0.002	0.06	0.08
APACHE II score (increments of 5 units)‡						
β coefficient	−33.2±14.9	−18.3±14.0	−21.6±14.0		−7.4±12.5	
P value	0.03	0.19	0.13		0.56	
Illness acquired during ICU stay involving ≥1 organ systems (vs. none)§						
β coefficient	−108.4±45.8		−140.9±39.0	−121.7±38.2	−150.0±37.4	
P value	0.02		0.001	0.002	0.69	
Maximal Lung Injury Score during ICU admission (increments of 0.5 unit)†						
β coefficient	−3.2±23.6		−47.9±20.0		−4.5±18.7	
P value	0.89		0.02		0.81	
Lung Injury Score <3.0 (vs. ≥3.0)†						
β coefficient	−1.0±77.7		−175.1±65.8		−14.4±62.2	
P value	0.98		0.009		0.82	
Maximal Multiple Organ Dysfunction Score during ICU admission (increments of 2 units)¶						
β coefficient	−32.9±14.9		−0.55±14.1		−11.4±12.6	
P value	0.03		0.97		0.37	
Slope of Multiple Organ Dysfunction Score¶						
β coefficient	−114.61±58.6		−165.96±47.3		−77.7±47.1	
P value	0.05		0.001		0.10	

Table 4. (Continued.)

Variable	3 Months (N=83)		6 Months (N=82)		12 Months (N=83)	
	Univariate Analysis	Multivariate Analysis	Univariate Analysis	Multivariate Analysis	Univariate Analysis	Multivariate Analysis
Total days of ventilator use (increments of 7 days)						
β coefficient	−17.2±5.3		−5.0±5.0		−3.7±4.5	
P value	0.002		0.32		0.41	
Use of any paralytic agent						
β coefficient	−20.94±46.8		−82.94±41.1		−33.94±38.0	
P value	0.66		0.05		0.37	
Any use of high-frequency ventilation during ICU admission						
β coefficient	−26.05±49.7		−27.51±44.1		−2.80±39.4	
P value	0.60		0.53		0.94	
Body-mass index‖						
β coefficient	3.7±3.8		0.81±3.2		0.66±2.6	
P value	0.33		0.80		0.80	

* Plus–minus values are standard errors.
† The Lung Injury Score did not include measures of static compliance.[34] The cumulative score was the sum of the chest radiography, hypoxemia, and positive end-expiratory pressure scores. Scores can range from 0 to 4; higher scores indicate more severe lung injury. The change in scores over time during ICU admission is expressed as the slope of the score.
‡ Scores for the Acute Physiology, Age, and Chronic Health Evaluation (APACHE II) can range from 0 to 71; higher scores indicate more severe illness.
§ Illness acquired duing the ICU stay was defined on the basis of documented diagnostic categories that included the following: renal (need for renal-replacement therapy), neurologic (new seizure, clinical suspicion of hypoxic brain injury, critical-illness polyneuropathy, meningitis, or stroke on computed tomography of the brain), gastrointestinal (clinical evidence of upper or lower gastrointestinal bleeding or new coagulopathy), and cardiac (malignant arrhythmia, documented myocardial infarction, or endocarditis).
¶ The Multiple Organ Dysfunction Score can range from 0 to 24; higher scores indicate more severe multiorgan dysfunction. The change in scores over time during the ICU admission is expressed as the slope of the score.
‖ The body-mass index (the weight in kilograms divided by the square of the height in meters) was calculated at each period.

tients was compromised 6 and 12 months after hospital discharge.[31] Impaired muscle function may explain the compromised functional ability and quality of life in our cohort and those studied by other investigators.

Many studies of patients with the acute respiratory distress syndrome have focused on pulmonary morbidity and have shown that pulmonary function returns to normal or is nearly normal by six months to one year, with the exception of a persistent reduction in carbon monoxide diffusion capacity.[6-21,27] A more recent study suggested that survivors of the acute respiratory distress syndrome have important pulmonary symptoms and may have substantial limitations as a result of pulmonary disease related to the syndrome.[30]

These variable results may be due to several factors. First, the heterogeneity of acute lung disease encompassed by the definition of the acute respiratory distress syndrome may be an important reason for reported differences in pulmonary sequelae. Some patients in this cohort did not have diffuse alveolar damage. We found a 5 percent prevalence of bronchiolitis obliterans organizing pneumonia and bronchiolitis obliterans. These cases were diagnosed by open-lung biopsy, and treatment resulted in good pulmonary function. If other cohorts had a significant prevalence of bronchiolitis obliterans organizing pneumonia or bronchiolitis obliterans that went unrecognized and untreated, this might explain prior reports of pulmonary fibrosis and other unfavorable pulmonary outcomes in other cohorts. Second, muscle weakness may account for the restrictive changes on pulmonary-function testing and symptoms of dyspnea, but we did not measure maximal inspiratory or expiratory efforts. Finally, the long-term effect of an episode of the acute respiratory distress syndrome may be related to age and preexisting pulmonary function and may thus be cohort-specific. In our cohort of patients

who survived the acute respiratory distress syndrome, the median age was 45 years, few patients had important pulmonary dysfunction before becoming ill, and only 6 percent of patients had persistent pulmonary morbidity at one year.

We found that survivors of the acute respiratory distress syndrome continue to have functional limitations one year after their discharge from the ICU. We still do not know how long it takes for these patients to recover fully from their critical illness or whether complete recovery is possible in every case. Since we did not follow a control group of ICU survivors who did not have the acute respiratory distress syndrome, the sequelae we observed may not be specific to the syndrome, but rather may represent the typical residua of any severe, critical illness. Our data demonstrate the need for a detailed study of the nature of muscle wasting and weakness in these patients to determine whether it is truly specific to the acute respiratory distress syndrome and how we can change practices in the ICU and after discharge to ameliorate this disability.

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REFERENCES

1. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149:818-24.
2. Milberg JA, Davis DR, Steinberg KP, Hudson LD. Improved survival of patients with acute respiratory distress syndrome (ARDS): 1983-1993. JAMA 1995;273:306-9.
3. Kollef MH, Schuster DP. The acute respiratory distress syndrome. N Engl J Med 1995;332:27-37.
4. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-8.
5. Bersten AD, Edibam C, Hunt T, Moran J, Australian and New Zealand Intensive Care Society Clinical Trials Group. Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian states. Am J Respir Crit Care Med 2002;165:443-8.
6. Downs JB, Olsen GN. Pulmonary function following adult respiratory distress syndrome. Chest 1974;65:92-3.
7. Yernault JC, Englert M, Sergysels R, De Coster A. Pulmonary mechanics and diffusion after "shock lung." Thorax 1975;30:252-7.
8. Lakshminarayan S, Stanford RE, Petty TL. Prognosis after recovery from adult respiratory distress syndrome. Am Rev Respir Dis 1976;113:7-16.
9. Klein JJ, van Haeringen JR, Sluiter HJ, Holloway R, Peset R. Pulmonary function after recovery from the adult respiratory distress syndrome. Chest 1976;69:350-5.
10. Richardson JV, Light RW, Baskin TW, George RB. Late pulmonary function in survivors of adult respiratory distress syndrome. South Med J 1976;69:735-7, 740.
11. Rotman HH, Lavelle TF Jr, Dimcheff DG, VandenBelt RJ, Weg JG. Long-term physiologic consequences of the adult respiratory distress syndrome. Chest 1977;72:190-2.
12. Simpson DL, Goodman M, Spector SL, Petty TL. Long-term follow-up and bronchial reactivity testing in survivors of the adult respiratory distress syndrome. Am Rev Respir Dis 1978;117:449-54.
13. Yahav J, Lieberman P, Molho M. Pulmonary function following the adult respiratory distress syndrome. Chest 1978;74:247-50.
14. Lakshminarayan S, Hudson LD. Pulmonary function following the adult respiratory distress syndrome. Chest 1978;74:489-90.
15. Shaw RA, Whitcomb ME, Schonfeld SA. Pulmonary function after adult respiratory distress syndrome associated with Legionnaires' disease pneumonia. Arch Intern Med 1981;141:741-2.
16. Elliott CG, Morris AH, Cengiz M. Pulmonary function and exercise gas exchange in survivors of the adult respiratory distress syndrome. Am Rev Respir Dis 1981;123:492-5.
17. Alberts WM, Priest GR, Moser KM. The outlook for survivors of ARDS. Chest 1983;84:272-4.
18. Halevy A, Sirik Z, Adam YG, Lewinsohn G. Long-term evaluation of patients following the adult respiratory distress syndrome. Respir Care 1984;29:132-7.
19. Elliott CG, Rasmusson BY, Crapo RO, Morris AH, Jensen RL. Prediction of pulmonary function abnormalities after adult respiratory distress syndrome (ARDS). Am Rev Respir Dis 1987;135:634-8.
20. Ghio AJ, Elliott CG, Crapo RO, Berlin SL, Jensen RL. Impairment after adult respiratory distress syndrome: an evaluation based on American Thoracic Society recommendations. Am Rev Respir Dis 1989;139:1158-62. [Erratum, Am Rev Respir Dis 1989;140:862.]
21. Peters JI, Bell RC, Prihoda TJ, Harris G, Andrews C, Johanson WG. Clinical determinants of abnormalities in pulmonary functions in survivors of the adult respiratory distress syndrome. Am Rev Respir Dis 1989;139:1163-8.
22. Hopkins RO, Weaver LK, Pope D, Orme JF, Bigler ED, Larson-Lohr V. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. Am J Respir Crit Care Med 1999;160:50-6.
23. Rothenhausler HB, Ehrentraut S, Stoll C, Schelling G, Kapfhammer HP. The relationship between cognitive performance and employment status in long-term survivors of the acute respiratory distress syndrome: results of an exploratory study. Gen Hosp Psychiatry 2001;23:90-6.
24. Schelling G, Stoll C, Haller M, et al. Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome. Crit Care Med 1998;26:651-9.
25. Jones C, Griffiths RD, Humphris G, Skirrow PM. Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. Crit Care Med 2001;29:573-80.
26. Hupcey JE, Zimmerman HE. The need to know: experiences of critically ill patients. Am J Crit Care 2000;9:192-8.
27. McHugh LG, Milberg JA, Whitcomb ME, Schoene RB, Maunder RJ, Hudson LD. Recovery of function in survivors of the acute respiratory distress syndrome. Am J Respir Crit Care Med 1994;150:90-4.
28. Schelling G, Stoll C, Vogelmeier C, et al. Pulmonary function and health-related quality of life in a sample of long-term survivors of the acute respiratory distress syndrome. Intensive Care Med 2000;26:1304-11.
29. Weinert CR, Gross CR, Kangas JR, Bury CL, Marinelli WA. Health-related quality of life after acute lung injury. Am J Respir Crit Care Med 1997;156:1120-8.
30. Davidson TA, Caldwell ES, Curtis JR, Hudson LD, Steinberg KP. Reduced quality

of life in survivors of acute respiratory distress syndrome compared with critically ill control patients. JAMA 1999;281:354-60.
31. Angus DC, Musthafa AA, Clermont G, et al. Quality-adjusted survival in the first year after the acute respiratory distress syndrome. Am J Respir Crit Care Med 2001; 163:1389-94.
32. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985; 13:818-29.
33. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple Organ Dysfunction Score: a reliable descriptor of a complex clinical outcome. Crit Care Med 1995;23:1638-52.
34. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988;138:720-3. [Erratum, Am Rev Respir Dis 1989;139:1065.]
35. Weisman IM, Zeballos RJ. Clinical exercise testing. Clin Chest Med 2001;22: 679-701.
36. McHorney CA, Ware JE Jr, Lu JFR, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36). III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care 1994;32:40-66.
37. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease patients. Am J Respir Crit Care Med 1997;155: 1278-82.
38. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med 1998;158: 1384-7.
39. Hopman WM, Towheed T, Anastassiades T, et al. Canadian normative data for the SF-36 health survey. CMAJ 2000;163:265-71.
40. Clements NC Jr, Camilli AE. Heterotopic ossification complicating critical illness. Chest 1993;104:1526-8.
41. Jacobs JW, De Sonnaville PB, Hulsmans HM, van Rinsum AC, Bijlsma JW. Polyarticular heterotopic ossification complicating critical illness. Rheumatology (Oxford) 1999; 38:1145-9.
42. Anzueto A. Muscle dysfunction in the intensive care unit. Clin Chest Med 1999;20: 435-52.
43. Cooper AB, Ferguson ND, Hanly PJ, et al. Long-term follow-up of survivors of acute lung injury: lack of effect of a ventilation strategy to prevent barotrauma. Crit Care Med 1999;27:2616-21.