Muscle Weakness and 5-Year Survival in Acute Respiratory Distress Syndrome Survivors

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Abstract

Objective—To longitudinally evaluate the association of post-ICU muscle weakness and associated trajectories of weakness over time with 5-year survival.

Design—Longitudinal prospective cohort study over 5 years of follow-up

Patients—156 acute respiratory distress syndrome (ARDS) survivors

Setting—13 ICUs in 4 hospitals in Baltimore, MD

Interventions—None

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Measurements and Main Results—Strength was evaluated with standardized manual muscle testing using the Medical Research Council sumscore (range: 0–60, higher is better), with post-ICU weakness defined as sumscore <48. Muscle strength was assessed at hospital discharge and at 3, 6, 12, 24, 36, and 48 months after ARDS. At discharge, 38% of patients had muscle weakness. Every 1 point increase in sumscore at discharge was associated with improved survival (hazard ratio (95% confidence interval) 0.96 (0.94–0.98)), with similar findings longitudinally (0.95, 0.93–0.98). Having weakness at discharge was associated with worse 5-year survival (1.75, 1.01–3.03); but the association was attenuated (1.54, 0.82–2.89) when evaluated longitudinally over follow-up. Occurring in 50% of patients during follow-up, persisting and resolving trajectories of muscle weakness were associated with worse survival (3.01, 1.12–8.04; and 3.14, 1.40–7.03, respectively) compared to a trajectory of maintaining no muscle weakness.

Conclusions—At hospital discharge, >1/3 of ARDS survivors had muscle weakness. Greater strength at discharge and throughout follow-up was associated with improved 5-year survival. In patients with post-ICU weakness, both persisting and resolving trajectories, were commonly experienced and associated with worse survival during follow-up.

INTRODUCTION

Despite improving in-patient mortality for patients with acute respiratory distress syndrome (ARDS) and other critical illnesses,(1–3) survivors face increased mortality after hospital discharge.(4–8) Survivors also face muscle weakness and related physical impairments that persist for months and years after ARDS,(9–11) with recent studies demonstrating that objective in-patient measures of muscle weakness were associated with hospital mortality(12;13) and worse survival up to 1-year later.(14;15)

These findings justify the need to better understand longer-term patient outcomes beyond the initial months of recovery, including patient survival and associations of muscle weakness with long-term survival. Our objective, therefore, was to longitudinally evaluate the association of post-ICU muscle weakness with long-term survival until 5-years after ARDS, specifically evaluating muscle strength measured prior to hospital discharge and longitudinally thereafter. Additionally, we evaluate the association of trajectories in patients' recovery from muscle weakness in the years after ARDS and their subsequent survival.

METHODS

Study Design and Patients

In this cohort study, conducted in 13 medical, surgical and trauma ICUs at four teaching hospitals in Baltimore, MD, we prospectively screened and enrolled consecutive mechanically ventilated patients meeting the American-European Consensus Conference criteria for acute lung injury(16) that were in effect during the time of enrollment. Throughout this report, we use the term ARDS, rather than acute lung injury, to be

consistent with the more recent Berlin definition.(17) Relevant exclusion criteria included: 1) high short-term mortality unrelated to ARDS (life expectancy <6 months due to pre-existing illness or a physician order limiting the use of life support therapies at onset of ARDS); 2) important barrier to exposure or outcome assessment (pre-existing cognitive impairment, communication/language barrier, or homelessness); and 3) substantial exposure to critical illness/critical care services prior to enrollment (mechanically ventilated for >5 days before ARDS onset or transfer from another hospital with pre-existing ARDS of >24 hours duration). Institutional review board approval was obtained from all participating sites and written informed consent was obtained from all participants.

Primary Outcome: 5-Year Survival

Consenting patients were prospectively evaluated at 3, 6, 12, 24, 36, 48, and 60 months after ARDS onset. Vital status along with date and cause of death were ascertained from family members, with death date verified via a commercial version of the Social Security Death Master File.(18) Patients for whom vital status could not be determined were censored at their last day known to be alive.

Primary Exposure: Muscle Strength

As commonly done in prior critical care research,(12;15;19–21) patients' muscle strength was evaluated via standardized physical examination using manual muscle testing and the Medical Research Council (MRC) sumscore (range 0–60, higher score is better). All strength assessors underwent initial training and ongoing quality assurance review by a reference-rater (co-author NDC) with high inter-rater reliability.(22) Patients' strength was evaluated prior to hospital discharge and at each follow-up assessment. Muscle strength was evaluated both as a continuous (MRC sumscore) and binary (MRC sumscore <48) exposure variable. The binary evaluation of muscle strength, referred to hereafter as post-ICU-weakness, was defined as per prior research.(10;13;15;20)

Potential Confounders

Based on a prior publication,(23) a subset of risk factors for mortality after ARDS was considered for inclusion in this analysis as potential confounders of the exposure-outcome relationship. These variables included patient factors: age, sex, body mass index, and baseline comorbidity (Charlson comorbidity index(24) >1), and the following ICU factors: Acute Physiology and Chronic Health Evaluation II (APACHE II)(25) score within the first 24 hours of ICU admission, ARDS risk factor (sepsis vs. non-sepsis), type of ICU (medical ICU vs. other), source of admission (e.g. emergency room), mean daily Sequential Organ Failure Assessment (SOFA)(26) score in the ICU, daily sedation (Richmond Assessment of Sedation Scale)(27) and delirium (Confusion Assessment Method for the ICU)(28) status, cumulative dose of systemic corticosteroids and neuromuscular blocking medications, and the number of days with these medications, cumulative fluid balance, mean daily positive end-expiratory pressure (PEEP), mean daily ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen (P_aO_2/FiO_2), mean daily static lung compliance, mean tidal volume (per kilogram of predicted body weight),(29) mean daily respiratory rate (breaths per minute), total days of mechanical ventilation, and ICU length of stay. Missing data among potential confounders was rare (<1%) except for sedation and delirium. Multiple

imputation was used for the missing sedation and delirium assessments as described elsewhere.(30)

Statistical Methods

Descriptive statistics included median and interquartile range (IQR) for continuous variables, and percentages for categorical variables, with comparisons conducted using Wilcoxon rank-sum and Fisher's exact tests, respectively. Locally weighted regression (LOESS) was used to assess for linearity of association between continuous variable and survival, and if not linear, then they were categorized, as appropriate, based on the LOESS (e.g. Charlson Comorbidity Index, see Supplementary Digital Content). A Kaplan-Meier curve was used to describe the survival from hospital discharge until 5-years after ARDS onset, and a lasagna plot (31) was created to visualize muscle weakness trajectories over 5-year follow-up (Supplementary Digital Content Figure 1).

To evaluate the longitudinal association of muscle weakness with survival until 5-years post-ARDS, we used Cox proportional hazards regression models. To prevent potential over-fitting of the regression model, an initial multivariable model was created that included only potential confounders that had a significant (p<0.05) unadjusted association with 5-year survival in simple Cox regression analyses. From this initial multivariable model, variables with p<0.2 were retained to create the minimum set of potential confounders for adjustment in the subsequent models evaluating exposure-outcome association; these variables were age, Charlson comorbidity index >1, and mean daily SOFA score (Supplementary Digital Content Table 1). *Post-hoc* analyses included evaluation of baseline activities of daily living (ADLs) and instrumental activities of daily living (IADLs) as potential confounders. Neither variable met inclusion into the minimum set of potential confounders (Supplementary Digital Content Table 1). Variance inflation factors were evaluated to confirm the absence of multicollinearity of these potential confounders. Both continuous and binary measures of muscle strength at hospital discharge were then evaluated in separate multivariable Cox regression models adjusting for these three potential confounders. Additionally, both measures of muscle strength were evaluated as time-varying exposures in separate multivariable Cox regression models adjusting for the same potential confounders. For each multivariable model, Martingale residual plots were assessed to confirm that there were no departures from linearity for continuous exposure and confounder variables. In addition, Schoenfeld residual plots were assessed to evaluate the proportional hazards assumption which demonstrated some evidence of non-proportional hazards over time for MRC sumscore and post-ICU weakness indicator; however, since the estimated hazard ratios within each year of follow-up were qualitatively similar, a single hazard ratio is reported for each exposure variable.

In addition to evaluating muscle strength at hospital discharge and each follow-up assessment, changes in post-ICU muscle weakness over time (i.e., trajectories of muscle weakness) were evaluated longitudinally, in a time-varying manner, using the same multivariable Cox regression model described above. For this analysis, patients needed to survive for at least 2 strength assessments to evaluate change over time (i.e. trajectory). This time-varying exposure of change in weakness from one time point to the next was

categorized as "No weakness" (i.e., consecutive assessments of No Weakness and No Weakness), "Persisting weakness" (i.e., from Weakness to Weakness), "Resolving weakness" (i.e., from Weakness to No Weakness), and "New weakness" (i.e., from No weakness at or after hospital discharge to subsequent Weakness).

RESULTS

There were 156 consenting and eligible patients for evaluation in this analysis (Figure 1). Of these 156 patients surviving until hospital discharge, 53 (34%) died after hospital discharge during 5-year follow-up (Figure 2), with the following categories for causes of death: infection 16 (30%), cardiovascular 11 (21%), cancer 6 (11%), gastrointestinal 4 (8%), respiratory 4 (8%), renal 3 (6%), other causes 3 (6%), and unknown cause 6 (11%) (see Supplemental Digital Content Table 2 for trends over time for top 2 causes of death). Those who died were significantly older with greater comorbidity, organ failure and days of delirium in the ICU, and hospital length of stay (Table 1). At hospital discharge, 38% of patients had post-ICU muscle weakness, and the median (interquartile range) MRC sumscore was significantly lower for those who died during 5-year follow-up vs. survivors (44 (36–52) vs. 51 (46–58), p<0.001), with 55% versus 30% (p= 0.003) having post-ICU muscle weakness (Table 1).

After adjusting for age, Charlson comorbidity index, and mean daily SOFA score, increased muscle strength at hospital discharge was associated with long-term survival (Table 2), with every 1 point increase in MRC sumscore (range: 0 to 60) associated with improved survival (hazard ratio for death (HR) 0.96, 95% confidence interval (95% CI) 0.94 – 0.98; p<0.001). When analyzed longitudinally as a time-varying exposure over 5-year follow-up, each 1 point increase in muscle strength sumscore demonstrated a similar association with survival (0.95, 0.93 – 0.98; p<0.001). Having post-ICU muscle weakness (i.e., strength score <48) at hospital discharge was associated with worse survival (1.75, 1.01 – 3.03; p=0.004), with attenuation of this association, to become non-significant, when analyzed longitudinally as a time-varying exposure over the 5-year follow-up (1.54, 0.82 – 2.89; p=0.174) (Table 2).

There were 588 consecutive assessments from 140 patients in this study, including, 38 (7%) assessments from 22 (16%) patients demonstrating persisting weakness, and 70 (12%) assessments from 63 (45%) patients demonstrating resolving weakness (Table 3, see Supplemental Digital Content Figure 1). Compared to a trajectory of maintaining no weakness, both persistent and resolving weakness trajectories were associated with significantly worse survival (3.01, 1.12 – 8.04; p=0.028, and 3.14, 1.40 – 7.03; p=0.005, respectively, Table 3), while a trajectory of "New weakness" (i.e. going from "No weakness" at or after hospital discharge to subsequent "Weakness") was not associated with subsequent survival (0.99, 0.22 – 4.43; p=0.985).

DISCUSSION

This 5-year, prospective multi-site longitudinal follow-up study of 156 ARDS survivors found that 38% had muscle weakness at hospital discharge, and that greater muscle strength at both hospital discharge and longitudinally during follow-up was independently associated

with improved survival. Trajectories of persistent and resolving weakness were experienced by 50% of patients and both trajectories were associated with a >3 times greater hazard of subsequent death.

Given improving in-patient survival for patients with ARDS and other critical illnesses,(1–3) but ongoing mortality after hospital discharge,(4–8) understanding potential risk factors or markers for decreased long-term survival can help identify potential interventions to evaluate in future studies. For example, muscle weakness is known to be associated with short-term in-hospital mortality, as shown in a study of mechanically ventilated patients (odds ratio [95% confidence interval], 7.8 [2.4, 25.3]),(12) and a study of surgical ICU patients (odds ratio 0.95 [0.90, 0.99] for 1 point increase in muscle strength sumscore).(13) Another study of mechanically ventilated patients reported decreased 90-day survival in those with post-ICU weakness at ICU discharge,(14) and a study of mostly surgical patients with ICU stay >7 days reported that weakness at ICU discharge was associated with 1-year survival (HR [95% CI] of 2.1 [1.1, 3.9] for those with MRC sumscore of 36 – 47, and 4.3 [2.1, 8.8] for those with sumscore <36).(15) We build on these prior studies by evaluating the association of post-ICU weakness with long-term survival over 5-years; where roughly half of the deaths occurred during years 2 through 5. In our study, we found that at hospital discharge, increased muscle strength is associated with improved survival and having muscle weakness (i.e., a sumscore <48) is associated with worse survival over 5-year follow-up.

Additionally, our study is novel in that muscle strength was assessed not only in-hospital, but also longitudinally over 5-year follow-up. Post-discharge muscle weakness is an important aspect of survivorship since it is associated with impaired respiratory muscle strength, physical functioning, and quality of life.(10) In our longitudinal analyses, greater muscle strength was associated with improved survival; however, the association with binary modelling of muscle weakness (i.e., sumscore <48) was attenuated, becoming non-significant, perhaps due to decreased prevalence of muscle weakness and mortality in the cohort over the duration of follow-up. Lastly, longitudinal evaluation of muscle strength allowed for a novel exploration of the association of trajectories of muscle weakness over time with subsequent survival, with our study demonstrating that both persistent weakness and recovering from weakness, which occurred in 50% of patients during follow-up, were similarly associated with worse survival compared to trajectories of no weakness.

Across the multivariable regression analyses in our study, age and baseline comorbidity remained significantly associated with post-hospital survival, while acute severity of illness in the ICU (e.g., daily SOFA score) was not; a finding that is consistent with previous studies.(32;33) Even after adjusting for these variables, post-ICU muscle weakness was associated with worse 5-year survival. Future studies should aim to elucidate the mechanisms that link muscle weakness with mortality. For example, muscle weakness in survivors may be a marker for new-onset frailty or pre-existing frailty worsened by critical illness,(34;35) The pathogenesis of frailty is hypothesized to involve multi-system dysfunction, including the musculoskeletal system, and be related to chronic inflammation, rendering patients vulnerable to deleterious health outcomes and setting them to a path of progressive decline(36;37) and decreased survival.(38)

Our analyses of post-ICU trajectories of muscle weakness yielded clues that there are likely complex associations of weakness with mortality. In our study, the trajectory of new weakness was not associated with worse survival, signaling that it may represent a period similar to that of a "pre-frail" state, a state in which patients are still resistant to physiologic challenges.(37) However, once weak, the patient becomes vulnerable resulting in adverse outcomes, including death. This vulnerability may continue for some time in those with a trajectory of recovery. The risk of adverse outcomes may be higher in ICU survivors, even in the recovery process, since they often experience profound and persistent muscle wasting and weakness in the ICU, along other complications of bed rest.(10;39;40) These ideas may explain our finding that even a trajectory of resolving weakness was associated with worse survival.

Understanding the mechanism(s) linking muscle weakness and mortality will help refine potential interventions to improve long-term survival, but also clarify if a multi-faceted approach is necessary to mitigate the post-hospital mortality in ICU survivors. For now, with currently available evidence, prevention of muscle weakness via starting rehabilitation interventions shortly after start of mechanical ventilation may be an important consideration for improving long-term outcomes.(41–43) For example, one study demonstrated that early ICU rehabilitation was associated with decreased 1-year re-hospitalization and mortality.(44)

This study has several strengths, including being a multisite, prospective study with long-term, longitudinal follow-up until 5-years after ARDS. This study also has potential limitations. First, this study could not prospectively measure pre-ICU muscle strength as these ARDS patients were typically admitted emergently; hence, just as in routine clinical practice, we are unable to determine if the post-ICU weakness is incident or prevalent. Nonetheless, these findings have clinical value in indicating that post-ICU weakness, irrespective of baseline status, has prognostic significance for long-term survival, even after accounting for patient age, comorbidity and severity of organ failure in the ICU. Second, 1/3 of patients could not be assessed for muscle strength prior to discharge, excluding them from analyses. However, these excluded patients were generally similar to the cohort of patients retained in this study, except for older age and greater dependency in activities of daily living at hospital discharge (Digital Supplement Content Table 3). Hence, the observed associations with survival may be conservative. Furthermore, only 3% of patients were unable to complete strength assessment at least once during the course of follow-up, helping minimize bias in our longitudinal assessments. Third, this study could not adjust for other factors (e.g. pre-ICU frailty, chronic inflammation, any interventions such as physical rehabilitation)(45) and potential time-varying confounders (e.g. re-hospitalizations,) that may have affected the association of muscle weakness with survival. Future studies of long-term survival should account for these issues to potentially refine these associations. Fourth, as an observational study, causality cannot be proven; hence, more research is needed to understand if post-ICU weakness is directly associated with mortality or if post-ICU weakness is a marker for another mechanism more directly responsible for mortality. Lastly, the results of this study may not be generalizable to other ICU populations since only ARDS patients, enrolled from 4 hospitals in a single city, were studied.

In conclusion, this multi-site, prospective longitudinal study found that over 1/3 of ARDS survivors had muscle weakness at hospital discharge. Increased strength at hospital discharge and longitudinally over follow-up was consistently, independently, and significantly associated with improved 5-year survival. Once weak, both resolving and persistent trajectories of weakness were associated with worse subsequent survival, with most patients experiencing these two trajectories during follow-up. Given a growing number of survivors of critical illness, future research should include larger-sized, multi-center studies to confirm these findings. Moreover, given these findings and complementary results of prior studies evaluating shorter-term survival outcomes, future research should evaluate potential mechanisms underlying the association between muscle weakness and survival, and whether early interventions can reduce post-ICU weakness and improve both physical function and survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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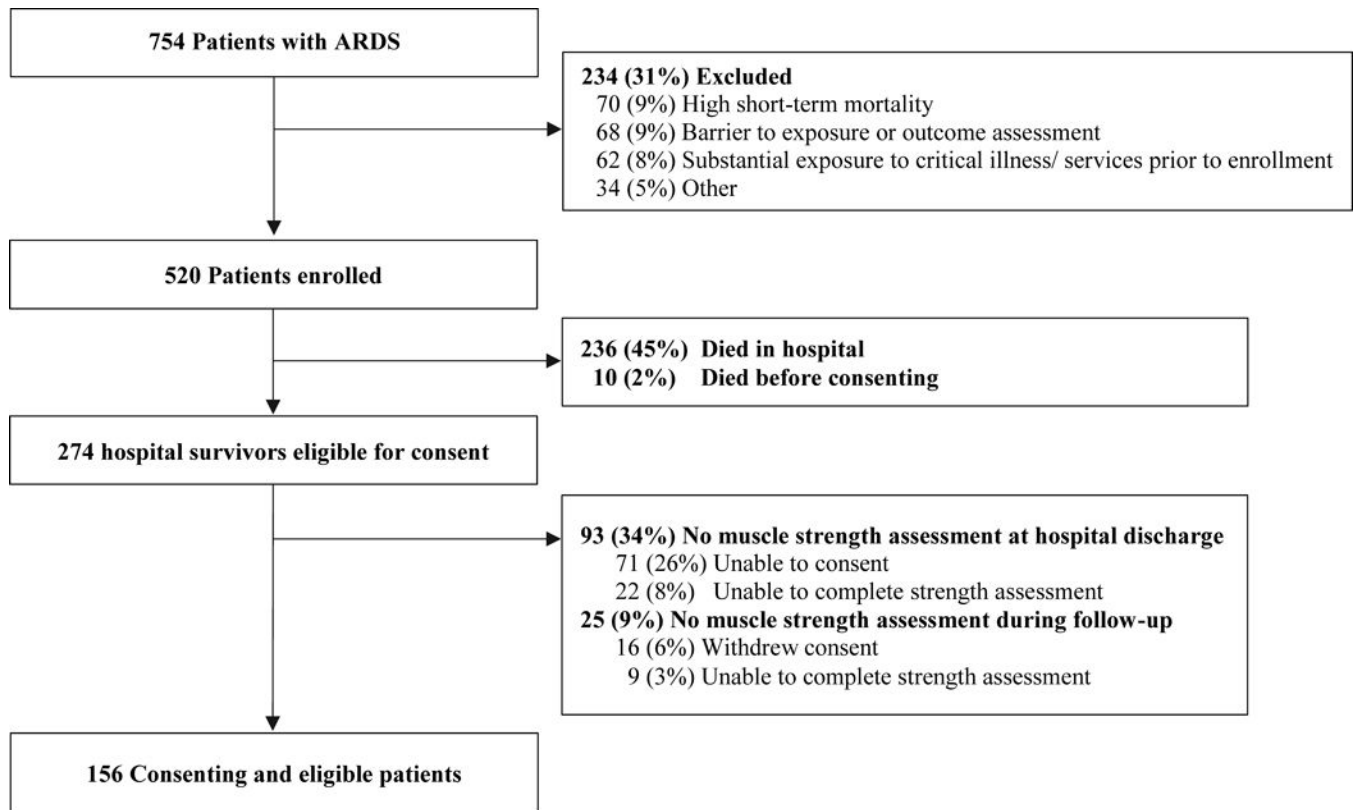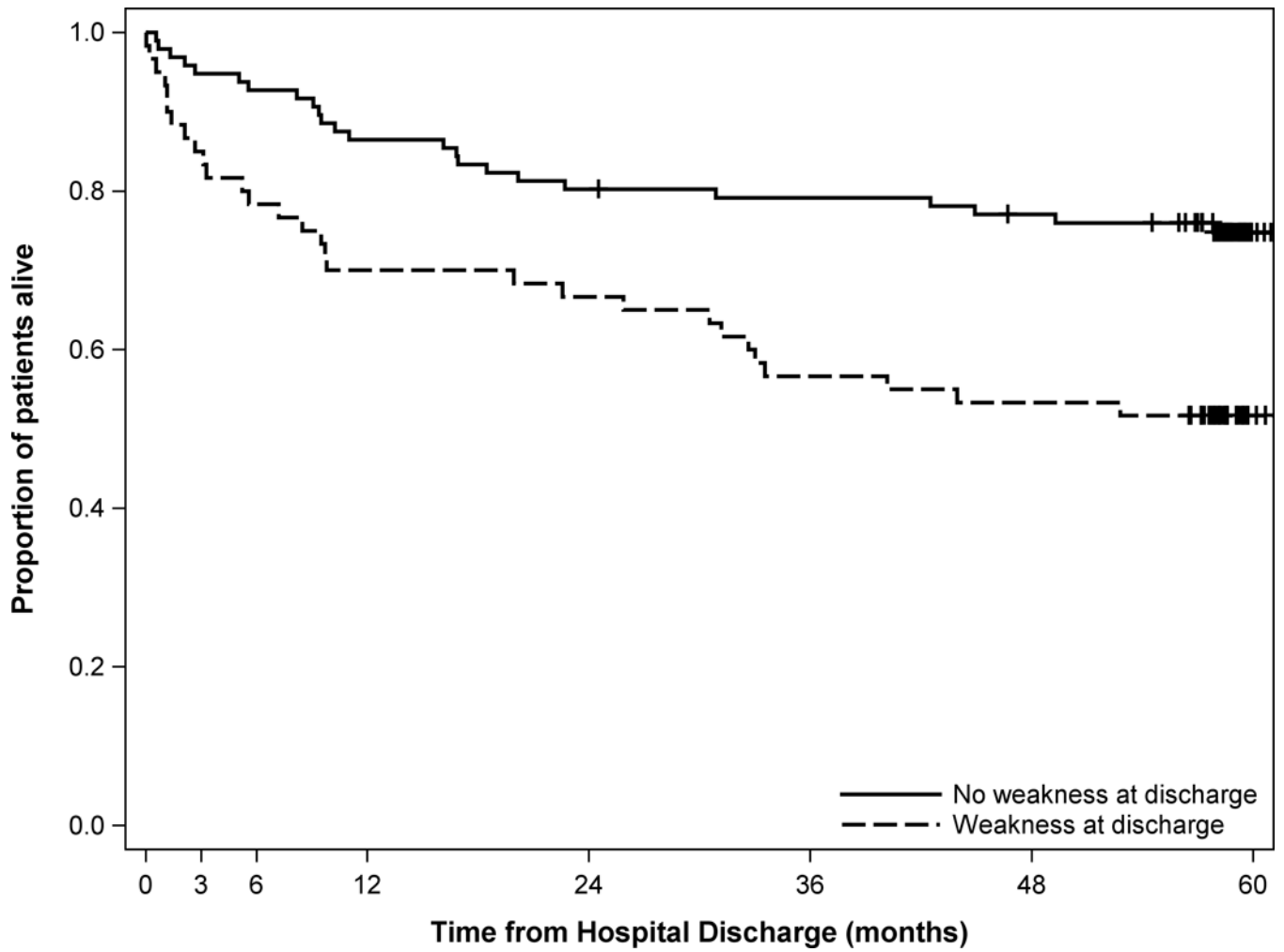
Figure 1.
Patient Flow Chart

Figure 2.
Kaplan-Meier curve of 5-year survival after hospital discharge for 156 ARDS patients
comparing those with muscle weakness vs. those without muscle weakness at hospital
discharge*

* Log-rank test p-value = 0.002

Table 1

Characteristics of 156 ARDS survivors, by subsequent mortality status at 5 years after ARDS onset

Characteristics	All patients (n=156)	Alive (n=103)	Dead (n=53)	p-value[*]
Baseline characteristics				
Male, No. (%)	84 (54)	57 (55)	27 (51)	0.615
Age (years)	47 (40–57)	45 (38–51)	56 (44–64)	<0.001
Body Mass Index, No. (%)				0.754
Underweight (<18.5 kg/m^2)	5 (3)	3 (3)	2 (4)	
Normal weight (18.5 – 24.9 kg/m^2)	44 (28)	28 (27)	16 (30)	
Overweight (25–30 kg/m^2)	50 (32)	36 (35)	14 (26)	
Obese (>30 kg/m^2)	57 (37)	36 (35)	21 (40)	
Charlson comorbidity index	1 (1–3)	1 (0–2)	3 (1–5)	<0.001
Critical illness/ICU characteristics				
APACHE II score	23 (17–29)	23 (17–28)	24 (17–30)	0.310
Non-pulmonary sepsis as ARDS risk factor	32 (21)	24 (23)	8 (15)	0.296
Admission from emergency department	74 (47)	50 (49)	24 (45)	0.737
Admission to medical ICU	127 (81)	80 (78)	47 (89)	0.128
Mean daily SOFA score	5 (4–7)	5 (4–7)	6 (5–8)	0.006
Days of delirium	5 (3–9)	5 (3–8)	7 (4–10)	0.009
Days of deep sedation	4 (2–8)	2 (2–9)	3 (0–8)	0.203
Corticosteroids use (ever), No. (%)	87 (56)	52 (50)	35 (66)	0.088
Days of corticosteroid use, if any	7 (4–13)	7 (3–11)	8 (5–15)	0.097
Cumulative prednisone dose, if any (mg) [**]	366 (193–1079)	403 (156–1169)	363 (288–840)	0.382
Neuromuscular blocker use (ever), No. (%)	32 (21)	27 (26)	5 (9)	0.020
Days of neuromuscular blocker use, if any	1 (1–2)	1 (1–2)	1 (1–1)	0.489
Cumulative vecuronium dose, if any (mg)	10 (10–37)	16 (10–39)	10 (8–10)	0.235
Cumulative fluid balance (liters)	3 (–2 to 10)	3 (–2 to 9)	5 (–3 to 14)	0.688
Days of mechanical ventilation	10 (6–17)	9 (6–16)	10 (7–21)	0.141
Length of stay in ICU (days)	15 (10–23)	14 (9–21)	17 (11–30)	0.068
Length of stay in hospital (days)	26 (17–36)	23 (16–34)	30 (21–45)	0.014
Hospital discharge muscle strength				
Muscle strength MRC sumscore (range: 0 – 60)	50 (42–55)	51 (46–58)	44 (36–52)	<0.001
Post-ICU weakness (MRC sumscore <48), No. (%)	60 (38)	31 (30)	29 (55)	0.003

Abbreviations: ARDS, acute respiratory distress syndrome; APACHE II=Acute Physiology And Chronic Health Evaluation II; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; MRC, Medical Research Council

Data are presented as median (interquartile range), unless stated otherwise. Proportions may not add to 100% because of rounding.

[*] Wilcoxon rank-sum and Fisher's exact tests were used for continuous variables (presented as median [inter-quartile range]) and categorical variables (presented as numbers [percentage]), respectively

[**] Corticosteroids doses converted to prednisone-equivalents using standard conversions(43)

[***] For continuous measures, the mean of all available measures for each patient were averaged, and these averages were summarized as median (interquartile range).

Table 2

Continuous and binary assessments of muscle strength and 5-year survival for 156 ARDS patients

Predictor	5-year Survival and Strength Assessment at Hospital Discharge[*]		5-year Survival and Strength Assessment over Longitudinal Follow-Up[**]	
	Adjusted hazard ratio (95% CI)	p-value[*]	Adjusted hazard ratio (95% CI)	p-value[**]
Multivariable Regression Model 1 (continuous)				
Manual muscle strength sumscore (for 1 point increase)	**0.96 (0.94 – 0.98)**	**<0.001**	**0.95 (0.93 – 0.98)**	**<0.001**
Age at enrollment	1.04 (1.02 – 1.06)	<0.001	1.04 (1.02 – 1.06)	<0.001
Comorbidity prior to ARDS (Charlson index(24) >1)	2.52 (1.35 – 4.73)	0.004	2.97 (1.53 – 5.74)	0.001
Mean daily SOFA score in ICU	1.08 (0.97 – 1.21)	0.154	1.09 (0.98 – 1.21)	0.125
Multivariable Model 2 (binary)				
Post-ICU weakness (strength score <48)	**1.75 (1.01 – 3.03)**	**0.044**	**1.54 (0.82 – 2.89)**	**0.174**
Age at enrollment	1.04 (1.02 – 1.07)	<0.001	1.04 (1.02 – 1.06)	<0.001
Comorbidity prior to ARDS (Charlson index(24) >1)	2.36 (1.25 – 4.46)	0.008	2.88 (1.48 – 5.59)	0.002
Mean daily SOFA score in ICU	1.10 (0.99 – 1.23)	0.079	1.10 (0.99 – 1.22)	0.086

Abbreviations: CI, confidence interval; SOFA, Sequential Organ Failure Assessment

[*] Muscle strength was assessed prior to hospital and evaluated in a multivariable Cox regression model adjusting for age, comorbidity, and daily SOFA score

[**] Muscle strength was assessed prior to hospital discharge and at 3, 6, 12, 24, 36, and 48-month follow-up points and evaluated as a time-varying exposure in a multivariable Cox regression model adjusting for age, comorbidity, and daily SOFA score

Table 3

Trajectory of muscle weakness and subsequent survival over 5-year follow-up [*]

Trajectory pattern (weakness status at consecutive assessments)	No. (%) of patients[**]	No. (%) of consecutive assessments over 5-year follow-up	Adjusted Hazard ratio[***] (95% CI)	p-value
No weakness (from No weakness to No weakness)	121 (86%)	443 (75%)	1.00	
Persisting weakness (from Weakness to Weakness)	22 (16%)	38 (7%)	3.01 (1.12 – 8.04)	0.028
Resolving weakness (from Weakness to No weakness)	63 (45%)	70 (12%)	3.14 (1.40 – 7.03)	0.005
New weakness (from No weakness to Weakness)	35 (25%)	37 (6%)	0.99 (0.22 – 4.43)	0.985

Abbreviations: ICU, intensive care unit; CI, confidence interval

[*] Change in post-ICU weakness status (i.e., MRC sumscore <48) from one longitudinal follow-up assessment to the next available assessment and its association with survival time after the second assessment during this 5-year prospective follow-up study. Longitudinal follow-up assessments were performed prior to hospital discharge and at 3, 6, 12, 24, 36, and 48-month follow-up

[**] Proportions will not add up to 100% since a patient can be in more than 1 category. For this analyses, patients must have at least 2 strength assessments for which 140 (90%) of 156 patients were eligible.

[***] Each trajectory pattern was modeled as a time-varying exposure in a multivariable Cox model that adjusted for age at enrollment, Charlson comorbidity index, and mean daily Sequential Organ Failure Assessment score in the ICU