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Physical declines occurring after hospital discharge in ARDS survivors: a 5-year longitudinal study

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Abstract

Purpose: Survivors of acute respiratory distress syndrome (ARDS) are at high risk for new or ongoing physical declines after hospital discharge. The objective of our study was to evaluate the epidemiology of physical declines over 5-year follow-up and identify patients at risk for decline.

Methods: This multi-site prospective cohort study evaluated ARDS survivors who completed a physical status assessment at 3 or 6 months post-discharge. Three measures were evaluated: muscle strength (Medical Resource Council sumscore); exercise capacity [6-min walk test (6MWT)]; physical functioning [36-Item Short Form Health Survey (SF-36 survey)]. Patients were defined as "declined" if a comparison of their current and prior score showed a decrease that was greater than the Reliable Change Index—or if the patient died. Risk factors [pre-ARDS baseline status, intensive care unit (ICU) illness severity, and other intensive care variables] were evaluated using longitudinal, generalized linear regression models for each measure.

Results: During the follow-up of 193 ARDS survivors (55 % male; median age 49 years), 166 (86 %) experienced decline in ≥1 physical measure (including death) and 133 (69 %) experienced a physical decline (excluding death). For all measures, age was a significant risk factor [odds ratios (OR) 1.34–1.69 per decade; $p < 0.001$]. Pre-ARDS comorbidity (Charlson Index) was independently associated with declines in strength and exercise capacity (OR 1.10 and 1.18, respectively; $p < 0.02$), and organ failure [maximum daily Sequential Organ Failure Assessment (SOFA) score in ICU] was associated with declines in strength (OR 1.06 per 1 point of SOFA score; $p = 0.02$).

Conclusions: Over the follow-up period, the majority of ARDS survivors experienced a physical decline, with older age and pre-ICU comorbidity being important risk factors for this decline.

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Take-home message: Over a 5-year longitudinal follow-up, 86 % of survivors experienced ≥1 episodes of physical decline (including death), and 69 % experienced a physical decline (excluding death). Age and pre-existing comorbidities were independently associated with declines in muscle strength and exercise capacity. Physical rehabilitation interventions should be specifically designed and evaluated for ARDS survivors who are older and have greater pre-ICU comorbidity.

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Keywords: Acute respiratory distress syndrome, Intensive care unit, Recovery of function, Physical function

Introduction

Survivors of acute respiratory distress syndrome (ARDS) and other critical illnesses frequently experience long-lasting physical complications [1–6]. Although not fully characterized, survivors have varying trajectories of physical recovery post-ARDS, including being at risk for ongoing or intermittent/relapsing patterns of decline after hospital discharge [2, 5, 6]. This impaired physical status poses high burdens for patients, caregivers, healthcare systems, and society [7–9]. Early identification of ARDS survivors at the highest risk for physical decline in the years after hospital discharge is important for creating targeted interventions that can reduce morbidity, mortality, and healthcare utilization. The objectives of this study were to evaluate the epidemiology of physical decline after hospital discharge in ARDS survivors and to identify patient and intensive care unit (ICU) risk factors for such decline over a 5-year follow-up. We hypothesized that patient characteristics (e.g., age, pre-ICU comorbidities) would increase the risk of physical decline.

Methods

Study design and population

This 5-year longitudinal analysis is part of the Improving Care for ALI Patients (ICAP) study which recruited mechanically ventilated patients with acute lung injury, as determined by the American–European Consensus criteria [10] in effect at the time of study recruitment (2004–2007) [11] (ClinicalTrials.gov identifier NCT00300248). Consistent with the more recent Berlin criteria [12], we used the term ARDS to describe these patients, who were followed until late 2012. The ICAP study recruited patients from 13 ICUs in four hospitals in Baltimore, MD [5]. Exclusion criteria, evaluated based on patients' status prior to ARDS, are described in the Electronic Supplementary Material (ESM). Written informed consent was obtained from patients, participants received financial compensation for research assessments at clinic visits, and all sites had Institutional Review Board approval for this research [11]. This research was performed in accordance with ethical standards established in the 1964 Declaration of Helsinki and later amendments.

To target patients who may be capable of engaging in post-discharge interventions, ICAP participants were included in this analysis if they completed ≥1 physical assessments at 3 or 6 months of follow-up. The characteristics of the 193 survivors included in this study are compared to the originally enrolled patients in ESM Table 1. Notably, the included population was younger and healthier (e.g., lower Charlson comorbidity score) than participants who died and were ineligible for this evaluation.

Physical status measures and outcomes

We evaluated three distinct measures of physical status spanning the World Health Organization's International Classification of Functioning, Disability and Health [13], namely, muscle strength, exercise capacity, and physical functioning. Muscle strength [14] measures "structure and functional impairment" and was scored as the percentage of the maximum Medical Research Council (MRC) sumscore (range 0–60, with higher scores indicating greater strength, and a score of <48 designated as "ICU-acquired weakness") [15]. Exercise capacity [evaluated using the 6-min walk test (6MWT)] [16, 17]) measured "activity limitation". The 6MWT was performed based on American Thoracic Society guidelines [16], using a single test and the longest walking distance available, and the results are reported as percent predicted value based on established norms [18]. Physical functioning [evaluated using the self-reported 36-Item Short Form Health Survey Physical Function domain (SF-36 PF)] measures "participation restriction." The SF-36 PF score was measured as the percentage of age-and sex-matched predicted value, with higher scores indicating better function.

Similar to previously published definitions [19, 20], each patient was defined as "declined" when a comparison of his/her current and prior score revealed a decrease that was greater than the Reliable Change Index (RCI) [21] for each physical measure at each follow-up. Patients who died were marked as "declined" in all measures. If a patient did not "decline", then the outcome was defined as "stable/improved". The RCI was calculated using previously published data [14, 22], and the RCI thresholds were 3.2, 13.9, and 26.5 for muscle strength (MRC percent of maximum score), exercise capacity (6MWT percent predicted), and physical functioning (SF-36 PF percent predicted), respectively. At the 1-year follow-up, a patient was determined to have declined versus being stable/improved using the measures of the earlier of the preceding 3- and 6-month assessments; thereafter decline was determined based on a comparison of consecutive annual visits (i.e., 12 vs. 24 months; 24 vs. 36 months, and so forth).

Prior to analysis, patients with a missing outcome had their data reviewed to determine if the data were missing due to a known decline in physical function (e.g.,

testing not done due to the patient being bed bound). If this were the case, the outcome for that time point was imputed as "declined" with 11 such imputations for strength (2 % of observations), 17 (3 %) for exercise capacity, and three (<1 %) for physical function. For the subsequent assessment, imputed values were counted as missing since there was no comparison value in the previous year. Missing data that could not be imputed remained missing.

Exposure variables

The exposure variables were selected a priori [23]. Patient baseline (pre-ARDS) variables included: age, sex, Charlson Comorbidity Index (CCI) [24], and Functional Comorbidity Index [25]. ICU severity of illness measures included: Acute Physiology and Chronic Health Evaluation II score at ICU admission [26], organ failure status [maximum daily Sequential Organ Failure Assessment (SOFA) score in ICU] [27], and acute renal failure requiring dialysis (ever vs. never). ICU variables included: mean daily blood glucose level (modeled as >150 vs. ≤150 mg/dl based on prior research [28], along with a separate indicator for pre-existing diabetes); mean daily doses of benzodiazepines (in midazolam-equivalents [29]), opioids (in intravenous morphine-equivalents [30]), and systemic corticosteroids (in prednisone-equivalents [31], and also modeled as ever vs. never); coma (proportion of ICU days with Richmond Agitation Sedation Scale score [32] −4 or −5); delirium (proportion of non-comatose ICU days with a positive Confusion Assessment Method score for ICU assessment [33]); durations of mechanical ventilation, bed rest (see ESM), and ICU stay. Multiple imputation with chained equations [34] was used to impute missing data for sedation and delirium assessments, similar to prior studies [35].

Statistical methods

Descriptive analysis, including lasagna and spaghetti plots [36] to longitudinally display each patients' outcome, was conducted.

For each outcome, a separate generalized linear mixed model, with a random intercept for each patient and main effects for each follow-up time, was used to evaluate bivariable associations with each exposure variable. Linearity of the association of each continuous exposure variable with each outcome was confirmed via inspection of locally weighted scatterplot smoothing (LOWESS) plots.

To avoid overfitting the multivariable models, we created three multivariable sub-models to separately evaluate exposure variables within each of the three categories, i.e., patient characteristics, severity of illness, and ICU variables. Pre-existing diabetes was included as an ICU exposure given its relevance with the hyperglycemia ICU variable. Exposure variables were included in their respective sub-model if the variable had a bivariable association, at $p < 0.15$, with any of the three physical status measures. Exposure variables with an independent association ($p < 0.05$) in the multivariable sub-models with any of the three physical status measures were included in a final multivariable model.

Standard regression diagnostics, including testing for multicollinearity [5, 37], were assessed. Due to collinearity with bed rest, ICU length of stay and mechanical ventilation were excluded from the ICU sub-model. A single statistical interaction evaluated the CCI and bed rest variables, revealing no important effect across common values of these variables. Hence, the interaction term was not included in the final model. To test the sensitivity of our results to a potential floor effect (i.e., patient scoring lower than the RCI and not be designated as "declined" in next assessment), the regression analyses were re-run as multinomial regression models with three possible outcomes, namely, stable/improved, decline, or not assessable due to floor effect, for comparison with the primary results. We also conducted a second sensitivity analysis using a multinomial regression model that separated mortality from physical decline to evaluate three distinct categories for patient outcome, namely, stable/improved, decline, or death, allowing a comparison of stable/improved versus decline without death. Additionally, a post hoc analysis assessed the impact of variables measuring ARDS severity (SOFA respiratory score at enrollment) and physical therapy in the ICU on the ICU sub-model (ESM). Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC) and STATA 13.0 (StataCorp LP, College Station, TX), with a two-sided $p < 0.05$ used to indicate statistical significance.

Results

Study population and physical status over 5-year follow-up

In total, 193 patients, with a median age of 49 (interquartile range 41–58) years, were eligible for the analysis, of whom 55 % ($n = 107$) were male (Table 1). Almost half of patients ($n = 79$, 41 %) were discharged home, with 31 % of all follow-up assessments conducted in the home setting ($n = 309/1013$) rather than at the research clinic. Summary data for the physical status measures over the 5-year follow-up period are given in Fig. 1 and ESM Table 2. The majority of patients ($n = 166$, 86 %) declined at least once in at least one outcome, with 133 (69 %) experiencing a physical decline ever (excluding death) and 64 (33 %) people eventually dying during the follow-up period (ESM Table 3; ESM Figure). Of the patients with any decline (including death), 153 (92 %) experienced decline(s) in muscle strength (MRC), 103 (62 %)

Table 1 Description of patient cohort ($N = 193$)

Variables	Values Median (IQR) or No. (%)
Patient baseline variables	
Age (years)	49 [41–58]
Male	107 (55)
Functional comorbidity index score	1 [1–3]
Charlson comorbidity index score	1 [0–3]
Severity of illness variables	
APACHE II score at ICU admission	23 [19– 28]
Maximum daily SOFA organ failure score in ICU	9 [7–11]
Dialysis in ICU	44 (23)
Severity of ARDS (respiratory SOFA score)[a]	4 (3, 4)
Physical therapy in the ICU	100 (52)
Intensive care unit variables	
Diabetes[b]	37 (19)
Mean daily glucose (mg/dl)	123 [114–136]
Mean glucose >150 mg/dl	31 (16)
Mean daily midazolam-equivalent dose, per patient[c] [29]	33 [8–83]
Mean daily, morphine-equivalent dose, per patient[c] [30]	94 [39–193]
Mean daily prednisone equivalent dose, per patient[c] [31]	4 [0–32]
Any steroids	106 (55)
Percentage ICU days in coma[d]	35 [16–52]
Percentage ICU days in delirium	68 [44–94]
Mechanical ventilation duration (days)	10 [6–17]
Bed rest duration (days)[e]	11 [6–18]
ICU length of stay (days)	15 [10–23]

Data in table are presented as the median with the interquartile range given in square brackets or as a number with the percentage in parenthesis

ARDS Acute respiratory distress syndrome, *APACHE* Acute Physiology and Chronic Health Evaluation, *SOFA* Sequential Organ Failure Assessment, *ICU* intensive care unit

[a] ARDS was measured using the respiratory component of the SOFA score at the time of study enrollment (range 0–4), where a score of 4 represents a $Pa0_2/Fi0_2$ ratio of <100

[b] Diabetes is included in the ICU characteristics model given its relevance with the hyperglycemia (i.e., the "Glucose >150") ICU variable

[c] If a patient did not receive a drug on a given day, a daily dose of 0 was used for calculating mean dose over all ICU days

[d] Coma is defined as the proportion of ICU days with a Richmond Agitation Sedation Scale (RASS) score [32] of −4 or −5

[e] Duration of bed rest was based on nursing documentation of activity level

had decline(s) in exercise capacity (6MWT), 109 (66 %) had decline(s) in physical functioning (SF-36 PF), and 78 (47 %) declined in all three physical status measures or died during follow-up. More than one-half of patients experienced decline(s) in strength and either exercise capacity or physical functioning (MRC and 6MWT $n = 99$, 60 %; MRC and SF-36 PF $n = 98$, 59 %), and 80 (48 %) patients experienced decline(s) in both exercise capacity and physical functioning (Fig. 2).

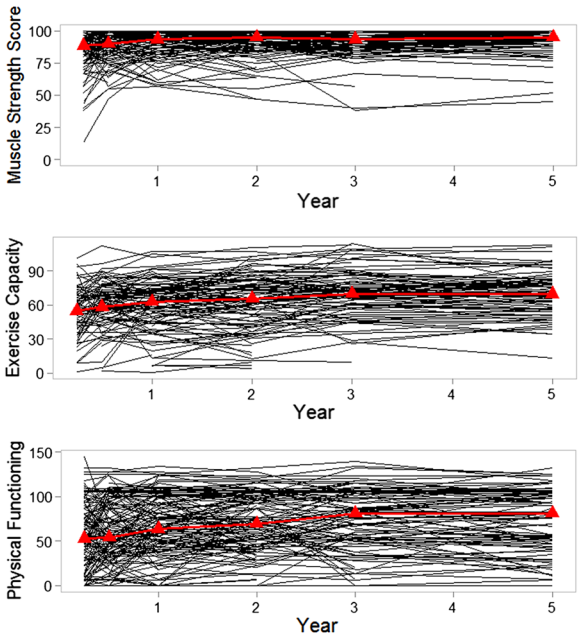

Fig. 1 Individual patient physical health status at each assessment over the 5-year longitudinal follow-up period. Each *black line* illustrates an individual patient's trajectory on the physical health outcome assessment between years 1 to 5. *Red triangles* Median outcome value at each time point. A total of 64 patients died during the study period

Figure 3 illustrates each individual patient's outcome over the follow-up period. The percentage of survivors with stable/improved status for all 5 years ranged from 9 to 36 % depending on the measure evaluated ($n = 18$ for strength, $n = 54$ for exercise capacity, $n = 70$ for physical functioning). More than 25 % of patients had a decline in physical status during their first year post-discharge, including 7 % who died during this time. Of the 36 patients who survived until their 12-month assessment and then died, 31 (86 %) experienced a decline in at least one outcome before death. A proportion of patients (11–23 %) who declined, but did not die in year 1, also declined at least once more in years 2–5 ($n = 42/185$ for muscle strength, $n = 23/182$ for exercise capacity, $n = 21/189$ for self-reported physical functioning). Within the cohort, 20–37 % were stable/improved in year 1 and then declined at least once in years 2–5 ($n = 68/185$ for muscle strength, $n = 37/182$ for exercise capacity, $n = 54/189$ for self-reported physical health).

Unadjusted bivariable associations of exposures with decline

Patient age, functional comorbidity index, and CCI were significantly associated with decline for all three physical measures. Each severity of illness exposure variable

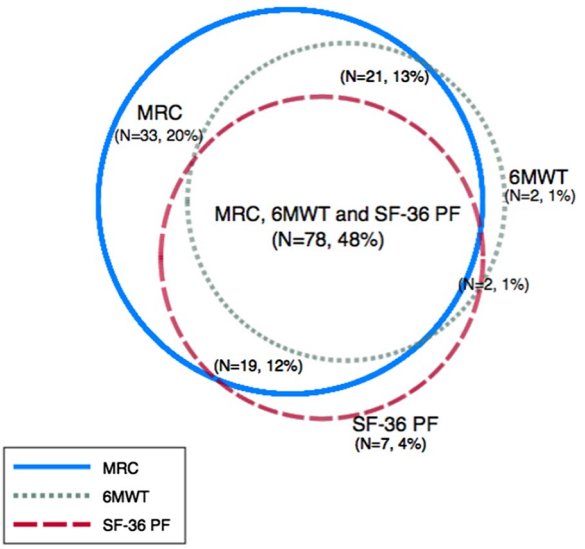

Fig. 2 Number and percentage of survivors of acute respiratory distress syndrome (ARDS) with at least one decline in one of the three physical status measures (muscle strength, exercise capacity, and physical functioning) over the 5-year longitudinal follow-up. Among the entire sample of 193 ARDS survivors over the follow-up, 166 (86 %) patients had at least one decline in at least one physical status outcome measure, or died; 21 (11 %) patients never declined; six patients (3 %) were missing one or more of the physical status outcomes. Four patients who declined but were missing outcome variables prohibiting assignment to the above categories are not shown. *MRC* Medical Research Council sumscore, *6MWT* 6-min walk test score, *36-SF PF* 36-Item Short Form Health Survey Physical Function domain

was significantly associated with ≥1 measures, and the following ICU exposures associated with ≥1 measures: mean daily glucose >150 mg/dl, pre-existing diabetes, midazolam-equivalent dose, percentage of ICU days in coma, and durations of mechanical ventilation, bed rest and ICU stay (ESM Table 4).

Adjusted multivariable associations of exposures with decline

In the multivariable sub-models evaluating patient characteristics (Table 2), age and CCI were independently associated with decline ($p < 0.05$). In the severity of illness sub-model, maximum SOFA score and need for dialysis were independently associated with decline in strength and exercise capacity, respectively. In the ICU sub-model, pre-existing diabetes, midazolam-equivalent dose, and bed rest duration were independently associated with decline in ≥1 measures.

In the final multivariable model, the significant independent association between age and decline in each of the three physical measures remained, with a 34–69 % increase in the odds of decline for every decade increase in age ($p < 0.001$). The CCI was independently associated with decline in strength [odds ratio (OR) 1.10, 95 % confidence interval (CI) 1.02–1.18], and exercise capacity (OR 1.18, 95 % CI 1.05–1.32), but did not reach statistical significance for self-reported physical functioning (OR 1.08, 95 % CI 0.98–1.18). ICU organ dysfunction had a significant association with decline in strength (OR 1.06; 95 % CI 1.01–1.11) (Table 3).

Over 5-year follow-up, the odds of decline did not change significantly over time, with the exception of a reduced odds of decline for muscle strength and exercise capacity comparing year 5 to year 1 [OR (95 % CI): 0.47 (0.27–0.82), and 0.45 (0.22–0.91), respectively].

Sensitivity analysis

Sensitivity analysis to evaluate for a potential floor effect of the outcome measures demonstrated similar findings to the primary results. Moreover, the exclusion of death from the composite outcome measure produced results similar to those of the primary analysis, except that the association of CCI was attenuated in the sensitivity analysis versus the primary results [OR for strength 1.07 ($p = 0.114$) vs. 1.10 ($p = 0.018$); OR for exercise capacity: 1.09 ($p = 0.159$) vs. 1.18 ($p = 0.006$); see ESM Table 5a–c].

Discussion

In this multi-site, prospective cohort study of 193 survivors of ARDS, over the 5-year longitudinal follow-up period, 166 (86 %) experienced decline(s) in physical status from their post-discharge state (including death), with 133 (69 %) experiencing a physical decline (excluding death). The majority had a decline in ≥1 measures (i.e., strength, exercise capacity, and self-reported physical functioning). Patients who had stable or improved physical status during the first year after discharge commonly experienced a subsequent decline. Older age and greater comorbidity prior to ARDS onset were significantly associated with a decline in at least two of the three physical measures, while severity of illness and ICU variables were not consistently and significantly associated with decline.

Our findings compliment those reported in prior studies. A multi-site Canadian study evaluating ICU survivors aged ≥80 years reported that age and comorbidity were significantly associated with recovery (measured using SF-36 domain PF) at 1 year [20]. Our study extends these findings to younger ARDS survivors, given the similar findings in our cohort with a median age of <50 years. Moreover, among the adults aged ≥70 years admitted to the ICU, those with a greater disability prior to hospitalization had a worse disability 1 year after discharge [38], and only one-half recovered their pre-ICU function at

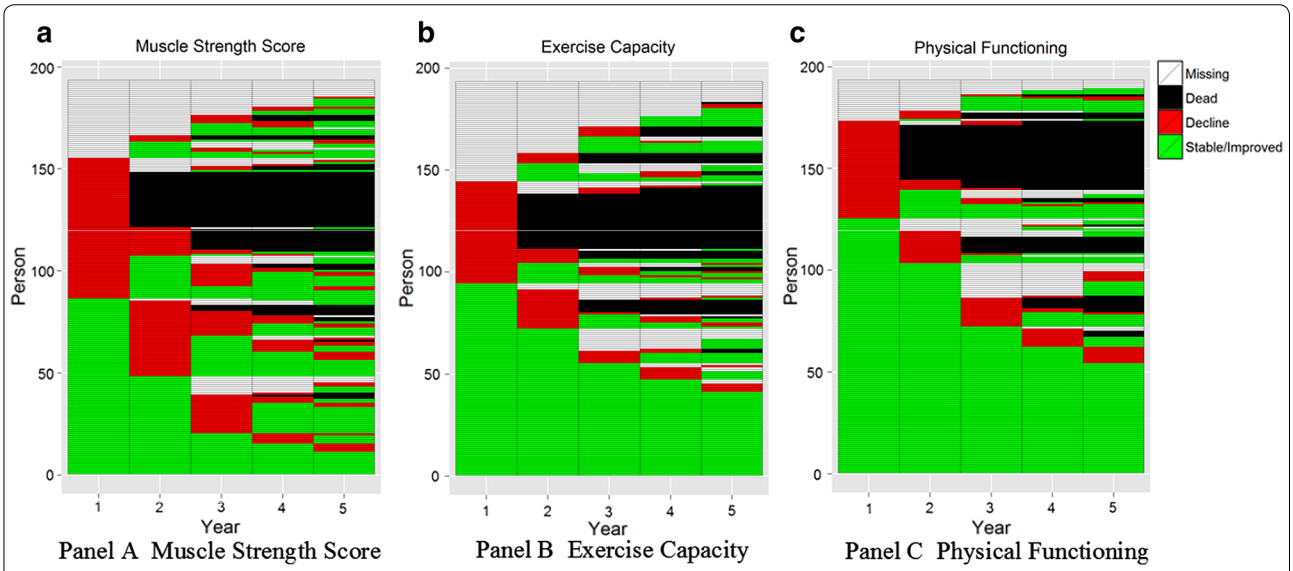

Fig. 3 Physical status outcome measure for each ARDS survivor over 5-year annual follow-up. **a** Muscle strength score, **b** exercise capacity, **c** physical functioning. Each *row* within each figure illustrates the outcome (e.g., decline, stable/improved) of one ARDS survivor at each assessment point between years 1 to 5. For each of the three physical status measures, the outcome for each individual patient was defined as "declined" if their current versus immediate prior score demonstrated a decrease greater than the Reliable Change Index [21] for the physical status measure or if the patient had died, as done in prior research [19, 20]. Cells shaded black represent a patient who died during the previous assessment and therefore no additional information is available. These graphs illustrate that, of the entire population, 153 patients (79 %) had ≥1 decline(s) in muscle strength (MRC sumscore), 103 (53 %) had ≥1 decline(s) in exercise capacity (6MWT), and 109 (56 %) had ≥1 decline(s) in self-reported physical functioning (SF-36 PF); declines in all outcomes include death as described in the "Methods" section

6 months post-discharge [39]. Our study furthers these findings by demonstrating that much younger survivors frequently have physical declines beyond 1 year of follow-up, even if they initially demonstrated improvement or stability.

Identifying survivors' trajectories of physical outcomes after hospital discharge is important in terms designing interventions at the most beneficial time and in the appropriate population [40]. A multi-center Canadian study recently identified four disability-risk groups with differing recovery trajectories based on age, ICU length of stay, and functional dependency [41]. The oldest patients (>65 years) with the longest ICU stay (≥2 weeks) had the worst outcomes, with 40 % dying within the first year [41]. Our study provides additional data on the trajectories of recovery by reporting 5-year outcomes. Within our younger and healthier population, >25 % declined in ≥1 physical measures in the year after discharge, with a majority declining again during years 2–5 of follow-up.

Our study adds novel empirical data on patterns of long-term trajectories after critical illness. Using a proposed framework of prototypical trajectories after acute illness [6], we found that (depending on the physical outcome measured) 9–36 % of our cohort were stable/improved over the entire 5-year period, in accordance with the "big-hit" trajectory (i.e., acute functional decline during ICU, but subsequent recovery). Among survivors with available measures, 11–23 % declined in year 1 of follow-up and then declined again in years 2–5, similar to the proposed "slow-burn" trajectory (i.e., consistent decline over time), and 20–37 % were stable/improved in year 1 subsequently declining at least once in years 2–5, similar to the "relapsing recurrences" trajectory (i.e., repeated acute exacerbations and partial recoveries). Hence, ARDS survivors frequently experience declines during their post-discharge "recovery", with approximately one-quarter to one-third fitting into each of three different proposed prototypical recovery trajectories.

This work emphasizes the importance of age and comorbidity [2, 8] in evaluating three distinct measures of physical status. Given the aging population [42, 43], more adults will be admitted to the ICU, survive, and be at risk of physical decline and increased healthcare utilization [8]. Our patient population was relatively young and still experienced substantial physical decline based on age- and sex-adjusted values. Identifying new interventions, such as rehabilitation and nutritional interventions, to keep vulnerable patients, such as older survivors with pre-existing comorbidity, from continued physical decline during recovery is important for improving healthcare quality and value. These findings are especially important in terms of targeting specific patient populations for future studies, given that existing research

Table 2 Adjusted associations with annual decline or death in each physical status measure over the 5-year follow-up

Risk factor[a]	Muscle strength[b] multivariable sub-model	*p* value[c]	Exercise capacity[d] multivariable sub-model	*p* value[c]	Physical function[e] multivariable sub-model	*p* value[c]
Patient characteristics multivariable sub-model:						
Age, per decade	1.34 (1.18, 1.52)	<0.001	1.69 (1.40, 2.04)	<0.001	1.54 (1.30, 1.82)	<0.001
Male	0.76 (0.55, 1.06)	0.110	0.78 (0.48, 1.28)	0.330	1.01 (0.65, 1.56)	0.970
Functional comorbidity index	1.06 (0.94, 1.20)	0.317	1.13 (0.94, 1.37)	0.201	1.04 (0.88, 1.22)	0.656
Charlson comorbidity index	1.11 (1.03, 1.20)	0.006	1.18 (1.06, 1.32)	0.004	1.11 (1.01, 1.22)	0.038
Severity of illness multivariable sub-model:						
APACHE severity of illness score	0.99 (0.97, 1.02)	0.580	1.03 (1.00, 1.07)	0.064	1.00 (0.98, 1.03)	0.830
Maximum daily SOFA organ failure score	1.08 (1.02, 1.15)	0.013	1.00 (0.92, 1.10)	0.914	1.04 (0.96, 1.13)	0.332
Need for dialysis	1.15 (0.69, 1.91)	0.595	1.46 (0.70, 3.05)	0.310	1.94 (1.04, 3.61)	0.037
Intensive care multivariable sub-model:						
Mean glucose over 150 mg/dl	0.75 (0.41, 1.36)	0.345	1.77 (0.91, 3.42)	0.091	1.76 (0.95, 3.29)	0.074
Diabetes	1.78 (1.05, 3.00)	0.031	1.80 (0.98, 3.30)	0.058	1.62 (0.92, 2.86)	0.094
Mean daily midazolam-equivalent dose, per 10 mg increase[f]	0.99 (0.98, 1.02	0.478	0.98 (0.95, 1.01)	0.170	0.96 (0.93, 1.00)	0.038
Mean daily, morphine-equivalent dose, per 10 mg increase[f]	0.99 (0.98, 1.00)	0.140	1.00 (0.98, 1.01)	0.879	1.00 (0.98, 1.02)	0.994
Any steroids	1.30 (0.90, 1.87)	0.165	1.17 (0.75, 1.84)	0.487	0.92 (0.59, 1.43)	0.723
Percentage ICU days coma, per 10 %	1.00 (0.93, 1.09)	0.913	0.90 (0.82, 1.00)	0.051	0.99 (0.90, 1.09)	0.797
Duration of bed rest, per week	1.14 (1.03, 1.26)	0.010	1.21 (1.08, 1.36)	0.001	1.22 (1.09, 1.36)	<0.001

Data are presented as the odds ratio (OR) with the 95 % confidence interval (95 % CI) given in parenthesis. Odds ratios of >1 are interpreted as an increase in the odds of decline

[a] All risk factors are listed for each sub-model and indicators for time (ORs for time are not presented)

[b] Muscle strength is reported as a percentage of maximum score, evaluated by manual muscle strength testing using the Medical Resource Council (MRC) sumscore (range, 0–60; <48 designated as "ICU-acquired weakness")

[c] *p* values were calculated using generalized linear models, with a random intercept for each patient

[d] Exercise capacity is reported as the percentage of predicted value for the 6-min walk test

[e] Physical Functioning is reported as the percent of age- and sex-matched predicted value on the self-reported physical functioning domain of the SF-36 Medical Outcomes Survey

[f] All drugs are modeled as mean daily dose per patient. If a patient did not receive a drug on a given day, the daily dose was zero. Mean dose was calculated over all ICU days

evaluating post-discharge interventions has proven challenging [44, 45].

In our prior research [5], the duration of bed rest in ICU was cross-sectionally associated with muscle weakness. In the current analysis, the ICU sub-model similarly demonstrated that bed rest was significantly associated with decline across strength, exercise capacity and physical functioning over the 5-year follow-up. However, in the final model, the association was attenuated, potentially because the current analysis is underpowered given differences in the prior versus current analysis (e.g., the prior analysis was cross-sectional evaluation in all patients versus the current analysis being a longitudinal analysis of a binary outcome of "decline" greater than the RCI for the measures).

The study strengths include multi-site enrollment across different types of ICUs, 5-year longitudinal follow-up, ascertainment of pre-ARDS comorbidities, and assessment of physical status using three distinct measures linked to clinically important outcomes [5, 17, 46, 47]. However, there are a number of limitations. First, this was an observational study, and we therefore cannot infer a cause–effect relationship between the risk factors and decline in physical outcome, nor can we

Table 3 Adjusted associations of decline in each physical status measure or death over each 5-year annual follow-up in the final multivariable model

Risk factor[a]	Muscle strength[b] multivariable model	*p* value[c]	Exercise capacity[d] multivariable model	*p* value[c]	Physical function[e] multivariable model	*p* value[c]
Age, per decade	1.34 (1.18, 1.52)	<0.001	1.69 (1.39, 2.05)	<0.001	1.48 (1.23, 1.77)	<0.001
Charlson comorbidity index	1.10 (1.02, 1.18)	0.018	1.18 (1.05, 1.32)	0.006	1.08 (0.98, 1.18)	0.131
Maximum daily SOFA organ failure score	1.06 (1.01, 1.11)	0.022	1.01 (0.94, 1.10)	0.756	1.05 (0.98, 1.12)	0.193
Diabetes	1.15 (0.74, 1.76)	0.537	1.59 (0.87, 2.93)	0.132	1.53 (0.90, 2.59)	0.117
Mean daily midazolam-equivalent dose, per 10 mg increase[f]	0.99 (0.97, 1.01)	0.512	1.00 (0.96, 1.03)	0.775	0.99 (0.96, 1.01)	0.327
Duration of bed rest, per week	1.07 (0.94, 1.23)	0.306	1.16 (0.97, 1.39)	0.113	1.14 (0.99, 1.30)	0.060

Data are presented as the OR with the 95 % CI given in parenthesis. Odds ratios of >1 are interpreted as an increase in the odds of decline

[a] All risk factors are listed for each sub-model and indicators for time (ORs for time are not presented)

[b] Muscle strength is reported as a percentage of maximum score, evaluated by manual muscle strength testing using the MRC sumscore (range, 0–60; <48 designated as "ICU-acquired weakness")

[c] *p* values were calculated using generalized linear models, with a random intercept for each patient

[d] Exercise capacity is reported as the percent of predicted value for the 6-min walk test

[e] Physical Functioning is reported as the percent of age-sex matched predicted value on the self-reported physical functioning domain of the SF-36 Medical Outcomes Survey

[f] Drug modeled as mean daily dose per patient. If a patient did not receive a drug on a given day, the daily dose was zero. Mean dose was calculated over all ICU days

determine the mechanisms for these findings. Second, because we focused on identifying risk factors available prior to hospital discharge, we did not account for any post-hospital events (e.g., repeat hospitalizations or rehabilitation/nutritional interventions) that may have affected patients' physical status. Third, generalizability is limited because all patients were ARDS survivors recruited from four teaching hospitals in a single city and we only evaluated three physical health outcomes, excluding mental health outcomes. Fourth, while we included 21 exposure variables of interest, future studies should include additional risk factors (e.g., frailty) which have gained greater awareness since inception of this study. Finally, while we believe that these results do not solely represent normal aging-related changes occurring over the 5-year follow-up (e.g., due to the relatively young age of the cohort and because two of the three outcome measures were evaluated in comparison to age- and sex-adjusted predicted values), the study did not include a control group which would have allowed us to definitively understand if these findings are beyond those expected due to aging or hospitalization without critical illness.

Conclusions

This multi-site, prospective longitudinal cohort study of 193 ARDS survivors found that during a 5-year post hospital discharge recovery period, 166 (86 %) survivors experienced decline(s) (including death) in ≥1 physical measures and 133 (69 %) experienced a physical decline (excluding death). Older age and pre-ICU comorbidity, rather than severity of illness and other ICU factors, were most strongly and consistently associated with this physical decline, and should inform target populations when designing interventions to improve long-term physical health.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-016-4530-1) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest
All authors declare that they have no conflict of interest to disclosure.

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