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Physical Complications in Acute Lung Injury Survivors: A 2-Year Longitudinal Prospective Study

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Abstract

Objective—Survivors of severe critical illness frequently develop substantial and persistent physical complications, including muscle weakness, impaired physical function, and decreased health-related quality of life (HRQOL). Our objective was to determine the longitudinal epidemiology of muscle weakness, physical function, and HRQOL, and their associations with critical illness and intensive care unit exposures.

Design—A multi-site prospective study with longitudinal follow-up at 3, 6, 12, and 24 months after acute lung injury.

Setting—13 intensive care units from 4 academic teaching hospitals.

Patients—222 survivors of acute lung injury.

Measurements and Main Results—At each time point, patients underwent standardized clinical evaluations of extremity, hand grip, and respiratory muscle strength; anthropometrics (height, weight, mid-arm circumference, and triceps skin fold thickness), 6-minute walk distance, and the Medical Outcomes Short-Form 36 (SF-36) HRQOL survey. During their hospitalization, survivors also had detailed daily evaluation of critical illness and related treatment variables. Over

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Authors' Contributions
EF, PJP, DMN participated in the conception of the study. EF, DWD, EC, PJP, DMN participated in study design. PAM, JES, CS, CRD, SVD, NC, DMN recruited patients and collected data. EF, DWD, EC, DMN analyzed the data. All author participated in the interpretation of the results. EF drafted the manuscript, and all authors contributed to critical review and revision of the manuscript. All authors have seen and approved the final version of the manuscript.

Potential Conflict of Interest
The authors have no potential conflict of interest to declare.

one-third of survivors had objective evidence of muscle weakness at hospital discharge, with most improving within 12 months. This weakness was associated with substantial impairments in physical function and HRQOL that persisted at 24 months. The duration of bed rest during critical illness was consistently associated with weakness throughout 24-month follow-up. The cumulative dose of systematic corticosteroids and use of neuromuscular blockers in the intensive care unit were not associated with weakness.

Conclusions—Muscle weakness is common after ALI, usually recovering within 12 months. This weakness is associated with substantial impairments in physical function and HRQOL that continue beyond 24 months. These results provide valuable prognostic information regarding physical recovery after ALI. Evidence-based methods to reduce the duration of bed rest during critical illness may be important for improving these long-term impairments.

Keywords

cohort study; intensive care units; muscle weakness; recovery of function; survivors; respiratory distress syndrome; adult

INTRODUCTION

Over recent decades, decreasing mortality from critical illness have contributed to an increasing number of intensive care unit (ICU) survivors (1-5), and a greater need to understand survivors' post-ICU morbidities and recovery process. Neuromuscular abnormalities associated with critical illness are of particular interest given their high prevalence among patients with severe or prolonged critical illness (6). Hence, there is interest in understanding the persistence of muscle weakness after ICU discharge, and its longitudinal associations with critical illness risk factors and long-term impairments in physical function and health-related quality of life (7-12).

Acute lung injury (ALI) is an archetype of severe critical illness (13). Studies of ALI have yielded many important insights into post-ICU patient outcomes (1-5, 13), including recognition that nearly all ALI survivors report substantial impairment in physical function and health-related quality of life (HRQOL) functional status up to 5 years after ICU discharge despite minimal pulmonary morbidity (6, 9, 10, 12). Whether these impairments longitudinally correlate with objective measures of muscle strength, and the associations of muscle weakness with ICU-related risk factors have not been comprehensively evaluated. Thus, we conducted a two-year prospective follow-up study of ALI survivors to evaluate these issues.

METHODS

Study Design

Mechanically ventilated patients with ALI(14) were consecutively enrolled in the prospective Improving Care of ALI Patients (ICAP) cohort study between October 2004 and October 2007 from 13 intensive care units (ICUs) at 4 hospitals in Baltimore, Maryland (13, 15). To avoid including patients with primary neurologic disease or head injury, neurologic specialty ICUs were excluded from enrollment. Key exclusion criteria were: 1) pre-existing illness with a life expectancy of <6 months; 2) pre-existing cognitive impairment or communication/language barriers; 3) no fixed address; 4) transfer to a study site ICU with pre-existing ALI of >24 hours duration; 5) >5 days of mechanical ventilation before ALI; 6) >4 days between ALI diagnosis and enrollment; 7) prior lung resection; and 8) a physician order for no escalation of ICU care (e.g., no vasopressors or hemodialysis) at the time of study eligibility.

Informed consent was obtained after patients regained capacity, typically around the time of hospital discharge (16). In-person patient evaluations occurred at 3, 6, 12, and 24 months after ALI onset. The institutional review boards of all study sites approved this research.

Muscle Strength and Outcome Measures

At each follow-up interval, patients were evaluated in a research clinic, their home, or health care facility, including standardized evaluation of extremity (17), hand grip (18) and respiratory muscle strength (maximum inspiratory pressure [MIP]) (19); anthropometrics (weight, body mass index (based on measured height), mid-arm circumference, triceps skin fold thickness, and arm muscle area) (20); 6-minute walk distance (21, 22); and HRQOL (using Medical Outcomes Short-Form 36 Health Survey (SF-36)) (23). As in prior research, we estimated pre-ALI HRQOL retrospectively from patients and focused on the Physical Function Subscale (PFS) of SF-36 (range 0-100, with higher score indicating better HRQOL) for this evaluation.

Peripheral muscle strength assessment was performed with standardized manual muscle testing (MMT), scored using the 6-point Medical Research Council (MRC) ordinal scale (range: 0 [paralysis] to 5 [normal strength]) (17, 24). Peripheral strength was evaluated bilaterally for 13 muscle groups (total of 26 groups), and corresponding MRC scores were summed to yield a composite score of overall strength (range 0-130) (25). To aid in comparison with prior studies, an abbreviated composite MRC score (range 0-60), calculated from a subset of 3 upper and 3 lower extremity muscle groups, was the primary measure of muscle strength in this evaluation (7, 26-31). As done in prior studies, clinically-significant muscle weakness (referred to hereafter as ICU-acquired weakness (ICUAW)) was defined as <80% of the maximum score (i.e., mean MRC score <4) (7, 31). Extensive training and quality assurance evaluation was undertaken to ensure high inter-rater reliability of these assessments (median intraclass correlation coefficient 0.99; 95% confidence interval [CI] 0.97-1.00) (32).

When calculating the composite MRC score, if data was missing for one muscle group (e.g., due to a radial arterial catheter limiting testing of one wrist), the MRC score for the contralateral muscle group was substituted given that ICUAW affects left and right sides similarly (7). If muscle strength data were missing bilaterally for a muscle group, it was imputed using the average score from the other muscle groups for purposes of calculating the composite MRC score (7, 32).

ICU Exposures and Confounders

We evaluated for associations of the outcome measures with a number of patient and ICU variables, selected *a priori* based on prior studies (33). We measured cumulative systematic corticosteroid use – our primary exposure – on a daily basis and converted to hydrocortisone-equivalents (34). The following baseline patient characteristics were evaluated: age, sex, admission location (e.g., home, rehabilitation facility, nursing home) and the Functional Comorbidity Index (35). ICU variables included severity of illness at ICU admission (Acute Physiology and Chronic Health Evaluation [APACHE] II score (36)); organ failure status (maximum daily Sequential Organ Failure Assessment [SOFA] score in ICU (37)); acute renal failure requiring dialysis (ever vs. never, and number of ICU days on dialysis); proportion of ICU days with sepsis (as per American College of Chest Physicians criteria) (38); mean daily blood glucose level (39); proportion of ICU days receiving <50% of goal nutrition intake; cumulative benzodiazepine dose in midazolam-equivalents (40); cumulative narcotic dose in intravenous (IV) morphine-equivalents (41); use of neuromuscular blocker medication (ever vs. never); duration of mechanical ventilation (number of days); duration of bed rest (number of days, based on nursing documentation of

activity level); length of stay (number of days); coma (proportion of ICU study days with Richmond Agitation-Sedation Scale [RASS] score (42) of −4 or −5); delirium (proportion of non-comatose ICU study days with a positive Confusion Assessment Method for the ICU [CAM-ICU] assessment (43)); and receipt of physical therapy in the ICU (ever vs. never, days from ALI onset until physical therapy initiation).

Statistical Analysis

Variables were modeled as continuous when appropriate (based on inspection of exposure-outcome plots during exploratory data analysis); otherwise, they were dichotomized at clinically-relevant thresholds. We assessed bivariate associations of study variables and ICUAW using the Wilcoxon rank-sum and Fisher's exact tests, as appropriate. Since the abbreviated composite MRC score has an upper bound of 60 (no weakness) and a skewed distribution with scores clustering within 10 points of this upper bound, the score transformed by subtracting it from 60 (such that 0 corresponds to no weakness) so that its distribution could be modeled by a gamma function (R^2=0.99 at baseline). Thus, our primary analysis used the transformed MRC score at each time point as the outcome and a generalized linear regression model, assuming a gamma distribution and log link function, with regression coefficients interpreted as the relative decrease from maximum MRC score for each unit change in the exposure variable. For secondary analyses in which the distribution of the outcome variable was less skewed (e.g., MIP), we modeled the outcome using a normal distribution; for regression of binary outcomes, we used a binomial distribution. All multivariable analyses were evaluated for multicollinearity using variance inflation factors (17, 44) and included the exposure and confounder variables described previously. Due to collinearity, we removed maximum SOFA score (collinear with APACHE II score) and the duration of mechanical ventilation and ICU length of stay (collinear with duration of bed rest) from our primary analysis. Based on prior literature (18, 45), we tested for interaction between blood glucose and cumulative corticosteroid dose. We assessed for goodness-of-fit by visual inspection of deviance residuals (including plots against predicted values) and for influence by assessment of Cook's distance. When influential points were identified, we evaluated alternative models with influence points removed to evaluate robustness of results, with our primary analysis retaining all data points. Statistical significance was defined as $p<0.05$ (two-sided). All analyses were conducted using STATA 11.0 (Stata Corporation, College Station, TX).

RESULTS

Patient Baseline Characteristics and Follow-Up Assessments

The ICAP study enrolled 520 ALI patients with high severity of illness (Table 1), of whom 274 (53%) survived to hospital discharge. Of 224 (82%) survivors who consented and were eligible for follow-up, 222 (99%) had muscle strength evaluated at least once during study follow-up and were followed longitudinally (Figure 1), with two excluded from this evaluation due to persistent vegetative state and bilateral above-knee amputations. Compared to those who died in hospital or did not participate in follow-up, participants were younger and less severely ill; had longer ICU stay and mechanical ventilation duration; but were more likely to receive physical therapy and had less sepsis, renal failure, delirium, coma, corticosteroid exposure, and reduced nutritional intake. Importantly, survivors continued to experience substantial mortality following ICU and hospital discharge.

Epidemiology of Anthropometric, Muscle Strength, Physical Function Assessments

The proportion of patients with ICUAW declined over time: 36% at hospital discharge, 22% at 3 months post-ALI, 15% at 6 months, 14% at 12 months, and 9% at 24 months. Corresponding 24-month trajectories of physical outcome measures are shown in Figure 2.

Specifically, the abbreviated composite MMT score increased from a median (IQR) of 50 (42-56) at hospital discharge to 57 (53-60) at 24 months post-ALI. All 3 measures of muscle strength were highly correlated over time (R^2 = 0.89 [hand grip vs. MIP], 0.94 [abbreviated MMT vs. MIP], 0.99 [abbreviated MMT vs. hand grip). Compared to matched population norms, 6MWD and SF-36 PFS (R^2 = 0.98) were substantially impaired at all follow-up times (range: 52-69% of predicted), and SF-36 PFS remained markedly impaired relative to retrospectively estimated pre-ALI baseline values (72% of baseline value at 24 month follow-up).

Participants' median (IQR) weight (kg) and body-mass index increased over time at 3, 6, 12, and 24 months: 72 (59-84), 74 (59-86), 76 (61-91), 77 (65-92) and 25 (21-29), 26 (22-31), 27 (23-32), 27 (23-32), respectively. Arm muscle area was significantly associated with decreased hand grip strength at all 4 time points (R^2 = 0.97) and with both MMT (at all time points) and ICUAW (at 6 and 12 months) (Figure 3). Arm muscle area was not associated with the other outcome measures at more than 1 time point during follow-up.

Risk Factors for the Development of ICU-Acquired Weakness

Patient and critical illness-related risk factors' associations with ICUAW were similar whether ICUAW was measured using the abbreviated (range: 0-60) or full (range: 0-130) composite MMT scores (data not shown). As all three measures of muscle strength (MMT, MIP and grip) were highly correlated, we focused on risk factor associations with our primary outcome, the abbreviated MMT composite score, to allow comparability with previous studies.

In multivariable regression analysis of all patient and critical illness-related risk factors, duration of bed rest was the single risk factor most consistently associated with muscle weakness throughout longitudinal follow-up (Table 2). After adjusting for all other risk factor, muscle strength was 3-11% lower for every additional day of bed rest. Other variables significantly associated with peripheral muscle weakness at hospital discharge included older age and proportion of ICU days alert (i.e., RASS −1, 0, or +1), but these associations were no longer significant at 3 months post-ALI.

In multivariable regression analysis, cumulative corticosteroid dose in the ICU was not significantly associated with peripheral muscle weakness at discharge, or any time in the first year after ALI (Table 2). Similarly, there was no significant association between corticosteroids and all other physical outcome measures any time point (data not shown). At all time points, there was no association between increased mean ICU blood glucose (defined as >150mg/dL) and muscle weakness (Table 2), and no significant interaction between increased blood glucose and corticosteroid dose. These findings were not affected by a differential effect of steroids on patient survival since cumulative corticosteroid dose was not significantly associated with hospital mortality after adjustment for potential confounders (as listed in Table 2).

Association of ICU-Acquired Weakness with Other Outcome Measures

The association between ICUAW and the other outcome measures are summarized in Figure 4. At all follow-up time points, patients with versus without ICUAW had significantly lower hand grip strength ($p<0.01$) and SF-36 PFS ($p\leq0.001$), and significantly lower MIP ($p<0.02$) and 6MWD ($p\leq0.01$) at all time points after 3 months post-ALI.

DISCUSSION

In this multi-site prospective cohort study of 222 ALI survivors, over one-third of participants were discharged from the hospital with objective evidence of ICUAW, with

most improving within 12 months. This muscle weakness was associated with substantial impairments in physical function and HRQOL that persisted at 24 months. These results provide valuable prognostic information for patients and their caregivers regarding longer-term physical recovery after ALI. Based on comprehensive evaluation of patient and critical illness-related risk factors for muscle weakness, we found that the cumulative dose of systemic corticosteroids and use of neuromuscular blockers in the ICU were not independently associated with muscle weakness at any time point, while the duration of bed rest was the only factor consistently associated with weakness throughout 24-month follow-up. Hence, evidence-based methods to reduce the duration of bed rest may be the most important target intervention for ameliorating these common and substantial long-term physical complications experienced by ALI survivors.

These data demonstrate that objectively-measured ICUAW has an important association with the substantial and persistent impairments in physical function and HRQOL observed in prior studies of ICU survivors (7-12, 19, 31, 46). The relative plateau in recovery of the physical outcome measures at 12 months post-ALI observed in our data is consistent with prior studies (9, 10, 47, 48). Given that muscle strength recovers more quickly than physical function and HRQOL, ALI survivors' persistent limitations in physical function and HRQOL are unlikely to be due to ICUAW alone, with many other factors (e.g., cognitive and mental health morbidity, home environment, caregiver support) likely playing an important role in determining physical limitations and disability (21, 22, 49-51). Furthermore, the muscle strength testing employed in our study does not reliably evaluate other neuromuscular factors which may have an important impact on physical function, such as pain and endurance. Thus, evaluating functional outcomes longitudinally may be especially important to evaluate in future studies on the long-term effects of ICUAW.

Survivors of ALI and other critical illnesses often have severe muscle wasting with loss 18% of their body weight during ICU admission (9, 52). Immobility and enforced bed rest are modifiable risk factors during critical illness can result in substantial disuse atrophy and accelerated muscle breakdown (17, 24, 53), contributing to the development of ICUAW (25, 54). Our study demonstrated significant associations of arm muscle area with strength measures during the 24-month follow-up. Furthermore, the duration of bed rest in the ICU was the single risk factor that was consistently associated with muscle weakness throughout the entire follow-up, with each additional day of bed rest having up to an 11% relative decrease in muscle strength at 24 months post-ALI (Table 2). Physical therapy, aimed at reducing bed rest via early rehabilitation interventions, was provided to approximately half of survivors while in the ICU and started, in those patients, at a median of 10 days after ICU admission, as there were no trials demonstrating the safety, feasibility and benefits of early rehabilitation interventions in the ICU during the time period of patient enrollment (7, 26-31, 54). New trials evaluating the longer-term impact of early ICU rehabilitation interventions are needed to demonstrate if these physical complications can be ameliorated.

A prospective observational study reported that exposure to corticosteroids was the strongest risk factor for ICUAW upon awakening after 7 days of mechanical ventilation (OR 14.9; 95% CI 3.2-69.8), but there was no significant association between ICUAW and cumulative corticosteroid dose or corticosteroid duration (7). However, the role of systemic corticosteroids in the development of ICUAW continues to be debated, with a number of subsequent studies and systematic reviews (7, 26, 27, 31, 32, 45, 55-60) failing to demonstrate a consistent association between corticosteroids and ICUAW. We found no significant association between ICUAW and corticosteroid use in the ICU in our cohort, whether corticosteroids were modeled as any exposure, cumulative dose, or treatment duration (data not shown). In contrast to a previous study (7, 9), we found no association between corticosteroids and 6MWD, or with any other physical outcome, at any point in

follow-up. Interestingly, a recent study reported that hyperglycemia may partially mediate the deleterious effects of corticosteroids on the neuromuscular system (7, 32, 45); however, we found no association between mean blood glucose levels and ICUAW, nor any evidence that the effect of corticosteroids on ICUAW was modified by blood glucose level. Our results support the notion that the current patterns of use of neuromuscular blockers are unlikely to be a significant independent risk factor for ICUAW (33, 61). Finally, our results regarding nutritional intake in the ICU are consistent with prospective follow-up studies of the NHLBI ARDS Network's EDEN trial that demonstrated no effect of initial trophic versus full enteral feeding on 6- and 12-month measures of muscle strength and physical function (62, 63).

Our results also suggest that future evaluations of post-ICU muscle strength may be simplified. Specifically, we evaluated three different objective measures of muscle strength and found that all measures were highly correlated. Especially for large-scale, multi-site studies, hand grip dynamometry may be simpler, more cost-effective, and efficient to perform than MMT, which requires rigorous training and ongoing quality assurance to ensure high inter-rater reliability (32, 34, 64, 65). However, greater evaluation, in future studies and in other populations of ICU survivors is required to confirm this finding.

There are several potential limitations of this study. First, as with all observational studies, due to a lack of randomization, we cannot assess causality of the associations reported. Second, we employed a clinical definition for ICUAW and did not measure mechanisms of muscle weakness (e.g., nerve conduction studies, electromyography, muscle and nerve biopsies). This approach is most clinically feasible across ICUs and ensures comparability of our findings with previous studies (7, 26-31). Moreover, we evaluated strength using 26 bilateral muscle groups using trained assessors with high inter-rater reliability (32). However, manual muscle testing requires appropriate patient motivation and engagement with the evaluation, and also has a ceiling effect compared to other measurement approaches (66-68). Third, given the acute and unpredictable nature of critical illness, we could not obtain prospective baseline measurements of muscle strength and physical function, requiring the use of population norms for presentation of results. Fourth, we did not account for effects of post-hospitalization interventions (e.g., physical rehabilitation, repeat hospitalizations) on the physical outcome measures which may have affected the recovery process. Fifth, the association between corticosteroids and ICUAW could have been impacted by an effect of corticosteroids on ICU mortality (i.e., survivor bias) (69). However, there was no independent association of corticosteroids with ICU mortality in our cohort to raise this potential bias. Finally, all the study sites were teaching hospitals, which may limit the generalizability of the findings. However, 4 hospitals with 13 ICUs participated, representing a heterogeneous group of patients and variability in the medical care provided, which may aid in generalizability.

In conclusion, survivors of ALI have substantial physical morbidity after ICU discharge, including impairments in muscle strength, physical function, and HRQOL. Recovery of muscle strength (evaluated by MMT) generally occurs within 12 months after ALI, but muscle weakness contributes to significant impairments in physical function and HRQOL which persist to 24 months post-ALI. The results of our study provide valuable prognostic information for patients and their caregivers regarding the physical recovery after ALI. Based on comprehensive evaluation of patient and critical illness-related risk factors for muscle weakness, the duration of bed rest during critical illness was the only factor consistently associated with weakness throughout 24-month follow-up. Hence, evidence-based methods to reduce bed rest (e.g., early physical and occupational therapy) during critical illness, may be the most important target interventions for ameliorating the common and substantial long-term physical complications experienced by ALI survivors.

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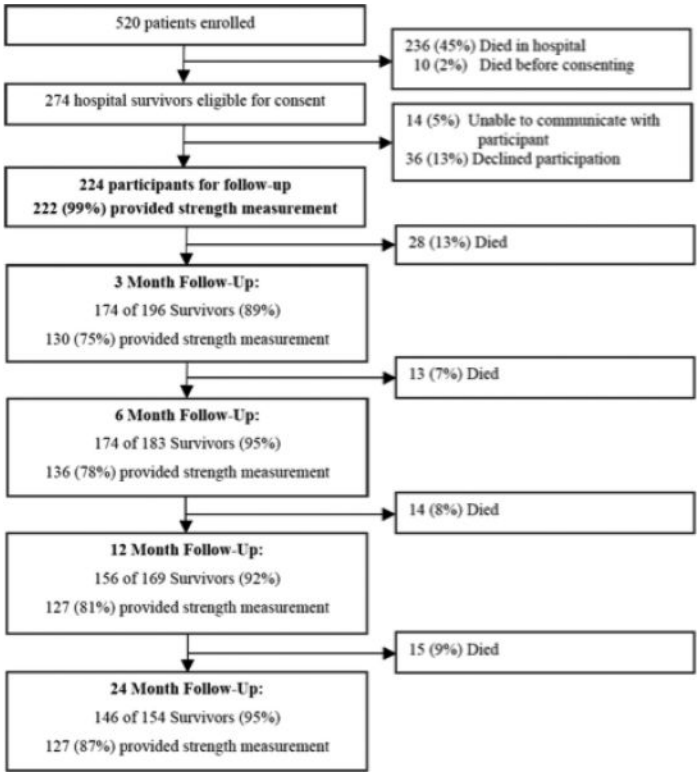

Figure 1.
Flow Diagram of Study Participants

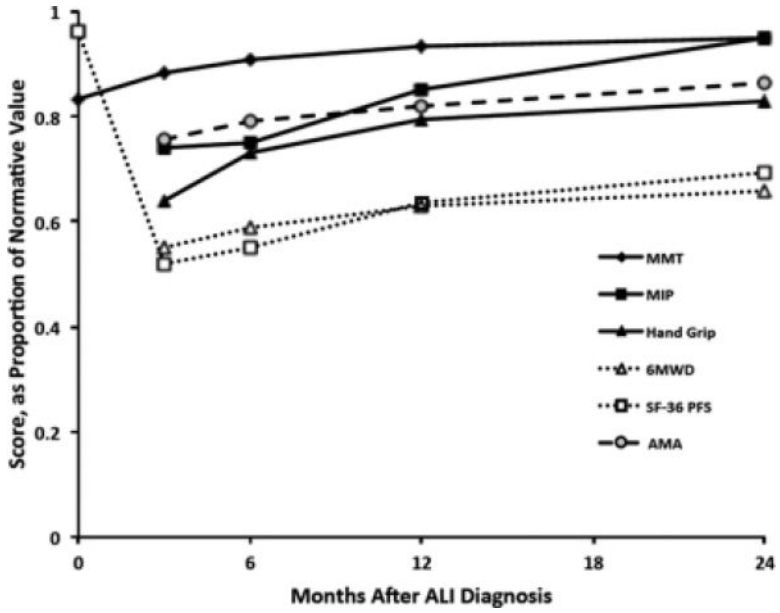

Figure 2. Anthropometric, Muscle Strength, Physical Function, and Health-Related Quality of Life Outcomes in ALI Survivors

The dashed line (gray circles) denotes an anthropometric measure (arm muscle area), solid lines (solid markers) denote measures of muscle strength, and the dotted lines (open markers) denote physical function (6MWD) and health-related quality of life (SF-36 PFS) outcomes. All outcomes are scaled as a proportion of normative values.

* The marker for MMT at the vertical axis (0 months after ALI onset) represents MMT obtained at hospital discharge. The marker (and corresponding sample size) for SF-36 PFS at the vertical access represents pre-ICU baseline SF-36 PFS obtained retrospectively from patients.

Abbreivations: 6MWD, 6-minute walk distance; ALI, acute lung injury; AMA, arm muscle area; MIP, maximal inspiratory pressure; MMT, manual muscle strength testing; SF-36 PFS, Short Form-36 Physical Function Subscale score

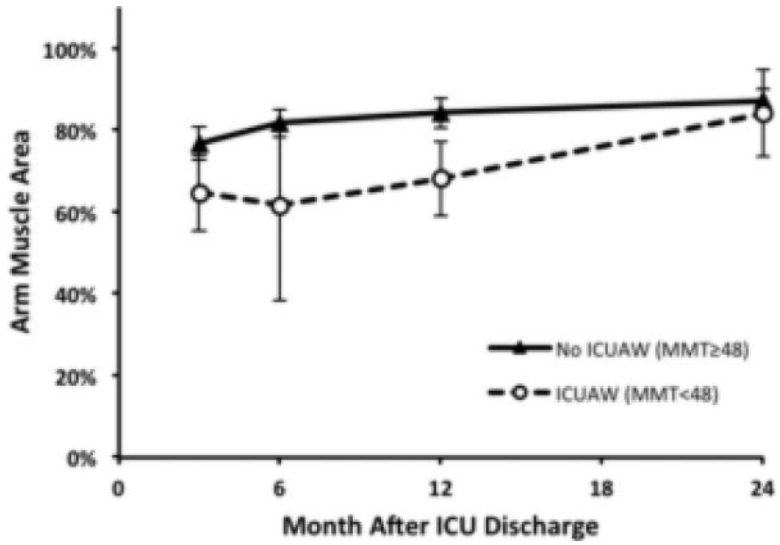

Figure 3. Arm Muscle Area and ICU-Acquired Weakness in ALI Survivors

Comparison of arm muscle area (as proportion of normative value) in patients with and without ICU-acquired weakness at each time point: p=0.32 at 3 months, p=0.02 at 6 months, p=0.03 at 12 months, and p=0.86 at 24 months. Markers represent median values, and error bars standard errors. The number of patients at each time point was: 116 at 3 months, 130 at 6 months, 127 at 12 months, and 126 at 24 months.

Abbreviations: ICU, intensive care unit; ICUAW, ICU-acquired weakness; MMT, manual muscle strength testing

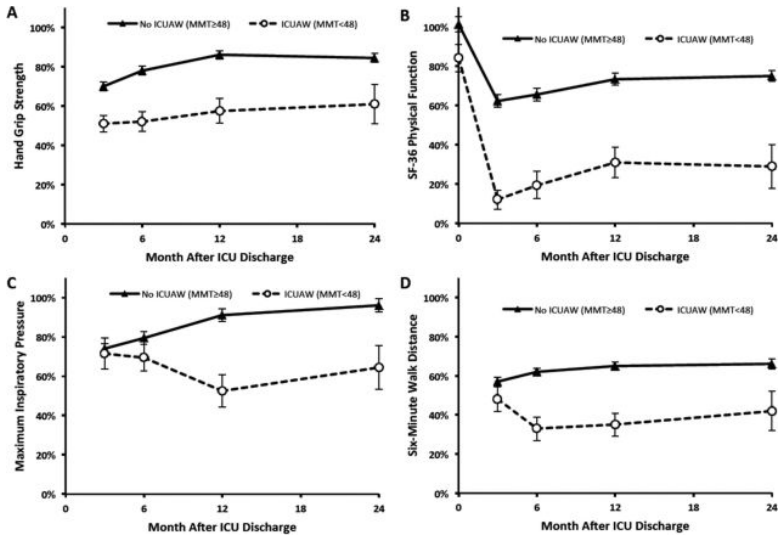

Figure 4. Association of ICU-Acquired Weakness with Outcomes in ALI Survivors

Outcomes are presented according to the presence or absence of ICUAW (abbreviated composite MMT score <48 out of 60) at each time point. Markers represent median values, and error bars standard errors. All values are presented as proportion of normative values, and p-values correspond to the comparison of participants with versus without ICUAW at the specific time point. The number of patients with ICUAW at each time point after ALI onset was: 28/130 (22%) at 3 months, 21/136 (15%) at 6 months, 18/127 (14%) at 12 months, and 11/127 (9%) at 24 months.

A. Hand grip strength, $p \leq 0.01$ at all time points.

B. Physical function subscale of the SF-36 quality-of-life instrument, $p \leq 0.001$ at all time points after ALI.

C. Maximum inspiratory pressure, $p=0.47$ at 3 months, and $p \leq 0.02$ at 6, 12, and 24 months post-ALI.

D. Six-minute walk distance, $p=0.10$ at 3 months, and $p \leq 0.01$ at 6, 12, and 24 months post-ALI.

Abbreviations: 6MWD, 6-minute walk distance; ALI, acute lung injury; ICU, intensive care unit; ICUAW, ICU-acquired weakness; MIP, maximal inspiratory pressure; MMT, manual muscle strength testing; SF-36, Short Form-36 survey

Sample size by follow-up time point for each outcome					
	Baseline*	3 months	6 months	12 months	24 months
MMT	173	130	136	127	127
MIP		115	129	122	127
Hand Grip		127	139	128	129
6MWD		99	117	115	95
SF-36 PFS	154	155	163	146	137
AMA		116	130	127	126

Abbreivations: 6MWD, 6-minute walk distance; ALI, acute lung injury; AMA, arm muscle area; MIP, maximal inspiratory pressure; MMT, manual muscle strength testing; SF-36 PFS, Short Form-36 Physical Function Subscale score

*The marker for MMT at the vertical axis (0 months after ALI onset) represents MMT obtained at hospital discharge. The marker (and corresponding sample size) for SF-36 PFS at the vertical access represents pre-ICU baseline SF-36 PFS obtained retrospectively from patients.

Table 1

Patient Characteristics[a]

Variable	All Patients (n = 520)	Patients with Strength Measurement (n = 222)	Patients who Died or with No Strength Measurement[b] (n=298)	p-value[c]
Demographics/Baseline Characteristics				
Age (years)	52 (42-63)	49 (40-58)	55 (44-67)	<0.001
Male	292 (56%)	123 (55%)	169 (57%)	0.79
ALI risk factor				<0.001
Pneumonia	226 (43%)	112 (50%)	114 (38%)	
Sepsis (non-pulmonary)	156 (30%)	44 (20%)	112 (38%)	
Aspiration	65 (13%)	29 (13%)	36 (12%)	
Trauma	12 (2%)	7 (3%)	5 (2%)	
Other	61 (12%)	30 (14%)	31 (10%)	
Functional comorbidity index score	1 (1-3)	1 (1-3)	1 (1-3)	0.91
ICU Characteristics – Severity of Illness and Organ Failure				
APACHE II score	26 (20-33)	23 (19-28)	29 (22-36)	<0.001
Maximum daily SOFA score	11 (8-15)	9 (7-11)	14 (10-18)	<0.001
ICU stay, days	13 (7-21)	14 (10-23)	11 (6-19)	<0.001
Mechanical ventilation, days	8 (4-16)	9 (5-17)	8 (4-15)	0.005
Proportion of ICU days with sepsis	96% (80-100)	92% (75-100)	100% (81-100)	0.01
Mean blood glucose over ICU stay >150mg/dL	108 (21%)	38 (17%)	70 (23%)	0.08
Ever use of dialysis in ICU	175 (34%)	51 (23%)	124 (42%)	<0.001
Number of days on dialysis	0 (0-5)	0 (0-0)	0 (0-6)	0.001
ICU Characteristics – Sedation and Delirium				
Cumulative dose of benzodiazepine (mg midazolam-equivalent)[d]	185 (37-667)	274 (72-922)	140 (20-515)	<0.001
Cumulative dose of narcotic (mg morphine-equivalent)[d]	1298 (361-3785)	1691 (512-3871)	933 (243-3480)	0.003
Ever use of NMB in ICU	122 (23%)	49 (22%)	73 (25%)	0.53
Alert (RASS −1, 0, or 1), % ICU days	25% (0-50)	38% (22-62)	0% (0-37)	<0.001
Comatose (RASS −4 or −5), % ICU days	44% (14-83)	29% (7-51)	69% (25-100)	<0.001
Delirious (CAM-ICU positive)[e], % ICU days	78% (50-100)	64% (33-100)	100% (67-100)	<0.001
ICU Characteristics – Nutrition, Corticosteroids, and Physical Therapy				
Proportion of ICU days receiving <50% of goal nutrition intake	59% (33-100)	50% (30-82)	68% (36-100)	0.007
Cumulative dose of corticosteroid (mg hydrocortisone-equivalent)	600 (0-2010)	400 (0-1909)	800 (0-2114)	0.005
Ever received PT in ICU	189 (36%)	120 (54%)	69 (23%)	<0.001
Days until PT started in ICU[f]	10 (6-16)	10 (6-17)	9 (6-14)	0.31
Number of days with bed rest as highest activity level	10 (5-17)	10 (6-18)	9 (4-16)	0.005

Abbreviations: ALI, acute lung injury; APACHE II, Acute Physiology and Chronic Health Evaluation II score; CAM-ICU; Confusion Assessment Method for the Intensive Care Unit; ICU, intensive care unit; NMB, neuromuscular blockade; PT, physical therapy; RASS, Richmond Agitation-Sedation Scale; SOFA, Sequential Organ Failure Assessment score

[a] Reported as n (%) or median (interquartile range)

[b] 236 patients died in hospital, 60 patients were not consented (due to death, unable to communicate, or declined – see Figure 1), and 2 patients provided no strength data.

[c] Comparing patients with strength measurement vs. patients who died or with no strength measurement, using Fisher's exact test, Wilcoxon rank-sum test, ANOVA, chi-square test, as appropriate

[d] Using standard conversion factors[40,41]

[e] Among days that patients were not comatose, as delirium cannot be assessed during coma.

[f] For patients who received PT in the ICU.

Table 2

Multivariable Predictors of Muscle Weakness in ALI Survivors[a]

Variable	Time Since Discharge				
	Discharge	**3 Months**	**6 Months**	**12 Months**	**24 Months**
Age (per 10 years)	**17% (3,34)**	4% (−12,23)	**19% (1,41)**	15% (−5,39)	**28% (2,60)**
Sex (female vs. male)	33% (−1,79)	26% (−17,91)	40% (−7,109)	7% (−30,64)	122% (24,298)
Functional comorbidity (per FCI point)	−9% (−20,4)	9% (−8,30)	8% (−8,26)	7% (−10,28)	13% (−10,41)
APACHE II score (per 5 points)	4% (−6,15)	−2% (−13,16)	−4% (−18,11)	5% (−10,22)	1% (−18,25)
Proportion of ICU days septic (per 10% change)	−4% (−9,1)	−3% (−10,6)	−4% (−11,4)	−2% (−11,7)	−7% (−16,3)
Mean blood glucose over ICU stay >150mg/dL (vs. <150)	48% (−3,125)	0% (−43,91)	−18% (−57,54)	−22% (−59,49)	−6% (−60,121)
Need for dialysis (ever vs. never)	68% (0,181)	55% (−35,274)	19% (−41,139)	17% (−43,139)	−24% (−71,102)
Days on dialysis (per day)[b]	−2% (−3,0)	0% (−3,4)	0% (−2,2)	0% (−2,3)	−3% (−5,0)
Total ICU dose of benzodiazepine (per 500 mg midazolam-equivalent)	1% (−4,5)	−1% (−6,3)	−1% (−6,4)	−3% (−10,4)	−20% (−30,−8)
Total ICU dose of narcotic (per 500 mg morphine-equivalent)	−1% (−1,0)	−1% (−2,0)	0% (−1,1)	−2% (−5,0)	−7% (−12,−2)
Any NMB received	4% (−33,60)	−42% (−69,7)	−15% (−51,50)	−6% (−44,60)	170% (20,508)
Proportion of ICU days alert (per 10% change)	11% (1,22)	4% (−8,18)	1% (−10,13)	2% (−10,15)	−11% (−25,4)
Proportion of ICU days comatose (per 10% change)	8% (−1,17)	3% (−9,16)	−5% (−15,7)	−4% (−15,8)	1% (−13,17)
Proportion of ICU days delirious (per 10% change)	−1% (−7,6)	−5% (−13,4)	−2% (−10,7)	−1% (−8,8)	−8% (−17,2)
Proportion of ICU days with <50% of goal nutrition intake (per 10% change)	−1% (−7,5)	−2% (−8,5)	1% (−4,8)	1% (−4,6)	−1% (−7,6)
Cumulative ICU steroid dose (per 500 mg hydrocortisone)	5% (0,10)	2% (−5,9)	0% (−6,7)	1% (−6,9)	11% (1,21)
Physical therapy in ICU (ever vs. never)	−3% (−38,51)	−27% (−62,39)	−41% (−69,14)	−59% (−79,−18)	−68% (−81,−2)
Days until PT started (per 5 days)	7% (−5,20)	3% (−16,26)	2% (−13,21)	7% (−9,27)	70% (13,157)
Duration of bed rest (per day)	**3% (0,7)**	**4% (0,8)**	3% (0,7)	**7% (3,12)**	**11% (4,19)**

Figures in **bold** represent statistically significant and consistent associations of exposure variables with muscle weakness (defined as those associations with $p < 0.05$ for at least 3 of the 5 time points evaluated).

Abbreviations: ALI, acute lung injury; APACHE II, Acute Physiology and Chronic Health Evaluation II score; CAM-ICU; Confusion Assessment Method for the Intensive Care Unit; ICU, intensive care unit; NMB, neuromuscular blockade; PT, physical therapy; RASS, Richmond Agitation-Sedation Scale; SOFA, Sequential Organ Failure Assessment score

[a] Results presented as a proportionate decrease (with 95% confidence interval) from the maximum abbreviated composite MRC score (i.e., 60) per unit change in the exposure variable at each time point, using a generalized linear regression model, assuming a gamma distribution for the outcome (transformed abbreviated composite MRC score) and log link function. A positive percent change represents a decrease in muscle strength, and a negative percent change represents an increase in muscle strength. For example, every additional day of bed rest in the ICU led to a 3% decrease in composite MRC score at hospital discharge.

[b] For patients who received dialysis in the ICU.