ICU-acquired Weakness, Morbidity, and Death

You admit a 72-year-old man to your intensive care unit (ICU) for further treatment of severe community-acquired pneumonia. He walked several blocks and climbed the stairs in his family home each day prior to this illness, but you note that he appears frail. He has a history of poorly controlled hypertension, a remote myocardial infarction, and chronic renal insufficiency and is being followed in an end-stage renal failure clinic at your hospital. His wife said that she and her husband would want aggressive treatment in the ICU and would want to do anything to save his life and restore him to functional independence in the community.

This gentleman remains in the ICU for 3 weeks, and by that time has had a tracheostomy and an episode of ventilator-associated pneumonia and line sepsis, is now dependent on renal replacement therapy, and has mild inattention but is able to communicate. He has had limited progress with early mobility and is still unable to walk. It seems as though his quadriceps muscles have almost completely disappeared.

He leaves the ICU and struggles after discharge with difficulty generating an adequate cough to mobilize secretions. One night he has a respiratory arrest from a mucous plug and returns to the ICU. It takes about 1 week for him to recover from this, and he again returns to the ward. His wife brings him some soup from home one day and he has an important episode of aspiration, and the nursing staff scold her because she knows that he is unable to swallow anything safely but thickened fluids. He returns to the ICU again, and you note on this admission that he looks profoundly cachectic. He again recovers and leaves the ICU and is successfully transferred to a rehabilitation hospital, where he has only partial recovery and is unable to return home. He is transferred to a chronic care facility because he cannot walk, climb stairs, bathe, or toilet on his own, he has important disturbances in his balance, and his ability to communicate has declined. You hear that he ultimately dies at the institution from complications of a bad fall and hip fracture within a few months of transfer there.

In the timely and very important publication by Hermans and colleagues (pp. 410–420) in this issue of the *Journal*, the presence of ICU-acquired weakness (ICUAW) is strongly associated with death (1). The pathway to death and the specific causes of death are not elucidated in this article, but the relationship is undeniable. Specifically, these authors showed that weak patients, defined by the Medical Research Council (MRC) score, had worse in-hospital morbidity—but not mortality—outcomes, incurred more hospital costs, and had a higher mortality 1 year after ICU admission than not-weak patients. Those patients who had persistent weakness at ICU discharge had a greater 1-year mortality, and this was increased when the weakness at ICU discharge was more severe.

These authors were resourceful in the conduct of their study and used data previously collected for a randomized controlled trial comparing early versus late administration of parenteral nutrition to these patients. Early parenteral nutrition did not prevent weakness, and may have exacerbated it. This is an important limitation in the study sample because the effect on outcomes and their inferences of combining patients across this intervention is uncertain. Propensity modeling was included to address this concern and is the subject of a separate commentary. Other important limitations that merit mention include the following: the lack of systematic screening and surveillance for ICUAW, lack of blinded assessment, the still contentious criteria used for the definition of ICUAW (2), and the important bias introduced by the inability to assess unconscious or nonresponsive patients or those who died during the ICU admission.

Each of these threatens the internal validity of this sample and its conclusions.

Phenotypic groups are linked to different mortality and morbidity trajectories in the ICU outcomes literature (3–5). Unroe and colleagues (6) showed that after chronic critical illness, many patients die and have complex and protracted courses among various institutions, with few regaining functional independence. Are these deaths ultimately related to the consequences of ICUAW as described in this article? Further, how does the development of ICUAW relate to compromised premorbid functional status, preexisting frailty, sarcopenia, the ravages of critical illness, and a long stay in the ICU?

Patient frailty, defined as a global loss of cognitive and physiologic reserve, has been suggested as a key risk stratifier for functional outcome and death after ICU admission. An important Canadian study by Bagshaw and colleagues (7) demonstrated that in-hospital and 1-year mortality were high in frail versus nonfrail patients. As well, frail patients were more likely to become functionally dependent, have a lower quality of life, and have more hospital readmissions in the year after admission. Frailty is a clinically important construct but does not lend itself to detailed insights into underlying physiology or mechanistics of decline.

Some equate sarcopenia with muscle injury and ICUAW. Current definitions of sarcopenia describe a loss of muscle mass *and* a loss of function or strength. This definition provides more information on potential pathophysiologic mechanisms. However, it may not be wholly appropriate or applicable to the critically ill patient. It may be overly simplistic and not fully account for the possibility that a spectrum of weakness phenotypes exist that are much more nuanced and complex. In an article by Clark and Manini (8), they discuss the importance of distinguishing between impaired muscle mass (sarcopenia) and compromised muscle force (dynapenia). They argue that it is important to delineate these as discrete entities because they define different contributors to disability and should direct distinct research efforts. As one example, dynapenia research may emphasize dysfunction of contractile proteins.

We know from recent literature (9, 10) that patients may have a similar pattern of proteolysis and muscle injury for the first several days after the onset of their critical illness. It is possible that the true determinant of recovery resides in the extent to which structure and function are each restored. As one theoretic molecular example, the maintenance of proteostasis could play a role. Ensuring the quality of protein and the integrity of coupling between profolding and degradative pathways such as the ubiquitin proteasome system could represent one potential derangement in tissue repair (11). There seems to be significant variability in

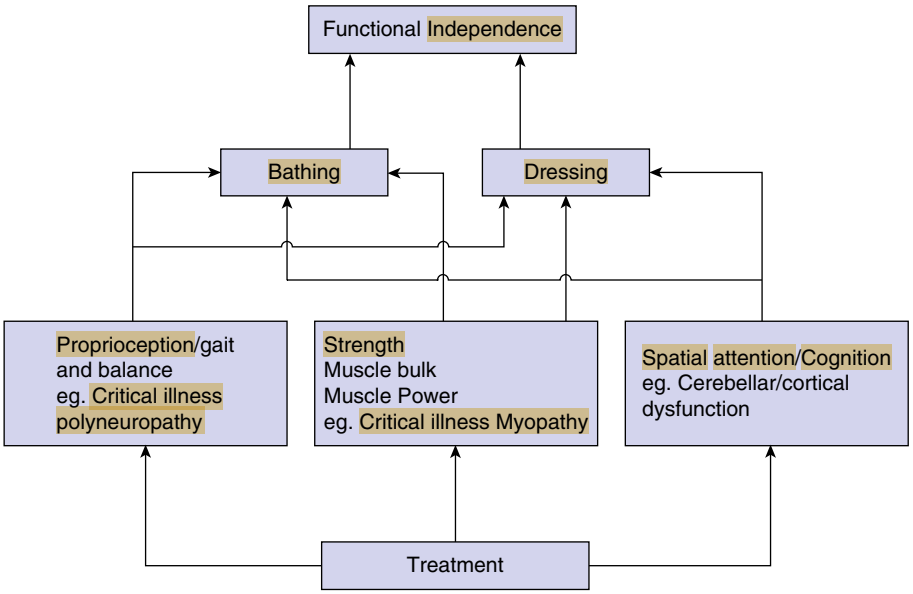

Figure 1. Multidimensional determinants of complex patient-centered functional outcomes. This illustrates how multiple intact domains are required to execute activities of daily living and how isolated intervention in only one of these domains—for example, sole focus on improvement in muscle bulk or muscle strength outcomes—may not be adequate to address a disability that relies on integration of multiple factors (bathing or dressing). Adapted by permission from Reference 12.

reparative mechanisms—perhaps due to different contributors to sarcopenia and dynapenia or other factors—and this should fuel future large-scale translational programs to evaluate the heterogeneity and complexity of repair.

Functional independence is complex and requires the integration of myriad factors (Figure 1). The activities of daily living are not solely dependent on ICUAW, and yet our community often emphasizes this as the most important outcome and isolated determinant of functional independence. There is no question that weakness is important, but it is weakness in combination with other equally important, and sometimes ignored, factors that compromises function. These need to be captured by an integrative, robust measure and to be rigorously evaluated. Walking requires strength but also intact proprioception and cognition and needs to be seen in an interdependent context. Many of our patients are unable to walk in the early period after ICU discharge, and our patient-centered outcome measures need to reflect this reality. These measures need to be practical, tangible, reproducible, integrative, and linked to daily activity that is meaningful. Also, this measure needs to capture a spectrum of functional dependencies because these are unlikely to be affected in the same way or to be perceived to have an equivalent impact on activities of daily living by the patient or caregiver. One might imagine that dependence for toileting and bathing is much less acceptable than requiring some assistance with eating. The MRC and 6-minute-walk scores now seem to fall short in their ability to capture the nuance of patient-centered outcomes.

So, why do patients who have ICUAW die? There are likely a multitude of reasons, and the preceding case scenario highlights a few: diaphragm and respiratory muscle weakness, pharyngeal muscle weakness, shoulder girdle and hip girdle weakness with their attendant functional impairments, cognitive dysfunction, and gait and balance disturbances that promote falls. To move our field forward now, we need to continue to understand the molecular details of muscle injury and repair, its genetic variability, and how it interfaces with other disabilities and maps to patient-centered functional dependencies. Only then can we identify when injury is potentially modifiable and amenable to targeted intervention. ■

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Propensity-Matching Analysis Is Not Straightforward

In the analysis of observational studies, clinicians often wish to understand the causal relationships between an exposure or an intervention and patient outcome. To do so, there has been a growing interest in propensity score (PS)-based approaches, which have become extremely popular for the last decade, notably in anesthesiology and intensive care (1). By creating a balancing score, these approaches aim at mimicking the gold standard randomized experiment where the two groups differ only by the nature of the exposure (intervention) irrespective of any confounders, so that some direct causal interpretation on the effect of that exposure (intervention) could be made (2). Nevertheless, PS approaches encompass different modeling and underlying assumptions that should be correctly performed and clearly reported, lest they be misused and misinterpreted. Briefly, similarly to the attrition biases that may occur even in randomized controlled trials, the "PS-based approach" should not be considered free of any source of bias and misconclusion. In other words, it is more complicated than it sounds.

The researcher who has decided to use a PS-based approach is confronted with questions regarding its implementation (Figure 1). First, the PS, which is the probability that any patient has been exposed to or has received the intervention of interest given his or her own characteristics, is unknown and has to be estimated from the data. Because the exposure or intervention of interest is usually present or absent (with two groups to be compared), PS estimation is performed using maximum likelihood estimation through parametric models, such as logistic models. The performance of a PS estimator highly depends on consistently and accurately estimating the PS. It has been well demonstrated that the inclusion of true confounders in the PS model is crucial to decreasing bias in the final estimation (3). Thus, all variables that may influence treatment assignment and potential outcomes simultaneously are assumed to be observed and included in the PS model.

Once the PS is estimated, several techniques have been used for estimating the causal effect of the exposure or intervention, either based on stratification on the quintiles of the PS or on adjustment on the PS. However, the most popular approach is to match cohort patients on the PS to artificially recreate the conditions

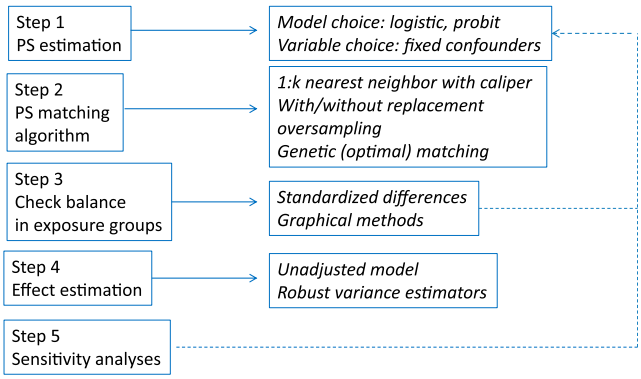

Figure 1. Propensity score (PS) matching: implementation steps and resulting questions.

ORIGINAL ARTICLE

Acute Outcomes and 1-Year Mortality of Intensive Care Unit–acquired Weakness

A Cohort Study and Propensity-matched Analysis

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Abstract

Rationale: Intensive care unit (ICU)-acquired weakness is a frequent complication of critical illness. It is unclear whether it is a marker or mediator of poor outcomes.

Objectives: To determine acute outcomes, 1-year mortality, and costs of ICU-acquired weakness among long-stay (≥8 d) ICU patients and to assess the impact of recovery of weakness at ICU discharge.

Methods: Data were prospectively collected during a randomized controlled trial. Impact of weakness on outcomes and costs was analyzed with a one-to-one propensity-score-matching for baseline characteristics, illness severity, and risk factor exposure before assessment. Among weak patients, impact of persistent weakness at ICU discharge on risk of death after 1 year was examined with multivariable Cox proportional hazards analysis.

Measurements and Main Results: A total of 78.6% were admitted to the surgical ICU; 227 of 415 (55%) long-stay assessable ICU patients were weak; 122 weak patients were matched to 122 not-weak patients. As compared with matched not-weak patients, weak patients had a lower likelihood for live weaning from mechanical ventilation (hazard ratio [HR], 0.709 [0.549–0.888]; $P = 0.009$), live ICU (HR, 0.698 [0.553–0.861]; $P = 0.008$) and hospital discharge (HR, 0.680 [0.514–0.871]; $P = 0.007$). In-hospital costs per patient (+30.5%, +5,443 Euro per patient; $P = 0.04$) and 1-year mortality (30.6% vs. 17.2%; $P = 0.015$) were also higher. The 105 of 227 (46%) weak patients not matchable to not-weak patients had even worse prognosis and higher costs. The 1-year risk of death was further increased if weakness persisted and was more severe as compared with recovery of weakness at ICU discharge ($P < 0.001$).

Conclusions: After careful matching the data suggest that ICU-acquired weakness worsens acute morbidity and increases healthcare-related costs and 1-year mortality. Persistence and severity of weakness at ICU discharge further increased 1-year mortality.
Clinical trial registered with www.clinicaltrials.gov (NCT 00512122).

Keywords: muscle weakness; costs and cost analysis; mortality; critical illness; muscle strength

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At a Glance Commentary

Scientific Knowledge on the Subject: Clinical weakness occurs frequently in prolonged critically ill patients. It remains controversial whether it is a marker or a mediator of poor outcomes.

What This Study Adds to the Field: After accounting for the potential confounding effects of other risk factors, it was shown that intensive care unit (ICU)-acquired weakness related to delayed weaning from mechanical ventilation, extended ICU and hospital stays, more healthcare-related hospital costs, and a higher risk of death at 1 year after ICU admission. These data support causality of the association between weakness and poor acute morbidity outcomes and, even more importantly, late death. The data underscore the importance of identifying strategies to prevent and treat this debilitating problem and suggest closer follow-up of patients with ICU-acquired weakness, also after hospital discharge.

Intensive care unit (ICU)-acquired muscle weakness (further referred to as weakness) is a frequent complication of critical illness. Patients with sepsis, multiple organ failure, or prolonged mechanical ventilation in particular are susceptible for development of weakness, which affects limbs and respiratory muscles (1). Given the strong association between weakness and multiple organ failure, weakness was considered to be the failure of just another organ in critically ill patients (2, 3). From this perspective and not surprisingly, observational studies revealed strong associations between weakness and poor prognosis (4–12), although this was not consistently confirmed (13, 14). Inferentially, weakness may generate more healthcare-related costs (15), but this has not been specifically investigated. It remains unclear to what extent weakness is more a marker than a mediator of poor outcomes. Also, it is unknown whether the degree of recovery from weakness at ICU discharge has any impact beyond the time of the index hospitalization, such as 1-year mortality. To address these questions, we investigated a large cohort of patients who were systematically screened for weakness after at least 1 week in ICU. We compared weak and not-weak patients after matching for potential confounders, using propensity score matching. This method is frequently used in observational studies to estimate effects if randomization is not feasible. It is more effective to reduce bias than multivariate regression analysis (16) and allows including a larger number of potentially confounding variables in the analysis (17). In this study we first described the characteristics of prolonged critically ill patients who developed weakness after an ICU stay of at least 8 days. We then evaluated the impact of weakness on short-term outcomes, healthcare-related in-hospital costs, and 1-year mortality. Finally, we assessed whether persistence of weakness at ICU discharge and the severity thereof had any impact on mortality 1 year after ICU admission. Some of these results have been previously reported in the form of an abstract to the International Symposium on Intensive Care and Emergency Medicine, 2014 (18).

Methods

Patients and Diagnosis of Weakness

This study was a prospectively planned subanalysis of the EPaNIC trial (19, 20). From December 2008 onward, patients still in ICU on Day 8 after admission (referred to as "long-stay patients") were systematically assessed for awakening and cooperation based on the response to five commands (4, 21). When adequate response to all of these was present, patients were evaluated for weakness by one of two trained physiotherapists. This evaluation was repeated three times a week until ICU discharge or death (22). Weakness was diagnosed when the Medical Research Council (MRC) sum score was less than 48 (21, 22).

At the same time points, inspiratory muscle strength was measured using a maximal volitional maneuver, excluding patients with an artificial airway (*see* online supplement). The study protocol and informed consent forms were approved by the Leuven University Hospital Ethics Committee (ML4190). All patients received progressive and systematic passive and active mobilization. Further details are described in the online supplement.

Data Collection and Endpoints

Baseline characteristics were collected on admission. Baseline risk factors for development of weakness and other studied outcomes were age, Acute Physiology and Chronic Health Evaluation (APACHE) II score, sex, body mass index (BMI), nutritional risk score (23), diabetes mellitus, malignancy, preadmission dialysis, sepsis, chronic obstructive pulmonary disease, admission category, and randomization group (early or late parenteral nutrition). Risk factors during ICU stay up to the time of first MRC sum score evaluation included treatment with corticosteroids and neuromuscular blocking agents, mean morning blood glucose, occurrence of new infections, and time to first MRC, reflecting the time to awakening. These were previously described (22). Further details are provided in the online supplement.

The acute primary endpoint was time-to-live hospital discharge; the medium-term primary endpoint was mortality 1 year after ICU admission. Secondary outcomes were time-to-live ICU discharge, time-to-live weaning from mechanical ventilation, inspiratory muscle strength, total billed healthcare costs per patient, ICU and hospital mortality rates, 6-minute-walk distance (6MWD) at hospital discharge, and categories of the healthcare-related billed costs. 6MWD at hospital discharge was analyzed on available data and after imputation of 0 m for patients unable to walk but not for nonsurvivors because we aimed to evaluate the functional impact of weakness at hospital discharge, independent of any possible mortality effect. Total healthcare-related costs billed to the health insurance and the patient were retrieved from the patients' invoices (24). Costs were divided into Period 1, covering ICU admission to ICU discharge, and Period 2, extending from ICU discharge until hospital discharge. Eight cost categories were explored: (*1*) fees (for medical and allied healthcare-related services), (*2*) pharmacy, (*3*) hospitalization costs per diem, (*4*) blood products and other fluids, (*5*) clinical chemistry, (*6*) radiology, (*7*) graft products (vascular grafts, mechanical valves, skin grafts, locomotor grafts, and so forth), and (*8*) miscellaneous.

The 1-year mortality was determined via the national registry for Belgian citizens and via direct contact with patient or relatives for foreigners. In a further exploratory and therefore inevitably retrospective analysis, we recorded the destination at hospital discharge and the details of ICU and hospital deaths (*see* online supplement).

Statistical Analyses

Descriptive statistics included median and interquartile ranges for continuous variables and numbers and percentages for categorical variables. Results were compared with Mann-Whitney *U* test and chi-square test as appropriate.

To examine the impact of the presence or absence of weakness among long-stay patients on outcome and healthcare-related costs, we selected a subset of patients with and without weakness matched for baseline risk factors and other risk factors that occurred during ICU stay up to the time of first MRC measurement and known to be associated with weakness or overall outcome (Table 1). Matching was based on propensity scores obtained by logistic regression and using one-to-one nearest neighbor matching without replacement

Table 1. Baseline Characteristics and Risk Factors for Weakness in the Total Long-Stay Population, Matched Population, and Unmatched Weak Patients

	Total Population			Matched Population			Unmatched Population	
	Weak (*n = 227*)	Not Weak (*n = 188*)	*P* Value	Weak (*n = 122*)	Not Weak (*n = 122*)	Standardized Mean Difference	Weak (*n = 105*)	*P* Value*
Baseline characteristics								
Age, yr, median (IQR)	64 (56–73)	61 (50–74)	0.097	64 (54–73)	65 (54–75)	−0.018	65 (57–73)	0.482
APACHE II score, median (IQR)	35 (29–40)	31 (23–37)	**<0.001**	33 (25–39)	34 (27–37)	−0.015	37 (33–42)	**<0.001**
Male sex, n (%)	127 (55.9)	120 (63.8)	0.103	71 (58.2)	72 (59)	−0.016	56 (53.3)	0.462
BMI < 25 or > 40, n (%)	130 (57.3)	96 (51.1)	0.206	62 (50.8)	64 (52.5)	−0.033	68 (64.8)	**0.034**
NRS < 5, n (%)	136 (59.9)	138 (73.4)	**0.004**	82 (67.2)	81 (66.4)	0.017	54 (51.4)	**0.016**
Diabetes mellitus, n (%)	35 (15.4)	28 (14.9)	0.882	22 (18)	21 (17.2)	0.023	13 (12.4)	0.240
Malignancy, n (%)	65 (28.6)	47 (25.0)	0.406	35 (28.7)	35 (28.7)	0	30 (28.6)	0.984
Preadmission dialysis, n (%)	4 (1.8)	1 (0.5)	0.253	1 (0.8)	1 (0.8)	0	3 (2.9)	0.245
Sepsis, n (%)	136 (59.9)	94 (50.0)	**0.043**	69 (56.6)	63 (51.6)	0.100	67 (63.8)	0.266
COPD, n (%)	44 (19.4)	42 (22.3)	0.459	24 (19.7)	23 (18.9)	0.021	20 (19.0)	0.906
Admission category								
Abdominal/pelvic surgery, n (%)	36 (15.9)	18 (9.6)	0.089	16 (13.1)	13 (10.7)	0.040	20 (19)	0.070
Cardiac surgery, n (%)	63 (27.8)	53 (28.2)		36 (29.5)	38 (31.1)		27 (25.7)	
Cardiovascular, n (%)	1 (0.4)	1 (0.5)		0 (0)	1 (0.8)		1 (1.0)	
Gastrointestinal/ hepatic, n (%)	16 (7.0)	12 (6.4)		11 (9)	11 (9)		5 (4.8)	
Hematologic/oncologic, n (%)	9 (4.0)	1 (0.5)		2 (1.6)	1 (0.8)		7 (6.7)	
Neurologic, n (%)	2 (0.9)	0 (0.0)		2 (1.6)	0 (0)		0 (0)	
Neurosurgery, n (%)	1 (0.4)	1 (0.5)		0 (0)	1 (0.8)		1 (1)	
Renal, n (%)	3 (1.3)	3 (1.6)		1 (0.8)	3 (2.5)		2 (1.9)	
Respiratory, n (%)	19 (8.4)	12 (6.4)		6 (4.9)	7 (5.7)		13 (12.4)	
Thoracic surgery, n (%)	20 (8.8)	16 (8.5)		14 (11.5)	12 (9.8)		6 (5.7)	
Transplant, n (%)	21 (9.3)	23 (12.2)		11 (9)	13 (10.7)		10 (9.5)	
Trauma/burns, n (%)	11 (4.8)	25 (13.3)		7 (5.7)	5 (4.1)		4 (3.8)	
Vascular surgery, n (%)	8 (3.5)	9 (4.8)		7 (5.7)	5 (4.1)		1 (1)	
Other, n (%)	17 (7.5)	14 (7.4)		9 (7.4)	12 (9.8)		8 (7.6)	
Randomization, late PN, n (%)	104 (45.8)	98 (52.1)	0.200	60 (49.2)	58 (47.5)	0.033	44 (41.9)	0.273
Risk factors occurring during ICU stay†								
Time to first MRC, d, median (IQR)	12 (9–20)	9 (8–12)	**<0.001**	11 (9–15)	11 (8–14)	0.019	16 (11–23)	**<0.001**
Corticosteroids, d, median (IQR)	3 (0–10)	0 (0–6)	**<0.001**	1 (0–8)	0 (0–6)	0.098	8 (0–15)	**<0.001**
NMBA, yes, n (%)	131 (57.7)	61 (32.4)	**<0.001**	56 (45.9)	50 (41)	0.099	75 (71.4)	**<0.001**
Mean morning glycaemia, mg/dl, median (IQR)	102 (96–109)	103 (98–110)	0.521	103 (96–110)	103 (97–108)	−0.013	101 (97–108)	0.694
New infection, n (%)	159 (70.0)	101 (53.7)	**0.001**	78 (63.9)	78 (63.9)	0	81 (77.1)	**0.030**

Definition of abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation; BMI = body mass index; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; IQR = interquartile range; NMBA = neuromuscular blocking agents; NRS = Nutritional Risk Score; PN = parenteral nutrition.

Bold values indicate $P < 0.05$.

*P value for not-matched versus matched weak patients.

†All risk factors were calculated up to the time of first Medical Research Council sum score evaluation for every patient individually.

with weakness as the dependent variable (25). To optimize matching for all variables of interest, time-to-first MRC was entered as a log10 transformed factor. The caliper was gradually narrowed, starting from 0.2, to obtain satisfactory matching as indicated by an absolute standardized difference in means less than or equal to 0.1 for all variables. The standardized mean difference was defined as the mean difference between the groups divided by the standard deviation of the control group (26). This was reached at a caliper of 0.1 (i.e., 0.1 × standard deviation of the logit of the propensity score). For time-to-event analyses, comparisons for patients with and without weakness were done with Cox proportional hazards analysis and visualized with Kaplan-Meier plots. Because the time-to-event analyses were performed in a subgroup matched for confounding factors, no additional adjustments for these were made in the Cox regression model. Time-to-alive weaning was calculated from ICU admission. Time-to-alive ICU and hospital discharge were calculated from the time of measurement of MRC sum score. A robust estimator of variance was used for analyses of paired data (27). To further assess the impact of persistence and severity of weakness at ICU discharge on medium-term prognosis, we analyzed the association between weakness at ICU discharge and 1-year survival among weak patients with multivariable Cox proportional hazards analysis. Patients were categorized as recovered from weakness (MRC sum score $\geqslant 48$) or with persisting weakness (with either $48 >$ MRC sum score $\geqslant 36$, or MRC sum score < 36). Analysis was performed with a forward stepwise method (likelihood ratio, probability for enter 0.05, removal 0.1), including all baseline risk factors potentially affecting survival, and the risk factors to which the weak patients were exposed before diagnosis of weakness and that were potentially related with survival. For this purpose, because limited confounders can be included in multivariable models, the 16 admission categories were grouped into four main categories for this analysis, as described (*see* Table E1 in online supplement) (22). This analysis was performed on the total population of weak patients, because we expected that the matched subset would be less severely ill and not completely representative for all weak patients. The time variable entered in the model was calculated from the last MRC measurement up to 1 year after ICU admission.

All analyses were performed with IBM SPSS-20 (IBM, Armonk, NY). Propensity score matching was performed with IBM SPSS-20 and R version R2.10.1 (R Foundation for Statistical Computing, Vienna, Austria) (26). Differences were considered significant when two-sided *P* values were 0.05 or less.

Results

Patient Characteristics

Between October 2008 and November 2010 MRC sum score was measured in 415 long-stay ICU patients (Figure 1). The population constituted of 28% admissions following cardiac surgery; 47.2% urgent admissions for complications after other surgery, burns, and trauma; 3.4% elective admissions following other surgery; and 21.4% admissions to the medical ICU. Weakness was present in 227 (55%) patients. Baseline characteristics and exposure to risk factors for weakness during ICU stay and up to the moment of actual measurement of MRC sum score are listed in Table 1. Weak patients were more severely ill on admission than not-weak patients as reflected by the APACHE II score (35 [29–40] vs. 31 [23–37]), less often had a low nutritional risk score (59.9% vs. 73.4%), and more often had sepsis on admission (59.9% vs. 50.0%). Weak patients were treated more often and longer with corticosteroids (3 d [0–10] vs. 0 d [0–6]), more frequently received neuromuscular blocking agents (57.7% vs. 32.4%), and experienced new infectious episodes between admission and MRC sum score evaluation (70% vs. 53.7%). Time-to-awakening and first MRC sum score measurement was significantly longer in weak than in not-weak patients (12 d [9–20] vs. 9 d [8–12]). Mortality rates of the studied patients were relatively low despite high severity of illness. This is caused by the selection of long-stay patients who were awake and fully cooperative in ICU. By this selection, we omitted severely ill patients who died early in ICU and long-stay patients who were not awake and

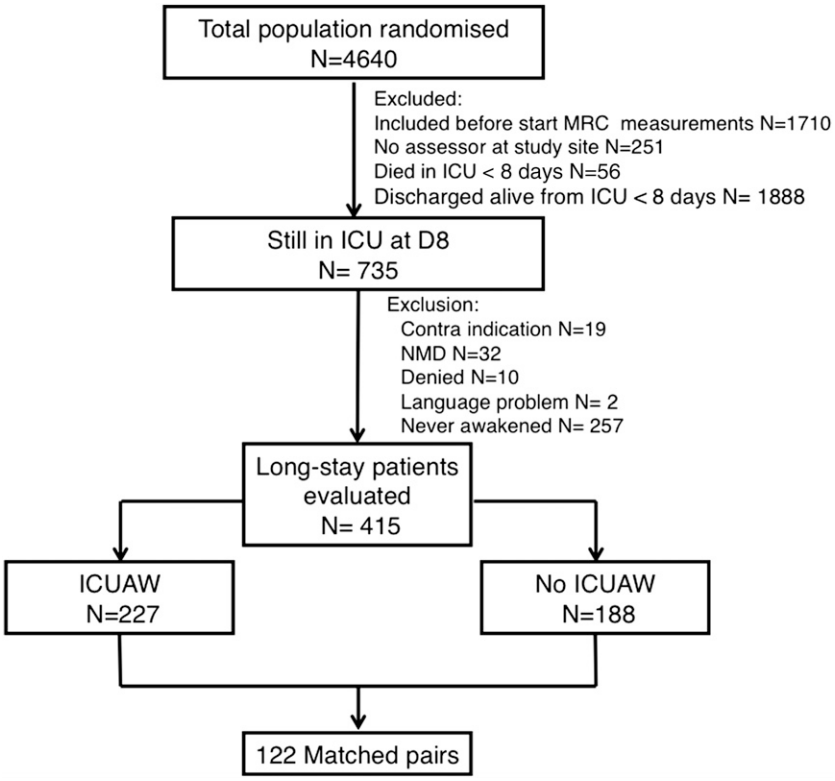

Figure 1. Flow chart of patients evaluated. ICU = intensive care unit; ICUAW = intensive care unit–acquired weakness; NMD = neuromuscular disease; MRC = Medical Research Council.

cooperative enough for testing and who clearly have worse outcomes than those who were studied (*see* Table E2). This selection also explained the substantial difference between ICU and hospital mortality for the studied population (data not shown).

Impact of Presence of Weakness in Long-Stay Patients on Outcomes and Healthcare-related Costs

Before matching and as compared with patients without weakness, weakness was associated with poorer acute outcomes. At any time, patients with weakness had a significantly lower likelihood of being alive and weaned, discharged from ICU and from the hospital than patients without weakness. Details on respiratory muscle strength are reported in Table E3. Weak patients had a higher ICU and hospital mortality (Table 2). The circumstances of these deaths were further analyzed retrospectively (*see* Table E4). Although statistically more weak patients were DNR coded at the time of death ($P = 0.044$), most patients died while care was withdrawn. No significant difference was detected in the incidence of readmissions, recurrence of respiratory failure, possible aspiration, tracheostomy, or cause of death. These data are limited by their retrospective nature and by the low statistical power because only 12 deaths occurred in not-weak patients. In fewer weak as compared with not-weak patients, 6MWD could be obtained at hospital discharge. Reasons for not being walked for 6 minutes varied for weak and not-weak patients. When tested, the distance walked in 6 minutes did not significantly differ. After imputation of 0 m for those patients who were unable to walk for physical or mental reasons, weak patients walked significantly less distance in 6 minutes. Similar results were obtained when also imputing 0 for nonsurvivors. Discharge destination was significantly different for weak versus not-weak patients. Weakness was associated with more incremental healthcare-related costs and higher 1-year mortality.

Because large imbalances in baseline characteristics and in other risk factors for the development of weakness were found between patient groups, the actual contribution of weakness to worse outcomes and increased healthcare costs, independent from other covariates, was examined in a matched subset of patients. This propensity score based matching procedure resulted in 122 unique pairs of patients with and without weakness, who were well matched for baseline characteristics and known risk factors for weakness to which they were exposed before the measurement of MRC sum score (Figure 2, Table 1). In this matched population, and as compared with not-weak patients, patients with weakness at any time had a significantly lower likelihood for being alive and weaned from mechanical ventilation (hazard ratio [HR], 0.709 [0.549–0.888]; $P = 0.009$) (Figure 3A), for being alive and discharged from the ICU (HR, 0.698 [0.553–0.861]; $P = 0.008$) (Figure 3B), and from the hospital (HR, 0.680 [0.514–0.871]; $P = 0.007$) (Figure 3C). In 14.8% of weak patients and in 27.9% of not-weak patients, 6MWD was obtained at hospital discharge ($P = 0.012$). Reasons for missing 6MWD data did not significantly differ between groups, and also distance walked within 6 minutes when tested did not differ. However, when a 0 value was imputed for patients with new physical or mental impairment precluding evaluation, the 6MWD distance was significantly lower ($P = 0.01$). Discharge destination was significantly different for weak versus not-weak patients ($P = 0.017$) with, respectively, 17.5% versus 9.8% of the patients being discharged to rehabilitation units and 18.4 versus 8.9% to other hospitals. ICU mortality ($P = 0.355$) and hospital mortality rate ($P = 0.075$) were not different, but mortality after 1 year was higher in weak than in not-weak patients (30.4% vs. 17.2%; $P = 0.015$). This effect remained when matching procedure was repeated with additional separation of BMI less than 25 and BMI greater than 40 (*see* online supplement).

Also after matching, total billed costs for the hospitalization remained higher in weak than in not-weak patients with a median difference of 5,443 Euros (+30.5%; $P = 0.04$). When dividing costs for the first ICU and second ward period, only costs for the ICU period were significantly higher (+3,794 Euros per patient or +27.9%; $P = 0.048$). The differences for this period were mainly attributable to costs for clinical chemistry, radiology, and graft products, but the latter was of no relevance because the median cost for this category was 0 Euros per patient for both groups (*see* Table E5). Costs of clinical chemistry ($R^2 = 0.886$) and radiology ($R^2 = 0.778$) were strongly related with duration of ICU stay. In bivariate analysis, the longer duration of ICU stay for weak as compared with not-weak patients explained the differences for clinical chemistry. Indeed, by adding the duration of ICU stay to the model, the independent association with weakness was lost ($P = 0.214$) and was taken over by that with duration of ICU stay ($P < 0.001$). For radiology, both presence of weakness and ($P = 0.03$) duration of ICU stay ($P < 0.001$) remained independently associated.

Notably, 105 of 227 (46%) weak patients could not be matched to patients without weakness (Table 1). These unmatched and weak long-stay patients were sicker at admission, with higher APACHE II scores, and more frequently had a high nutritional risk score (nutritional risk score >5) and low or high BMI, as compared with the weak patients who did get matched. The unmatched group had significantly more exposure to known risk factors for weakness before assessment, such as corticosteroids and neuromuscular blocking agents, as compared with the weak but matched patients (Table 1). Time-to-awakening and first MRC sum score measurement was also significantly higher and not-matched patients more often developed new infections in ICU before MRC sum score evaluation. The not-matched weak patients had significantly worse outcomes than the matched weak patients with a median increase of time-to-live weaning of 9 days, time-to-live ICU discharge of 4 days, and time-to-live hospital discharge of 16 days. Total billed cost for this unmatched subgroup of weak patients was median 8,057 Euros higher (+35%; $P < 0.001$) than in the matched weak patients.

Impact of Recovery of Weakness at ICU Discharge on 1-Year Mortality

Among the 227 weak long-stay patients, risk of death at 1 year after ICU admission was dependent on the persistence of weakness at ICU discharge and on severity of such persistent weakness ($P < 0.001$) (Figure 4). At any time within the first year following ICU admission, compared with

Table 2. Outcome Characteristics in the Total Long-Stay Population, Matched Population, and Unmatched Weak Patients

	Total Population			Matched Population			Unmatched Population	
	Weak (*n* = 227)	Not Weak (*n* = 188)	*P* Value	Weak (*n* = 122)	Not Weak (*n* = 122)	*P* Value	Weak (*n* = 105)	*P* Value*
Strength data								
First MRC sum score	42 (34–44)	52 (49–56)	**<0.001**	42 (35–44)	52 (49–56)	**<0.001**	39 (33–44)	0.077
MRC sum score < 36	69 (30.4)	0 (0)	**<0.001**	31 (25.4)	0 (0)	**<0.001**	38 (36.2)	0.078
ICU stay								
Time to alive weaning from MV, d†	14 (8–30)	7 (4–12)	**<0.001**	11 (7–22)	8 (5–14)	**0.009**	20 (11–41)	**0.001**
Time to alive ICU discharge, d†	7 (3–19)	3 (1–6)	**<0.001**	6 (2–14)	3 (0–8)	**0.008**	10 (3–30)	**0.015**
ICU mortality, n (%)	18 (7.9)	5 (2.7)	**0.02**	7 (5.7)	4 (3.3)	0.355	11 (10.5)	0.188
Hospital stay								
Time to alive hospital discharge, d†	43 (21–114)	22 (13–41)	**<0.001**	36 (16–83)	23 (13–41)	**0.007**	52 (24–312)	**0.009**
Hospital mortality, n (%)	46 (20.3)	12 (6.4)	**<0.001**	19 (15.6)	10 (8.2)	0.075	27 (25.7)	0.058
6MWD performed, n (%)	36 (15.9)	53 (28.2)	**0.002**	18 (14.8)	34 (27.9)	**0.012**	18 (17.1)	0.623
6MWD, reasons not performed			**0.002**			0.328		0.211
Death	46 (24.1)	12 (8.9)		19 (18.3)	10 (11.4)		27 (31.0)	
Physical or psychological impairment	27 (14.1)	14 (10.4)		16 (15.4)	9 (10.2)		11 (12.6)	
Assessments not completed before discharge	86 (45)	78 (57.8)		49 (47.1)	49 (55.7)		37 (42.5)	
Premorbid limitation/refusal/ assessor not available/not classifiable	32 (16.8)	31 (23)		20 (19.2)	20 (22.7)		12 (13.8)	
6MWD available data, m	223 (120–280)	244 (185–300)	0.102	199 (120–264)	214 (163–286)	0.277	239 (105–319)	0.406
6MWD with imputation data, m‡	78 (0–240)	200 (104–287)	**0.002**	66 (0–207)	191 (90–270)	**0.010**	103 (0–260)	0.301
Discharge destination survivors			**0.001**			**0.017**		0.197
Home	114 (63)	142 (80.7)		66 (64.1)	91 (81.2)		48 (61.5)	
Rehabilitation unit	39 (21.5)	17 (9.7)		18 (17.5)	11 (9.8)		21 (26.9)	
Other hospital	28 (15.5)	17 (9.7)		19 (18.4)	10 (8.9)		9 (11.5)	
Costs								
Total billed costs per patient	26,348 (16,637–44,519)	17,356 (11,507–30,205)	**<0.001**	23,277 (15,370–36,147)	17,834 (12,227–31,306)	**0.040**	31,334 (19,866–60,331)	**<0.001**
Period 1	19,678 (12,186–33,901)	12,517 (7,692–20,523)	**<0.001**	17,416 (10,083–28,470)	13,622 (8,539–20,847)	**0.048**	25,539 (15,048–50,623)	**<0.001**
Period 2	3,633 (1,143–8,597)	2,712 (1,127–6,886)	0.148	3,289 (1,054–8,267)	2,904 (1,095–6,911)	0.675	4,293 (1,313–9,258)	0.290
Medium-term								
One-year mortality, n (%)	72 (31.9)	27 (14.4)	**<0.001**	37 (30.6)	21 (17.2)	**0.015**	35 (33.3)	0.658

Definition of abbreviations: 6MWD = 6-minute-walk distance; ICU = intensive care unit; MRC = Medical Research Council; MV = mechanical ventilation.
Period 1 covered ICU admission to ICU discharge; Period 2 covered ICU discharge to hospital discharge.
Duration of mechanical ventilation was calculated from ICU admission; ICU and hospital stay were calculated from time of measurement of MRC sum score.
Bold values indicate $P < 0.05$.
*P value for not-matched versus matched weak patients.
†P values for time-to-event analysis were calculated using Cox regression analysis.
‡Imputation of 0 m was performed for bad outcomes including nonpreexisting physical or mental reasons, which precluded performing 6MWD.

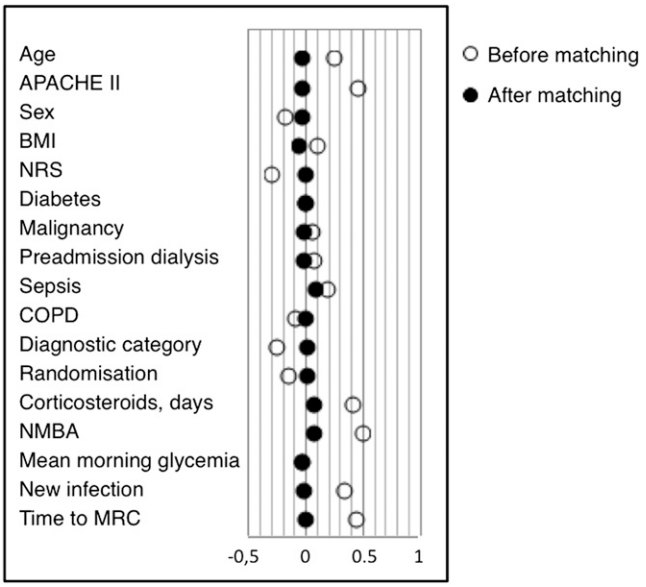

Figure 2. Mean standardized differences for baseline characteristics, illness severity, and risk factor exposure before MRC evaluation before and after propensity score matching. The *horizontal axis* represents the mean standardized difference, *open dots* reflect values before matching, and *black dots* values after matching. If both values overlap, only the *black dot* is visible. Matching procedure aimed at, and succeeded in, reducing mean standardized difference to an absolute value of maximally 0.1. APACHE II = Acute Physiology and Chronic Health Evaluation; BMI = body mass index; COPD = chronic obstructive pulmonary disease; MRC = Medical Research Council; NMBA = neuromuscular blocking agents; NRS = nutritional risk score.

patients who recovered from weakness and adjusted for potential confounders, those with persistent weakness and MRC sum between 36 and 47 at ICU discharge had a higher likelihood of death (HR, 2.104; 95% confidence interval, 1.134–3.903; $P = 0.018$). This likelihood of late death was even higher for patients with a more severe degree of persistent weakness (MRC sum < 36; HR, 4.273; 95% confidence interval, 2.085–8.754; $P < 0.001$) (Figure 4).

Discussion

We present a large cohort of long-stay ICU patients prospectively evaluated for weakness. Using a one-to-one propensity score matched analysis, we assessed impact of weakness on short-term outcomes, 1-year mortality, and in-hospital healthcare-related costs. Weak patients had worse in-hospital morbidity (but not mortality outcomes), generated more hospital costs, and revealed a higher mortality 1 year after ICU admission than not-weak patients. The 1-year mortality of patients who developed weakness during ICU stay was further increased when weakness persisted at ICU discharge, and was even higher when persistent weakness at ICU discharge was more severe. This suggests that ICU-acquired weakness independently contributes to the legacy of critical illness.

Neuromuscular complications of critical illness are common and represent major functional morbidity (28, 29). Strategies to prevent weakness are limited in number and effectiveness (15, 30). These include aggressive treatment of the underlying condition, glycemic control (31, 32), and implementing an early rehabilitation strategy with minimal sedation (33, 34). Higher protein delivery in the first week was recently associated with greater muscle wasting (35). Also, avoiding parenteral nutrition in the first

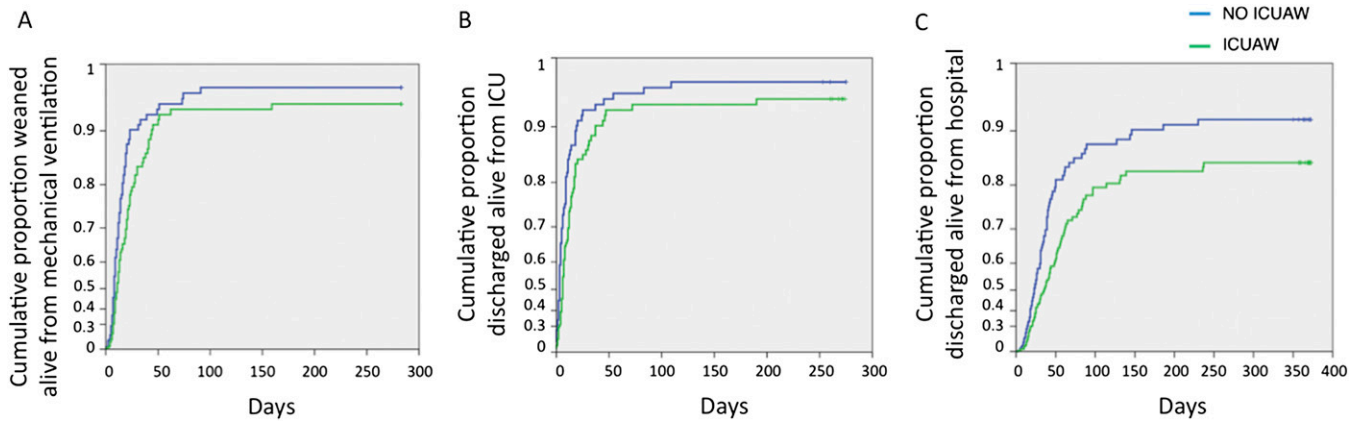

Figure 3. Kaplan-Meier plots depicting the proportion of propensity score matched patients over time that were alive and weaned from the ventilator, discharged from intensive care unit (ICU) and from the hospital. The cumulative proportion of patients weaned alive from mechanical ventilation (*A*), discharged alive from the ICU (*B*), and discharged alive from the hospital (*C*) are shown for the matched weak and not-weak long-stay patients. Data for patients who died were censored after the last patient had been weaned alive (*A*), or discharged alive from the ICU (*B*) or the hospital (*C*). Time-to-alive weaning was calculated from ICU admission. Time-to-alive ICU and hospital discharge were calculated from the time of measurement of Medical Research Council sum score. ICUAW = intensive care unit–acquired weakness.

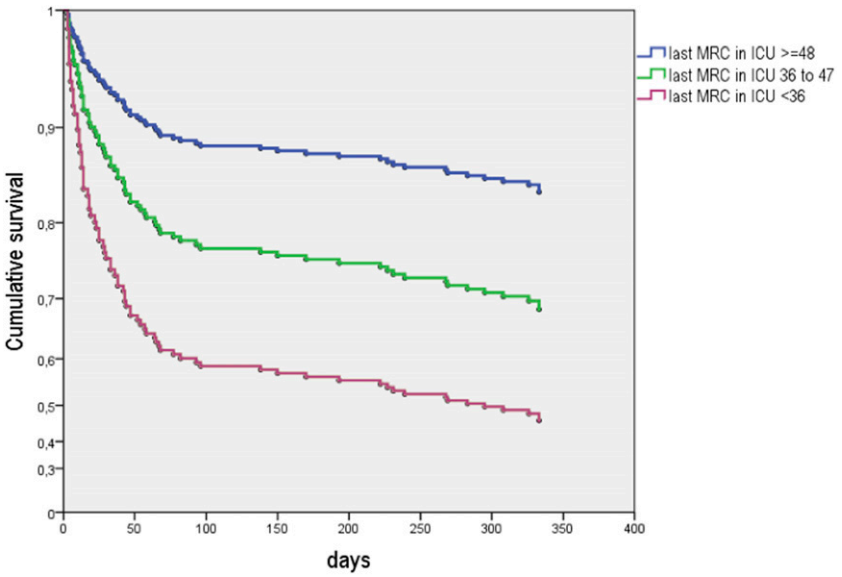

Figure 4. Cox regression estimates for survival in the first year after intensive care unit (ICU) admission in the total population of weak patients according to persistence and severity of weakness at final examination in the ICU. The survival curve visually displays the model predicted survival time for the "average" patient (that is other covariates are fixed at their average values) according to the Medical Research Council (MRC) sum score at final examination in the ICU: the plot shows the effect of recovery from weakness, persisting weakness with MRC from 36 to 47, and persisting weakness with MRC less than 36 by the end of ICU stay. The time variable entered in the model was calculated from the last MRC measurement up to 1 year after ICU admission.

week in ICU reduced weakness (22). Several observational studies indicated that weakness is associated with poor outcomes, including longer duration of mechanical ventilation, ICU stay and hospital stay, and higher ICU and hospital mortality. Others could not confirm an independent relationship of neuromuscular complications in the ICU with outcome (14, 36). This controversy is at least partially explained by the difficult clinical diagnosis of weakness and by the fact that randomized studies to address the question of causality are not possible. ICU-acquired weakness could indeed be just a marker of illness severity and of poor prognosis. To examine any potential causal impact of ICU-acquired weakness on outcome in a mixed population of long-stay patients, we created 122 unique pairs of weak and not-weak patients with similar baseline characteristics and risk factors for weakness. The population studied was a subgroup of EPaNIC, a randomized controlled trial examining the effects of early versus late parenteral nutrition on overall outcome. In this trial, early parenteral nutrition negatively affected muscle strength, although clearly the nutritional strategy was unable to fully prevent weakness (22). For this reason, we included the randomization arm in the propensity model. This analysis was performed using one-to-one propensity score matching procedure without replacement. Other methods, such as multiple regression, tend to inflate effects in observational studies, especially when the number of prognostic factors is high (16) and when there is insufficient overlap of covariates between the two groups of interest (37). By stringent and conservative matching analysis, we attempted to get as close as possible to causal inference of weakness (37).

We found that weak patients had worse morbidity outcomes than patients without weakness, as reflected by a lower likelihood at any time for live weaning, ICU discharge, and hospital discharge. A possible mechanism explaining worse short-term outcome is coexistence of respiratory muscle weakness. Both peripheral and respiratory muscle weakness are related with severity of illness and sepsis (38–40) and may be the reflection of organ failure. Also, respiratory muscle weakness is associated with peripheral muscle weakness (6). A clear relationship between respiratory muscle weakness measured using magnetic stimulation, a method not requiring patient cooperation, and worse outcome has been demonstrated (38, 39). Using volitional measurements of respiratory muscle strength, we could not confirm reduced respiratory muscle strength in the matched population. This may be because of bias induced by the selection of patients tested for maximal inspiratory pressure, which did not allow an artificial airway. Therefore, partial recovery could have been present at the time of measurement. Also, sample size reduction with the matching procedure inevitably further reduced statistical power. Pharyngeal dysfunction and symptomatic aspiration, related to limb muscle weakness in chronically ventilated patients (41), could be another explanation for the worse outcome. We cannot confirm this relationship because we did not systematically assess swallowing in our patients.

ICU and hospital mortality were not different. Strikingly, patients who acquired weakness in the ICU did have higher 1-year mortality than matched patients without weakness. Other available data on medium-term mortality of critically ill patients with neuromuscular complications are scarce. Leijten and coworkers (42) reported in a small subset of 50 severely ill patients with critical illness polyneuropathy that hospital mortality was increased, but the sample size did not have the statistical power to address significance of the seemingly higher 1-year mortality (52% vs. 43%).

Our findings suggest that weakness diagnosed clinically in ICU affects patients' health beyond ICU and hospital discharge. This confirms the association between muscle weakness and impaired physical function and health-related quality of life in patients with acute lung injury, shown to persist up to 24 months after admission (43). The absence of any significant impact of weakness on ICU and hospital mortality in our population may indicate that the predominant immediate impact of weakness is morbidity and delayed recovery rather than increased risk of death in the hospital. Alternatively, sample size reduction by the matching procedure may have reduced statistical power to detect differences in ICU and hospital mortality. Also, the robustness of the statistical methods we used may explain why an immediate risk of death was not associated with weakness, because it was present before matching. A substantial amount of long-stay patients (105 of 227) diagnosed with weakness could not be matched to patients without weakness, and these

patients were sicker, had more risk factors for weakness, and had worse outcomes than the matched weak patients. Hence, the propensity-matched analysis represents a very conservative approach toward the impact of weakness on outcomes.

With this methodology, increased late mortality of patients who acquired weakness during the ICU stay is striking and could have important implications for patient care. The shorter distance walked in 6 minutes at hospital discharge, apparent after imputation of a poor score for patients unable to walk for reasons that may mask weakness, as previously done (44), suggests that the weakness had functional impact at hospital discharge. This is further confirmed by the *post hoc* analysis of the discharge destination showing clearly different proportions of patients being discharged to rehabilitation units, other hospitals, or home. Our finding that persistence of weakness at ICU discharge, and the severity thereof, further increased the risk of death after 1 year as compared with patients who were weak but recovered from weakness before ICU discharge suggests longer-term consequences and implications for patient care. Fan and coworkers (43) recently reported substantial mortality among survivors of acute lung injury long after ICU and hospital discharge. This concurs with the concept that critical illness–induced neuromuscular complications may represent a rapid-onset frailty across a range of age strata (45), which itself has been related with increased risk of adverse events, morbidity, and mortality (46). Patients diagnosed with weakness after prolonged ICU stay could possibly benefit from closer follow-up after ICU and hospital discharge to prevent late death.

Limitations

Results apply to the subgroup of long-stay but cooperative ICU patients and therefore cannot be extrapolated to short-stayers or to long-stayers who never regained enough cooperation to allow testing. An important fraction of patients indeed could not be tested for weakness because they did not regain adequate awakening at the three weekly screening moments. Daily screening could potentially have decreased this number. We did not use a validated delirium scale, but requested patients to correctly respond to five out of five complex commands to avoid testing patients unable to remain attentive for a sufficiently long period or to perform the complex commands. We did not measure or adjust for baseline muscle weakness before ICU admission because, in general, it is not feasible to prospectively evaluate this because of the unplanned nature of critical care admissions. A comorbidity-derived measure, such as the Functional Comorbidity Index (47), designed as a predictor of physical functioning in ICU survivors could have been useful for this purpose. We cannot exclude residual confounding by this or any other unmeasured factors. Because of the one-to-one propensity score matching procedure with narrow caliper, the sample size was reduced. We did not formally address the causes of late mortality. Therefore, the mechanisms leading to increased 1-year mortality remain to be unraveled. Also, the low percentage of patients that were evaluated for the 6MWD with a substantial number of assessments not completed before discharge may limit conclusions that can be drawn from these results. To avoid bias by omitting patients unable to walk for reasons that may mask weakness, we imputed 0 values. However, in addition to weakness, other factors, such as cognitive or psychiatric complications, gait or balance disturbances, contractures, or fixed flexion of joints from heterotopic ossification, can limit functionality. Since the completion of the early exercise training study in February 2007 performed in some of the participating ICUs (34), mobilizing critically ill patients early became standard of care. Such care was provided in a protocolized manner (48) and to the best abilities of the physical therapy team. We did not actually record number and duration of sessions. We cannot exclude that optimal treatment provided in a randomized setting (33, 34) could have resulted in better functional outcomes, although the setting reflected well the daily practice. Finally, although we and others found good reproducibility of MRC sum score in various clinical settings (49–51), including critically ill patients (9, 21), others could not confirm this (14, 36), which may limit generalizability of conclusions.

Conclusions

Screening for clinical muscle weakness in patients in ICU for at least 8 days allows identifying patients with ICU-acquired weakness that seems to expose them to an increased risk of short-term morbidity and a higher risk of late death 1 year after the acute event. Weakness generated extra healthcare-related costs predominantly during the time in ICU rather than on the regular hospital wards. Our findings also stress the importance of further research aimed at prevention and/or treatment of this detrimental complication that seems to contribute to the legacy of critical illness. These findings also suggest that weak patients should be closely monitored following ICU and hospital discharge to prevent complications that lead to late death. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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