The Post-Intensive Care Syndrome (PICS)

Impact of ICU-stay on functioning and implications for rehabilitation care

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CHAPTER 4

Functional recovery in patients with and without Intensive care unit acquired weakness

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ABSTRACT

Objective
The aim of this work was to compare the patient-reported functional health status with regard to physical, psychological, and social functioning of intensive care unit (ICU) survivors with and without ICU-acquired weakness (ICU-AW).

Design
Single-center prospective study in ICU patients who were mechanically ventilated for more than 2 days and who survived to ICU discharge. Functional health status was assessed at 3, 6, and 12 months after ICU discharge, using the Sickness Impact Profile 68 (SIP68). The independent effect of ICU-AW on impaired functional status (SIP68 scores > 20) was analyzed using a multivariable logistic regression model.

Results
A total of 133 patients were included, 60 with ICU-AW. Intensive care unit-acquired weakness was an independent predictor for impaired functional health status at 3 months after ICU discharge (odds ratio, 0.27; 95% confidence interval, 0.08-0.94; P = 0.04) but not at 6 and 12 months. Physical functioning was significantly more impaired in patients with ICU-AW at 3 and 12 months. Psychological functioning and social functioning were comparable between the groups, with little restrictions in psychological functioning, and severe long-lasting restrictions in social functioning.

Conclusions
The findings of this study urge the need to develop interdisciplinary rehabilitation interventions for ICU survivors, which should be continued after hospital discharge.
INTRODUCTION
Survival from critical illness has improved dramatically over the past 20 years, leading to growing awareness of the long-lasting physical and psychological complications, and the reduced health-related quality of life in intensive care unit (ICU) survivors. Intensive care unit-acquired weakness (ICU-AW) is a frequently occurring neuromuscular complication in critically ill patients, with an estimated incidence of 46% (95% confidence interval, 43-49) in patients with sepsis, prolonged mechanical ventilation, or multiple organ failure. Intensive care unit-acquired weakness is defined as muscle weakness that develops after the onset of critical illness and is diagnosed by manual muscle strength assessment. It can be further differentiated into critical illness polyneuropathy, critical illness myopathy, or a combination of both (critical illness neuro-myopathy). The exact pathophysiological mechanisms underlying ICU-AW have not yet been fully elucidated but are believed to be multifactorial, including microvascular ischemia, catabolism, and immobility. Previous studies showed that ICU-AW is associated with increased physical limitations and mortality. Physical limitations, in turn, can lead to long-lasting restrictions in participation. Approximately 50% of survivors of critical illness have not returned to work 1 year after ICU discharge. Early rehabilitation in the ICU and beyond hospital discharge is recommended to reduce physical deconditioning and improve functional outcome in ICU survivors. These studies, however, did not differentiate between ICU survivors with and without ICU-AW, and only focused on physical functioning. An optimal multidisciplinary care pathway, integrating the 3 health domains (i.e., physical, psychological, and social) described by the World Health Organization has yet to be determined. To support informed decision making concerning the rehabilitation care pathway for ICU survivors after ICU and hospital discharge, more insight in long-term functional recovery of patients with and without ICU-AW is needed. Therefore, the objective of the present study was to compare the course of functional recovery with regard to physical, psychological, and social functioning, in a general population of ICU survivors with and without ICU-AW. It was hypothesized that patients with ICU-AW would have worse functional status during the first year after ICU discharge compared to patients without ICU-AW.

METHODS
Study Design, Setting, and Participants
A single-center, prospective, longitudinal cohort study was conducted between May 2011 and January 2014 in the Academic Medical Center (AMC) in Amsterdam, the Netherlands. Results regarding the impact of ICU-AW on physical functioning and mortality at 6 months have been described previously. Newly admitted adult (age ≥ 18 years or older) patients, who were mechanically ventilated for 2 days or more at the tertiary mixed medical-surgical ICU, and who survived to ICU discharge, were included. Patients with neurological
conditions (e.g., neuromuscular disorders, stroke, spinal cord lesions, and out-of-hospital cardiac arrest) as reason for admission, and patients with poor functional status before ICU admission (modified Rankin score ≥ 4) were excluded. Patients with preexisting neuromuscular disorders with a Rankin score of less than 4 not leading to ICU admission were included in this study. When manual muscle strength could not be assessed because of prolonged delirium or limited attentiveness to follow instructions, patients were excluded, as well as patients who were unable to complete the Dutch questionnaires. As an integral part of care, all patients received early rehabilitation in the ICU, consisting of daily passive range of motion exercises (including passive cycling) for unconscious patients, and active exercise therapy (e.g., in-bed exercises, active cycling, balance training at the edge of the bed, out-of-bed mobilization, standing, walking) as soon as possible. Other rehabilitation interventions, such as occupational therapy, speech therapy, or psychological support were initiated if required. After transfer to a regular ward, the rehabilitation treatment was continued until hospital discharge. The institutional review board of the Academic Medical Center, University of Amsterdam, the Netherlands, waved the need for informed consent because of the nonintrusive nature of this study (METC 10/219). Still, verbal and/or written informed consent of all surviving patients was obtained.

Assessment of ICU-AW

Intensive care unit-acquired weakness was diagnosed using manual muscle strength testing, which is the current diagnostic reference standard. As part of routine care, physical therapists performed manual muscle strength assessments using the Medical Research Council (MRC) scale when patients were awake (Richmond Agitation Sedation Scale between -1 and +1) and attentive (able to follow verbal commands using tongue or eyelids). The MRC scores of 6 different muscle groups were assessed bilaterally: shoulder abduction, elbow flexion, wrist dorsiflexion, hip flexion, knee extension, and ankle dorsiflexion. To achieve diagnostic accuracy, MRC sum score was assessed by different therapists and neurologists (L.W., J.H.) on 2 or more occasions separated by more than 24 hours. Intensive care unit-acquired weakness was defined as an MRC sum score less than 48 of 60 (average MRC score < 4 in tested muscle groups).

Outcome Measures

Before contacting the patient, for each follow-up measurement at 3, 6, and 12 months after ICU discharge, the patient records were verified whether patients were still alive. Functional health status was assessed using the Sickness Impact Profile 68 (SIP68). This self-report questionnaire was sent to all participants. If questionnaires were not returned within 3 weeks, patients were contacted again to remind them about returning the questionnaire. The SIP68 is a validated short version of the 136-item SIP and is a widely used generic instrument to measure functional health status at the levels of activities
and participation. It consists of 68 statements divided into 6 categories, evaluating changes in activities of daily living as a consequence of illness: somatic autonomy (17 items), mobility control (12 items), emotional stability (6 items), psychological autonomy and communication (11 items), mobility range (10 items), and social behavior (12 items). These categories form 3 dimensions of functional status: the physical dimension consists of the somatic autonomy and mobility control scales, the psychological dimension includes the psychological autonomy and communication and emotional stability subscales, and the social dimension consists of the mobility range and social behavior subscales. For each item of the SIP68, respondents are asked to indicate whether their health condition currently limited this activity (no, zero; yes, 1). The subscale, dimension, and total scores of the SIP68 are determined by adding the confirmed sickness impact items. To facilitate comparison with previous studies, we transformed all scale scores to a 0-to-100 scale, with higher scores indicating more severe functional limitations. Patients with scores of 0 to 10 are classified as doing well in daily life, scores of 10 to 20 indicate mild restrictions, and scores greater than 20 indicate severe restrictions in performing daily activities. The Dutch version of the SIP68 shows good reliability, responsiveness, and validity in different populations. During the 12-month follow-up after final ICU discharge, all-cause mortality was registered. Mortality of patients who were lost to follow-up was obtained by checking municipal registries.

Baseline Characteristics
Information on patients’ characteristics was obtained from the electronic patient record, including age, sex, body mass index (BMI; kg/m2), Charlson co-morbidity index, admission type, severity of illness (Acute Physiology and Chronic Health Evaluation IV score), organ failure during ICU stay (maximal Sequential Organ Failure Assessment score), sepsis, days with mechanical ventilation, ICU and hospital length of stay (LOS) and discharge destination from the hospital.

Statistical Analysis
Descriptive statistics were computed for the baseline data and outcome measures, whereby continuous data were expressed as mean and standard deviation (SD) values. In case of a skewed distribution, medians and interquartile ranges (25th-75th percentile) were reported. Data presented as categorical variables were expressed as percentages. Baseline characteristics between patients with and without ICU-AW were compared using the Student t test, Mann-Whitney U test, and X² or Fisher exact test, when applicable. The course of functional outcome between groups at the different time points was assessed using mixed model analyses. Univariate logistic regression analysis was performed to determine the contribution of baseline characteristics (i.e., age, sex, obesity (BMI >30), comorbidity, Acute Physiology and Chronic Health Evaluation IV, maximal Sequential Organ
Failure Assessment score, sepsis, ICU-AW, days with mechanical ventilation, LOS at the ICU and in the hospital) to impaired functional status (SIP68 score >20) at each follow-up moment, using a cut-off $P$ value of 0.3. Subsequently, all identified variables were included in the multivariable model. A series of multivariable logistic regression analyses was performed to determine the impact of ICU-AW on impaired functional status at 3, 6, and 12 months, controlling for multicollinearity. Statistical significance was defined as $P \leq 0.05$, and statistical uncertainty was expressed using 95% confidence intervals (CIs). All statistical analysis were conducted using Statistical Package of Social Science (SPSS) version 20.0 for Windows (IBM, Armonk, NY).

RESULTS
Between May 2011 and January 2013, 513 ICU patients were screened, of whom 156 met the inclusion criteria. Eighty patients had a diagnosis of ICU-AW. Of this population, 133 (85%) survived until ICU discharge, of whom 60 had ICU-AW. As a result of death and loss to follow-up (unable to contact patients, no return of questionnaires, unknown reason), the population evaluated at 3, 6, and 12 months consisted of different subgroups. Completely, SIP68 data from all measurement points were available from 22 patients with ICU-AW and from 12 patients without ICU-AW. The response rate during follow-up was 68% to 74% in survivors with ICU-AW compared to 33% to 47% in survivors without ICU-AW. Figure 1 shows the flowchart of the study population. Comparisons of the baseline characteristics between patients with and without ICU-AW are shown in Table 1. Additional file 1 in the supplement shows the baseline characteristics of the population at 3 follow-up measurements. Patients with ICU-AW were more severely ill, had a significantly higher degree of organ failure and sepsis, and longer duration of mechanical ventilation during ICU stay. Of the patients with ICU-AW, 32% were discharged home from the hospital compared to 75% of the patients without ICU-AW. The 1-year mortality rate after ICU discharge was 37% for patients with ICU-AW and 12% for patients without ICU-AW ($P = 0.02$).
LONG-TERM IMPACT OF ICU-ACQUIRED WEAKNESS ON FUNCTIONAL RECOVERY

Excluded patients: 357
  Stroke: 129
  OHCA: 78
  Neuromuscular disorder: 8
  (previous) spinal injury: 12
  Modified Rankin score ≥ 4: 16
  Died before MRC assessment: 41
  Missed MRC assessments: 19
  No MRC possible: 13
  Language barrier: 27
  No consent: 14

ICU patients screened: 513

Patients included: 156

ICU-AW: 80

Survived to ICU discharge: 60

Died in the ICU: 20

Died: 13

Alive at 3 months: 47
  32 SIP68 questionnaires

Died: 4

Alive at 6 months: 43
  32 SIP68 questionnaires

Died: 5

Alive at 12 months: 38
  26 SIP68 questionnaires

Survived to ICU discharge: 73

Died in the ICU: 3

Died: 4

Alive at 3 months: 69
  23 SIP68 questionnaires

Died: 4

Alive at 6 months: 65
  28 SIP68 questionnaires

Died: 1

Alive at 12 months: 64
  30 SIP68 questionnaires

Figure 1  Flowchart of the study population
<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>ICU-AW (N=60)</th>
<th>no ICU-AW (N=73)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>65 ±16</td>
<td>59 ±14</td>
<td>0.03</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>27 (45)</td>
<td>30 (41)</td>
<td>0.78</td>
</tr>
<tr>
<td>BMI (kg/m²), mean ± SD</td>
<td>26.8 ±5.1</td>
<td>26.9 ±5.2</td>
<td>0.86</td>
</tr>
<tr>
<td>BMI &gt;30, n (%)</td>
<td>14 (23)</td>
<td>16 (22)</td>
<td>1.00</td>
</tr>
<tr>
<td>Pre-existing neuromuscular disorder, n (%)</td>
<td>3 (5)</td>
<td>1 (1)</td>
<td>0.33</td>
</tr>
<tr>
<td>Charlson co-morbidity index, median (IQR)</td>
<td>0 (0-1)</td>
<td>0 (0-2)</td>
<td>0.05</td>
</tr>
<tr>
<td>Admission type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical, n (%)</td>
<td>34 (63)</td>
<td>41 (57)</td>
<td>0.99</td>
</tr>
<tr>
<td>Surgical elective, n (%)</td>
<td>15 (21)</td>
<td>18 (24)</td>
<td></td>
</tr>
<tr>
<td>Surgical emergency, n (%)</td>
<td>11 (16)</td>
<td>14 (19)</td>
<td></td>
</tr>
<tr>
<td>APACHE IV score, mean ± SD (2 missing)</td>
<td>81 ±23</td>
<td>73 ±28</td>
<td>0.10</td>
</tr>
<tr>
<td>CNS disorder as reason of admission, n (%)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0.45</td>
</tr>
<tr>
<td>Maximal SOFA score during admission, mean ± SD</td>
<td>12 ±3</td>
<td>9 ±4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sepsis during admission, n (%)</td>
<td>56 (93)</td>
<td>57 (78)</td>
<td>0.03</td>
</tr>
<tr>
<td>Severe sepsis during admission, n (%)</td>
<td>49 (82)</td>
<td>42 (58)</td>
<td>0.01</td>
</tr>
<tr>
<td>Septic shock during admission, n (%)</td>
<td>35 (58)</td>
<td>26 (36)</td>
<td>0.01</td>
</tr>
<tr>
<td>Renal replacement therapy during admission, n (%)</td>
<td>23 (38)</td>
<td>19 (26)</td>
<td>0.18</td>
</tr>
<tr>
<td>ARDS during admission, n (%)</td>
<td>28 (47)</td>
<td>32 (44)</td>
<td>0.88</td>
</tr>
<tr>
<td>Days with mechanical ventilation, median (IQR)</td>
<td>11 (6-17)</td>
<td>5 (4-7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Length of stay in ICU (days), median (IQR)</td>
<td>14 (9-20)</td>
<td>7 (5-10)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Average MRC score, median (IQR)</td>
<td>2.8 (1.8-3.5)</td>
<td>4.7 (4-5)</td>
<td>NA</td>
</tr>
<tr>
<td>Days free from hospital/alive at 3 months after ICU discharge, median (IQR)</td>
<td>57 (15-71)</td>
<td>75 (56-82)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Discharge destination from index hospital if discharged alive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other hospital, n/total n (%)</td>
<td>22/53 (41)</td>
<td>14/71 (20)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Rehabilitation facility, n/total n (%)</td>
<td>14/53 (27)</td>
<td>4/71 (6)</td>
<td></td>
</tr>
<tr>
<td>Home, n/total n (%)</td>
<td>17/53 (32)</td>
<td>53/71 (76)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: APACHE IV, Acute Physiology and Chronic Health Evaluation IV; ARDS, Acute Respiratory Distress Syndrome; BMI, body mass index; CNS, central nervous system; ICU-AW, ICU-acquired weakness; IQR, interquartile range; MRC, muscle strength as assessed with Medical Research Council scale; NA, not applicable; SD, standard deviation; SOFA, Sequential Organ Failure Assessment score.

* overall test for differences between groups.
Long-term Impact of ICU-Acquired Weakness on Functional Recovery

Functional Status
The functional health status during follow-up is shown in Table 2. Owing to the skewed distribution of data, mixed model analyses were not attainable. Therefore, differences between patients with and without ICU-AW at 3, 6, and 12 months were assessed using the Mann-Whitney U test. Three months after ICU discharge, patients with ICU-AW had a significantly higher total SIP68 score ($P = 0.012$), which indicates worse functional status compared to patients without ICU-AW. Disabilities were particularly found in the physical dimension ($P = 0.000$). At 6 and 12 months after ICU discharge, higher SIP68 scores were found in almost all subscales in patients with ICU-AW, but significant differences were only found in the physical dimension ($P = 0.023$) at 12 months. No statistical differences were found between the groups regarding the psychological and the social dimension during the 1-year follow-up. The median psychological subscale scores were low (<10) at 3, 6, and 12 months, indicating good psychological functioning. The median social subscale scores varied between 9 and 36 during follow-up, indicating moderate to severe restrictions in social functioning. Using the SIP68 cutoff score of greater than 20, we found that 42% to 63% of the patients with ICU-AW had severe restrictions in performing activities of daily living at 3, 6, and 12 months, compared to 20% to 35% of the patients without ICU-AW (Fig. 2). The highest percentage of dysfunctional items were found in the categories “mobility control” (i.e., walking short distances, walking more slowly, problems with climbing stairs) and “social behavior” (i.e., restrictions in doing heavy work around the house, doing less regular daily work, restrictions in visiting friends and social activities). Differences between the groups were, however, only significant for the physical categories ($P = 0.01$ to $P = 0.05$) and the total SIP68 score at 3 months ($P = 0.02$).

Prognostic and Explanatory Factors
From univariate logistic regression analysis, the following variables were identified ($P < 0.3$) as contributors to impaired functional health status: ICU-AW ($P = 0.02$), age ($P = 0.11$), female sex ($P = 0.19$), comorbidity ($P = 0.28$), BMI > 30 ($P = 0.11$), days on mechanical ventilation ($P = 0.06$), total ICU LOS ($P = 0.05$), and hospital LOS ($P = 0.13$). Adjusted for gender, comorbidity and obesity, the odds of having impaired functional status at 3 months after ICU discharge was 0.27 higher (95% confidence interval, 0.08-0.94) in patients with ICU-AW than in patients without ICU-AW. Intensive care unit-acquired weakness was not associated with impaired functional health status at 6 and 12 months.
### Table 2  Functional status (SIP68) at 3, 6 and 12 months after ICU discharge

<table>
<thead>
<tr>
<th>SIP68 (0-100), Median (IQR)</th>
<th>3 Months after ICU discharge</th>
<th>6 Months after ICU discharge</th>
<th>12 Months after ICU discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICU-AW (n=32)</td>
<td>No ICU-AW (n=23)</td>
<td>ICU-AW (n=32)</td>
</tr>
<tr>
<td><strong>Physical dimension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatic autonomy</td>
<td>24 (7-34)</td>
<td>4 (0-14)</td>
<td>12 (4-27)</td>
</tr>
<tr>
<td>Mobility control</td>
<td>6 (0-12)</td>
<td>0 (0-0)</td>
<td>0 (0-10)</td>
</tr>
<tr>
<td><strong>Psychological dimension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychol. Autonomy and communication</td>
<td>6 (0-22)</td>
<td>0 (0-12)</td>
<td>6 (0-29)</td>
</tr>
<tr>
<td>Emotional stability</td>
<td>5 (0-25)</td>
<td>0 (0-9)</td>
<td>5 (0-36)</td>
</tr>
<tr>
<td><strong>Social dimension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobility range</td>
<td>36 (23-66)</td>
<td>23 (14-41)</td>
<td>31 (9-49)</td>
</tr>
<tr>
<td>Social behavior</td>
<td>30 (10-68)</td>
<td>10 (0-20)</td>
<td>15 (0-30)</td>
</tr>
<tr>
<td><strong>Total score</strong></td>
<td>24 (14-38)</td>
<td>10 (7-27)</td>
<td>14 (9-36)</td>
</tr>
</tbody>
</table>

P < 0.01.

P < 0.05.

ADL: activities of daily living; IQR: interquartile range; SIP68: Sickness impact Profile 68, scores ranging from 0-100 with higher scores indicating poorer functioning.
Figure 2  Number of patients with severe restrictions in performing activities of daily living (SIP score >20).
DISCUSSION
This study shows that patients with ICU-AW have significantly worse functional health status at 3 months, but not at 6 and 12 months after ICU discharge compared to patients without ICU-AW. Besides this primary outcome, physical functioning remains lower in patients with ICU-AW, and most of the study participants reported severe restrictions in social functioning, up to 1 year after ICU discharge.

Given the results of previous studies, reporting persistent functional limitations and decreased quality of life in ICU survivors, the expectation was that ICU-AW would also affect the overall long-term functional health status. This apparent discrepancy could be explained by the small number of survivors in our study, which may limit the generalizability of our results and by the different focus of the measurement instruments that have been used. In most outcome studies, the Short-Form Health Survey (SF36) is used to measure health status or quality of life in ICU survivors. The SF-36 is a generic measure for assessing health-related quality of life. Empirical studies have shown mixed results for its construct validity ($r > 0.6$). In this study, we preferred the SIP68 because it provides comprehensive information on the different dimensions of functional status. The SIP68 offers insight in the specific consequences of illness for functioning and the performance of activities of daily living, which in turn enables tailored rehabilitation treatment goal setting. Furthermore, the SIP68 received support for its excellent construct validity ($r = 0.94$). The SIP68 has also been used previously to evaluate functional recovery in ICU survivors. Interestingly, the SIP68 scores in this recent study were lower in all dimensions compared to the latter study, indicating better functional status. This can be explained by the fact that in this recent study, patients with preexisting poor functional status (Modified Rankin Scale of >4) were excluded. Consequently, they had a relative good health status before ICU admission. Furthermore, in the past 10 years, early mobilization and more comprehensive rehabilitation have been implemented in the ICUs of this hospital. Given the fact that early rehabilitation in critically ill patients is associated with improved functional recovery, it is supposed that the overall long-term functional status of our ICU patients might have been improved in the past decade.

With regard to the physical dimension, it was expected that patients with ICU-AW would have significantly more impairments at all follow-up measurements than patients without ICU-AW. In our previous study, ICU-AW was independently associated with clinically relevant lower physical functioning at 6 months after ICU discharge. This discrepancy in study results could be explained by the use of different outcome measures (physical functioning subscale of the SIP68 vs physical functioning domain of the SF-36). Additionally, in this recent study, patients without ICU-AW reported more restrictions in physical functioning at 6 months than at 3 and 12 months, whereas in patients with ICU-AW, physical functioning increased over time. This finding might have resulted in the nonsignificant differences in physical functioning between patients with and without ICU-AW at 6 months.
With regard to the psychological dimension, more limitations in all patients with and without ICU-AW were expected because it is known that ICU survivors frequently experience long-lasting mental and/or cognitive problems (e.g., posttraumatic stress disorder, anxiety and depression, impaired memory and concentration).\textsuperscript{41-43} Although the psychological dimension of the SIP68 contains items on psychological autonomy and emotional stability, a possible explanation for this finding could be that these items do not fully cover the range of specific ICU-related psychological and cognitive problems of ICU survivors. Furthermore, it has described that during the first year after ICU discharge, patients focus on recovering physical strength and regaining functional capacity during the initial stage of rehabilitation. This may take precedence of the focus on psychological recovery.\textsuperscript{10} Most severe impairments were found within the social dimension in this study population, independent from the diagnosis of ICU-AW. Although physical and psychological functioning increased during follow-up, the social dimension scores improved only little. Apparently, social functioning does not only depend on physical and psychological capacities, but as an integral part of interaction with others and the environment, it demonstrates the performance level of an individual.\textsuperscript{18} In agreement with previous studies,\textsuperscript{17,44,45} it is very likely that impairments in body functions (e.g., muscle weakness and impaired sensory) result in limitations in mobility-related activities (e.g., problems with walking and using transportation), which in turn may lead to restrictions within the social dimension (e.g., restrictions in doing daily work, visiting friends or fulfill social activities).

Limitations
Some limitations of this study should be considered in the interpretation of the results. This single-center study resulted in a limited number of patients that could be included during the study period. Furthermore, the small number of patients who completed the questionnaires and the different subgroups of patients at each follow-up measurement might have led to selection bias and may limit the generalizability to other ICU survivors. Moreover, no information about complications and rehabilitation treatment that had occurred after hospital discharge, and that might have affected the course of recovery, was collected. Owing to the limited number of participants and skewed distribution of data, mixed model analyses were not attainable to analyze the course of recovery at different time points. Moreover, the findings from the multivariable regression analyses should be taken with caution because by reducing an ordinal or even metric variable to dichotomous level, information is lost.

Despite the restrictions of this study, it provides useful information about the long-term functional health status of ICU survivors with and without ICU-AW and complements the current understanding of post-ICU recovery. Given the increasing number of ICU survivors with long-lasting restrictions on various dimensions of functioning, these patients
represent a new and important population with special need for rehabilitation treatment. Therefore, interdisciplinary rehabilitation interventions (e.g., physiotherapy, occupational therapy, social work, etc.) should be continued after hospital discharge to support long-term functional recovery in these vulnerable patients.

CONCLUSIONS In critically ill patients, the development of ICU-AW is independently associated with worse functional health status at 3 months and impaired physical functioning up to 1 year after ICU discharge. Independent from ICU-AW, social functioning remains severely restricted in most ICU survivors. These findings underline the need for interdisciplinary rehabilitation interventions for ICU survivors after hospital discharge to improve functional recovery.

Acknowledgements
The authors thank the patients for their participation, and Juultje Sommers, Dennis Gommers, and Tineke van Heuveln for their assistance with the manual muscle strength measurements. This research was performed within the framework of CTMM, the Center of Translational Molecular Medicine (www.ctmm.nl) project MARS (grant 04I-201). LW was supported by a personal grant from the Netherlands Organization for Health Research and Development (ZonMw-AGIKO grant 2011 [project number 40-00703-98-11636]).
**Additional file 1: Baseline characteristics for ICU survivors at 3, 6 and 12 months after ICU discharge**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>3 months after discharge</th>
<th>6 months after discharge</th>
<th>12 months after discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICU-AW (n=32)</td>
<td>no ICU-AW (n=23)</td>
<td>ICU-AW (n=32)</td>
</tr>
<tr>
<td>Age, mean ± SD</td>
<td>61 ± 15</td>
<td>60 ± 13</td>
<td>62 ± 17</td>
</tr>
<tr>
<td>Gender female, n (%)</td>
<td>19 (60)</td>
<td>9 (39)</td>
<td>18 (56)</td>
</tr>
<tr>
<td>BMI &gt; 30, n (%)</td>
<td>8 (25)</td>
<td>5 (22)</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Charlson co-morbidity index, median (IQR)</td>
<td>0 (0-2)</td>
<td>0 (0-2)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Admission type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical, n (%)</td>
<td>17 (53)</td>
<td>17 (74)</td>
<td>17 (53)</td>
</tr>
<tr>
<td>Surgical elective, n (%)</td>
<td>7 (22)</td>
<td>3 (13)</td>
<td>7 (22)</td>
</tr>
<tr>
<td>Surgical emergency, n (%)</td>
<td>8 (25)</td>
<td>3 (13)</td>
<td>8 (25)</td>
</tr>
<tr>
<td>APACHE IV score, mean ± SD</td>
<td>84 ± 21</td>
<td>78 ± 27</td>
<td>81 ± 19</td>
</tr>
<tr>
<td>Maximal SOFA score during ICU-stay, mean ± SD</td>
<td>13 ± 4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10 ± 4</td>
<td>13 ± 4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sepsis during ICU-stay, n (%)</td>
<td>30 (94)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16 (70)</td>
<td>31 (97)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Average MRC score, median (IQR)</td>
<td>3 (1-3)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 (4-5)</td>
<td>3 (2-3)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Days with mechanical ventilation, median (IQR)</td>
<td>13 (6-19)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 (4-7)</td>
<td>12 (5-19)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Length of stay in ICU (days), median (IQR)</td>
<td>22 (11-36)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7 (6-10)</td>
<td>19 (10-36)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total length of stay in hospital (days), median (IQR)</td>
<td>62 (38-84)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25 (21-35)</td>
<td>60 (37-84)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Discharge destination from hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other hospital, n (%)</td>
<td>12 (38)</td>
<td>5 (22)</td>
<td>11 (34)</td>
</tr>
<tr>
<td>Rehabilitation facility, n (%)</td>
<td>7 (22)</td>
<td>0 (0)</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Home, n (%)</td>
<td>13 (41)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18 (78)</td>
<td>13 (41)</td>
</tr>
</tbody>
</table>

<sup>a</sup> P < 0.01.<br>
<sup>b</sup> P < 0.05.

ICU-AW: Intensive Care Unit – acquired weakness; BMI: body mass index; SOFA: Sequential Organ Failure Assessment score; MRC: muscle strength as assessed with Medical Research Council scale; APACHE IV score: Acute Physiology and Chronic Health Evaluation IV score; ARDS: Acute Respiratory Distress Syndrome; SD: standard deviation; IQR: interquartile range.
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