The Post-Intensive Care Syndrome (PICS):

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

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Faculteit der Geneeskunde

CONTENTS

CHAPTER 1

General introduction

Each year about 86.000 adults are admitted to intensive care units (ICUs) in the Netherlands.[1] The advancements in critical care in the last decades have resulted in higher survival rates, despite an ageing population and an increased severity of illness. However, surviving critical illness has shown to be associated with a wide range of long-lasting negative health outcomes, which include physical and cognitive impairments, as well as mental health problems, which negatively affect daily functioning and health-related quality of life (HRQoL).[2-10] Early rehabilitation in the ICU is beneficial in reducing physical impairments and ICU and hospital length of stay.[11-14] Evidence for the effectiveness of interventions for ICU survivors after ICU and hospital discharge is limited.[15-17] Moreover, the optimal care pathway addressing the whole spectrum of ICU-related physical, cognitive and mental consequences has yet to be determined. This thesis aims to explore the course and prognosis of functioning in ICU survivors, and to investigate means for early identification of patients with need for rehabilitation care. This knowledge will contribute to the development of an optimal care pathway, in order to improve the quality of survivorship. This chapter describes the background and rationale underlying the aims of this thesis.

Post-Intensive Care Syndrome

Due to the increase in survival rates of ICU patients, the long-term consequences of critical illness have become increasingly recognized as an important healthcare issue.[4,6,18,19] In 2012, the Society of Critical Care Medicine introduced the term 'Post-Intensive Care Syndrome' (PICS), to describe the complex of "new or worsening impairments in physical, cognitive, or mental health status arising after critical illness and persisting beyond acute care hospitalization". The term can be applied to a survivor (PICS) or family member (PICS-F) (Figure 1).[20] Although the exact prevalence of PICS among ICU survivors is unknown, it is estimated that 25-50% of patients will suffer from some component of PICS after ICU and hospital discharge.[21-24]

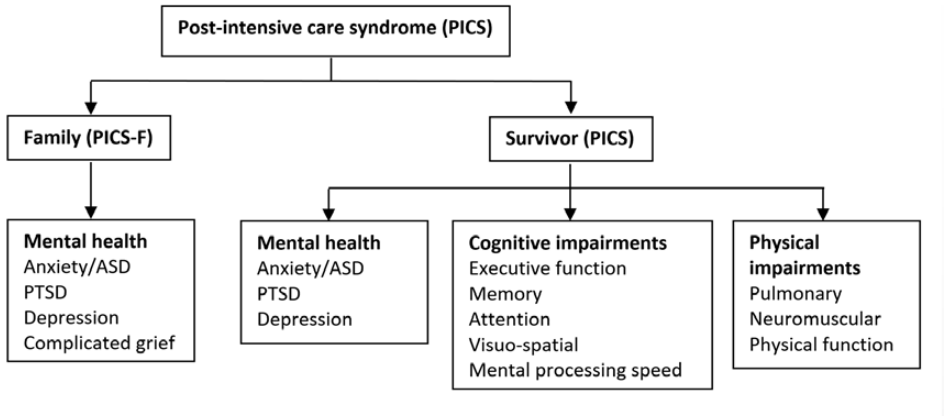

Figure 1 Post-intensive care syndrome (PICS) conceptual diagram
ASD, acute stress disorder; PTSD, posttraumatic stress disorder. *From: Needham et al. (2012).[20] Reproduced with permission form Wolters Kluwer Health, Inc.*

The concept of PICS includes all domains of the World Health Organization's International Classification of Functioning, Disability and Health (ICF).[25] The ICF provides a conceptual framework for the definition and measurement of health and disability.[26,27] It describes a person's level of functioning (i.e., body structures and functions, activities and participation in society) as a dynamic interaction between health conditions (i.e., disorder or disease), environmental factors, and personal factors (Figure 2). Disability is complementary to functioning and encompasses impairments, limitations in activities, and restrictions in participation.[25] Integrating the concept of PICS into the ICF framework is beneficial to further describe the impact of critical illness on functioning and disability.[28]

Impairments

Physical impairments following critical illness include loss of muscle mass, neuromuscular weakness, sensory and nociceptive changes, impaired lung function, fatigue and weight loss. Intensive care unit acquired weakness (ICU-AW) is the most common form of physical impairment with an estimated incidence of 46% (95% CI: 43-49) in patients with sepsis, prolonged mechanical ventilation or multiple organ failure.[29] ICU-AW is defined as muscle weakness with a diffuse (symmetric and flaccid) pattern, which develops after the onset of critical illness. A Medical Research Council sum score (MRC-SS) of < 48 is used as a cut-off for the diagnosis of ICU-AW.[30]

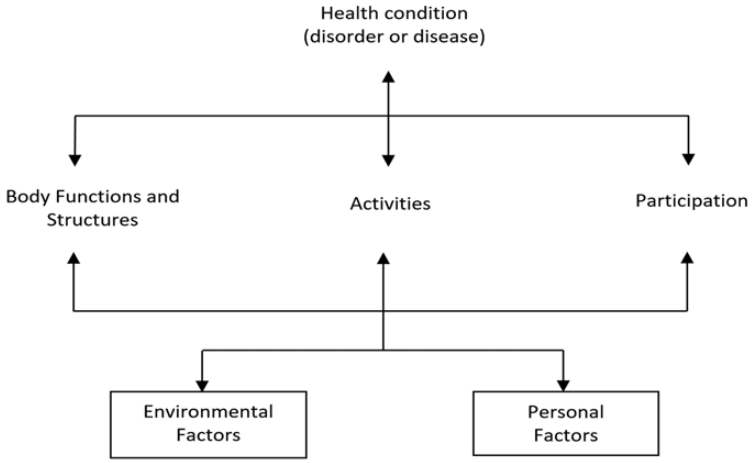

Figure 2 The ICF model (WHO, 2001)[25]

Besides physical impairments, many patients develop delirious states or experience delusional memories regarding their time in ICU, which can lead to mental health problems, such as anxiety, depression, and post-traumatic stress disorder (PTSD).[5,20,31] Furthermore, cognitive impairments (e.g., problems with concentration, attention, memory, executive functions) are common in survivors of critical illness.[8,20,21,31,32]

Limitations in activities

These physical, cognitive and mental impairments impede daily functioning and can lead to long-lasting functional disabilities (e.g., limitations in showering/washing, dressing, getting out of bed or getting up from a chair, walking, climbing stairs, sexual activities, working around the house, shopping and preparing food, managing money, using the telephone, taking medication).[8,10,33,34] Several studies showed, that the majority of patients who were mechanically ventilated for more than 48 hours required short- or long-term institutional (rehabilitation) care;[35] and from the patients who were discharged home, many required caregiver assistance, varying from little help with some basic everyday activities to full care.[21,36,37]

Restrictions in participation

The functional limitations, in turn, can lead to restrictions in fulfilling domestic roles, and to participate in social activities.[38] Around 50% of patients have not returned to work 1 year after ICU discharge.[5,39,40] Moreover, the long-term consequences of critical illness in ICU survivors can also affect family members, resulting in psychological, physical, and social problems (PICS-F).[20,41] The persisting disabilities also negatively affect health-

related quality of life (HRQoL) in ICU survivors.[4-6,21,42] Although, QoL improves over time, it remains lower in the first year in comparison with the general population. Moreover, many people do not return to the same functional level as before ICU admission.[8,18,43,44]
Ultimately, surviving critical illness has large social and financial implications for patients, their families, caregivers, and society.[20,36,41,45-48] Therefore, reducing the prevalence of PICS and improving the functional outcome in ICU survivors should be the ultimate goal in the care for ICU patients. Given the broad spectrum of different health domains of PICS, the expertise of rehabilitation medicine provides a valuable contribution to develop and manage optimal multidisciplinary care for this vulnerable patient group.

Functional recovery after ICU discharge

PICS is not related to a specific medical diagnosis, and to date it is difficult to predict at an early stage, which patients are at highest risk for poor functional outcome.[21,49] The investigation of potential prognostic and explanatory factors of functional recovery may help to identify patients with needs for multidisciplinary care. Moreover, a better understanding of the short- and long-term consequences of critical illness would support the development of targeted multidisciplinary care to improve long-term functioning and quality of life. Therefore, more insight in the course of functional recovery in ICU survivors after discharge from the ICU and hospital is needed.[28]

Impact of ICU-AW on functional recovery

Based on the fact that many, but not all ICU survivors develop PICS after critical illness, the question arises whether patients with the most severe ICU-related impairments at ICU discharge are - by definition - the patients with the worst long-term outcome. ICU-AW is a frequently occurring neuromuscular complication in ICU-patients,[29] and can be further differentiated into critical illness polyneuropathy (CIP), critical illness myopathy (CIM), or critical illness neuro-myopathy (CINM).[30,50] The exact pathophysiological mechanisms underlying ICU-AW have not yet been fully elucidated, but are believed to be multifactorial.[51] Possible mechanisms include microvascular ischemia,[52-54] mitochondrial dysfunction,[55,56] and sodium channelopathy[57] leading to neuronal injury and axonal degeneration. Several studies in patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) have shown that ICU-AW negatively influences physical functioning and is associated with higher mortality rates.[8,58-60] However, the impact of ICU-AW on long-term physical functioning and mortality in a general critically ill population is unknown, because many studies[61-63] lacked a properly selected control group or did not adjust for confounders. With an improved life expectancy, a larger aging population, and improvements in the delivery of healthcare, the demand for critical care also increases,[64] and ICU-AW becomes an extensive and complex health problem requiring comprehensive care. Recent studies suggested that patients with ICU-AW should be closely monitored following ICU- and

hospital discharge to support recovery and improve outcome.[12,65] In order to support informed decision-making concerning the rehabilitation care pathway for ICU survivors with and without ICU-AW, more insight into the short- and long term functional status, with regard to physical, psychological and social functioning is needed.

Coping with the consequences of critical illness

Several studies have shown that surviving critical illness is not only associated with a wide range of undesirable long-lasting restrictions in daily functioning (PICS), but also with reduced quality of life (QoL).[3-6,8] While functioning refers to limitations and restrictions related to a health problem, QoL refers to how someone feels about these limitations and restrictions.[66] In clinical practice we have recognized that ICU survivors with similar degrees of physical impairments and functional disabilities showed considerable individual differences in QoL after discharge from the hospital. We hypothesized that personal coping style might be associated with QoL, as found in various patient groups with chronic disease or traumatic injury.[67-73] The ability to cope effectively with the physical and emotional impact of an illness is essential for achieving long-term recovery and maintaining high QoL.[74,75] Several studies showed that an active, task-oriented coping style is associated with better QoL, whereas passive, emotion-oriented and avoidance coping styles are generally associated with lower QoL.[68,70,76-79] With respect to survivors of critical illness, the relationship between coping style and QoL has scarcely been investigated to date. In order to develop effective rehabilitation strategies, investigating the individual coping styles used by these patients, as well as the association between individual coping styles and subsequent QoL is highly relevant.

Post-Intensive Care Unit Clinics

Although recovery after critical illness is possible, many of the symptoms of PICS, and reduced QoL, persist for months to years.[20,80,81] Therefore, ICU survivors with symptoms of PICS require a structured follow-up and comprehensive interdisciplinary after care. However, ICU survivors experience inadequate and disjointed care after hospital discharge, with inconsistent service provision.[21] ICU follow-up clinics have been advocated to manage ICU-related problems in survivors,[82-84] but to date such clinics are scarce, their organization varies, and their optimal structure, timing, and care content has not been established yet. Furthermore, there is no direction or consensus on how to implement after care. In 2011, we developed and implemented a post-ICU clinic in a tertiary university hospital and in a general hospital in the Netherlands, based on the recommendations from the National Institute for Health and Clinical Excellence (NICE) guidelines.[85] We assumed that the programmatic evaluation of both approaches would provide important practical information for the set up and wider implementation of post-ICU clinics.

AIMS AND OUTLINE OF THIS THESIS

The general aim of this thesis is to explore the course and prognosis of functioning in ICU survivors, and to investigate means for early identification of PICS. This knowledge contributes to the development of an optimal care pathway for ICU survivors and their families, in order to improve the quality of survivorship.

The studies included in this thesis focus on adult ICU-patients who were mechanically ventilated in the ICU for 48 hours or more. Patients who were in the ICU fewer than 48 hours – which particularly comprise patients who are admitted for observation or routine post-surgical care, and are not likely to develop ICU-related sequelae – were excluded.

Chapter 2 describes the functional status of ICU survivors immediately after discharge from ICU. In this observational study, basic activities of daily living, muscle strength, sensitivity of the limbs, walking capacity, and cognitive functioning were assessed. In addition, the predictive value of functional status prior to ICU-admission, age, severity of illness, and duration of mechanical ventilation as potential determinants for functional status within the first week after ICU discharge was examined.

The next chapters concern studies which compared functional outcome between patients with and without ICU-acquired weakness (ICU-AW). We hypothesized that survivors with ICU-AW have more short- and long-term physical impairments and functional disabilities than ICU survivors without weakness.

Chapter 3 describes the impact of ICU-AW on survival and physical functioning at 6 months after ICU discharge.

Chapter 4 outlines the course of functional recovery, with regard to physical, psychological and social functioning, in ICU survivors with and without ICU-AW at 3, 6 and 12 months after ICU discharge.

Chapter 5 focuses on coping styles and quality of life (QoL) in ICU survivors. In an observational study, we explored the coping styles (measured with the CISS-21) and its association with QoL (measured with the SF-36), 3 months after discharge from the ICU.

Chapter 6 describes the implementation of two post-ICU clinics in different hospital settings. In a multicentre observational study, the feasibility of the post-ICU clinics was evaluated as 1) the number of eligible ICU survivors and the proportion that attended, 2) the prevalence of ICU-related abnormalities that required referral for for further treatment, and 3) patient satisfaction.

Chapter 7 discusses the main findings, strengths and limitations of this thesis. Finally, the implications for clinical practice are discussed, and recommendations for rehabilitation care as well as for future research are provided.

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CHAPTER 2

Poor functional status immediately after discharge from an intensive care unit

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Disability and Rehabilitation 2008;30:1812-1818

ABSTRACT

Purpose

To evaluate the functional status within the first week of discharge from an intensive care unit (ICU), and to identify predictors and explanatory factors of functional status.

Method

A prospective, observational, cohort study was conducted with consecutive ICU patients who had stayed in a mixed, closed format, university-level ICU for longer than 48 hours.

Results

Between 3 and 7 days of discharge from the ICU, functional status (as primary outcome), walking ability, muscle strength, and sensory and cognitive functioning were assessed in 69 survivors. The overall functional status was poor (median Barthel Index 6). In their ability to perform basic activities of daily living, 76% were severely dependent, 15% were moderately dependent, and 9% were slightly dependent on other people. Independent walking was impossible for 73% of participants, grip strength was reduced for 50%, and 30% had cognitive impairments. Duration of ventilation was associated with functional status after ICU discharge. Reduced grip strength and walking ability were identified as explanatory factors for poorer functional status shortly after discharge from the ICU.

Conclusion

In the first week after discharge from the ICU, the majority of the patients had substantial functional disabilities in activities of daily living. These disabilities were more severe in patients who experienced ventilation for a longer period of time. There is a need for prospective studies focusing on functional recovery to support informed decision-making concerning the care of critically ill patients after ICU discharge.

INTRODUCTION

In intensive-care patients, outcome is most frequently expressed in terms of mortality.[1] However, due to the increase in the number of intensive care unit (ICU) patients who survive a critical illness, the focus of interest has shifted towards studies of long-term morbidity and health-related quality of life (QoL).[2] Several long-term studies have demonstrated reduced health-related QoL of survivors after ICU discharge.[2-5] To improve outcome, the expertise of rehabilitation medicine could be useful, as reducing functional impairments and limitations in activities should be primary treatment goals.

In order to develop optimal and adequate rehabilitation care at an early stage, information about the long-term outcome of ICU patients and insight into their functional status shortly after ICU discharge is needed. Moreover, the identification of prognostic and explanatory factors of functional status shortly after discharge would support informed decision making with regard to the care that is provided for critically ill patients. The objectives of the present study were to assess the functional status of ventilated ICU patients within the first week after discharge, and to identify prognostic and explanatory factors of functional status.

METHODS

Study population

Between May 15 and August 31 2005, all adult patients (aged ≥ 18 years) who were consecutively admitted to the 28-bed, mixed medical and surgical closed-format ICU in the Academic Medical Center (university hospital) in Amsterdam, and who had received mechanical ventilation for more than 48 hours, were eligible for participation in the study. Patients with insufficient knowledge of the Dutch language were excluded. Eligible patients who were readmitted to the ICU in the study period were only included once, and assessed only after their final discharge from the ICU. The Ethical Review Board of the Academic Medical Center waived the need for informed consent because of the non-interventional nature of the study.

In the ICU, patients are weaned from mechanical ventilation according to the local nurse-driven ventilation protocol. Patients are discharged to the medium-care ward or regular ward if they are stable in terms of respiratory and hemodynamic function, are breathing without assistance from the ventilator, and are being weaned from inotropics. Physiotherapy becomes an integral part of the management of patients in the ICU as soon as patients have passed through the acute phase. Physiotherapy treatment is aimed at enhancing the patient's overall functional capacity and at decreasing the risks of complications associated with bed rest.

Data-collection

Baseline assessment

The following data were obtained from the patients' medical records and from the Dutch National Intensive Care Evaluation database: age; gender; diagnosis on admission to the ICU; duration of mechanical ventilation; length of stay in the ICU; mortality; and health classification assessed according to the Acute Physiology and Chronic Health Evaluation II (APACHE II)[6], the Simplified Acute Physiology Scores II7 and the Sequential Organ Failure Assessment.[8]

Primary-outcome measures

In order to gain insight in the need for care and rehabilitation intervention before patients are discharged from the hospital, the primary outcome was assessed 3-7 days after discharge from the ICU, after a habituation period of 2 days on the ward. The primary-outcome measure was the Barthel Index. The Barthel Index measures the capacity to perform ten basic activities of daily living (ADL) and gives a quantitative estimation of the patient's level of dependency, with scoring from 0 (totally dependent) to 20 (totally independent). The scale has frequently been used to measure physical functioning in clinical settings.[9-11]

Secondary-outcome measures

The following functions were assessed 3-7 days after discharge from the ICU: muscle strength, according to the Medical Research Council scale;[12,13] grip strength, expressed in Newton, using the digital handgrip dynamometer (Lode BV, Groningen, The Netherlands);[14] sensory functions, using the Semmes Weinstein monofilaments[15] and the Rydel-Seiffer tuning fork;[16] and cognitive state, via the Mini Mental State Examination.[17] Walking ability was also assessed 3-7 days after discharge from the ICU, via the Functional Ambulation Categories (FAC).[18] Additionally, the patient's QoL prior to admission to the ICU was obtained via the proxy version of the Dutch validated version of the Short Form 36 (SF-36) questionnaire. The proxy, who had to be in close contact with the patient on a regular basis, was asked to mark the statement that best described the patient's state of health in the 4 weeks prior to ICU admission. The SF-36 is a widely used, standardized, generic QoL instrument.[19,20] All assessments were standardized, and carried out by experienced senior physiotherapists.

Data analysis

Patient characteristics and outcome measures were analyzed with descriptive statistics. The data are expressed as mean ± SD, and if the distribution was skewed medians and interquartile ranges are presented. Student's t-test and nonparametric tests were performed when appropriate. The SF-36 scores of ICU patients at baseline were compared with those of the age-matched Dutch general population using the Z-score (difference

between patient and Dutch general population mean score, divided by general population SD), in which a value of at least 0.8 represents a difference of at least four-fifths of the baseline SD and is viewed as a deviation from the norm score.[21] Length of stay can be influenced by factors that are not related to health status, such as the available facilities in the medium-care unit and nursing wards; therefore, only the duration of mechanical ventilation was included in the analyses. Univariate associations between functional status and potential prognostic factors (age, scores on the pre-ICU SF-36 physical and social-functioning domains, and APACHE II score) and duration of ventilation were assessed with Spearman's rho; a *P* value of <0.05 was considered statistically significant.

Linear regression analysis was performed to identify explanatory factors of functional status. Variables considered included grip strength, sensory function, walking ability, and cognitive functioning. Variables found to be significant by univariate analysis were entered into a stepwise multiple linear regression analysis (with a stepwise forward-selection strategy), to determine their independent relation to functional status. A P value of <0.05 was considered statistically significant. Residual analysis was performed to search for violations of necessary assumptions in multiple regression in terms of linearity, equality of variance, independence of error, and normality. The possible presence of collinear data was investigated via tolerance statistics. All statistical analyses were performed using SPSS 12.0 software (SPSS Inc, Chicago, IL).

RESULTS

Study population

During the 15-week inclusion period, 525 patients were admitted to the ICU. Of these, 386 were excluded because they were ventilated for less than 48 hours. Another 9 patients were excluded because of insufficient knowledge of the Dutch language, and another 21 patients were excluded as they could not be assessed within the first week after discharge from the ICU because of transfer to another hospital (n=16) or to a nursing home (n=1), or discharge to their home (n=4). Consequently, a total of 109 patients participated in the study. The mortality rate in the period before assessment was 36% (n=39). The functional status of one patient was assessed on the eighth day after ICU discharge, and these data were not included in the analysis; the data analysis included information from 69 ICU patients. Figure 1 presents a flow diagram of the study population. The patient characteristics are presented in Table 1.

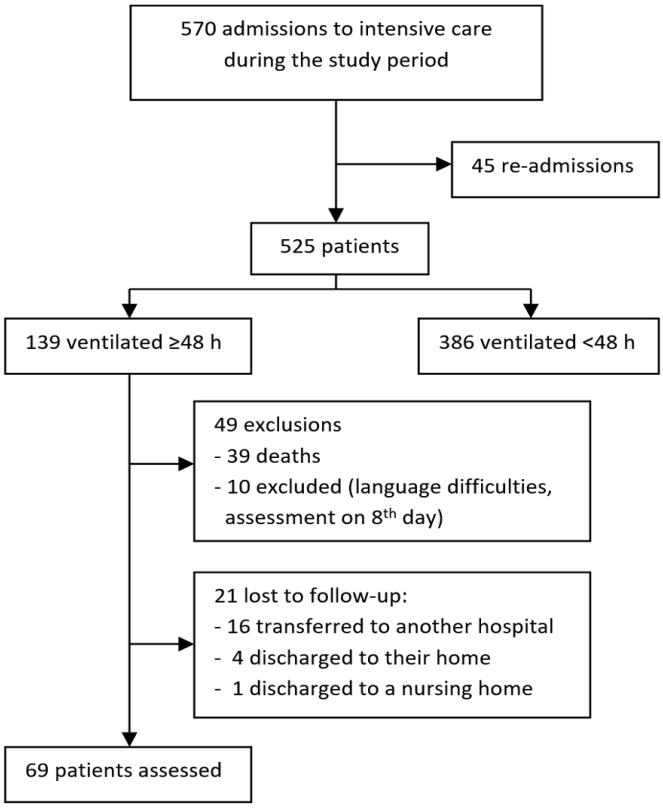

Figure 1 Flow diagram of the study population

The length of stay in the ICU was highly associated with the duration of mechanical ventilation (r = 0.87, $P < 0.001$). The SF-36, providing information on patients' QoL prior to admission to the ICU, was returned by 38 (55%) proxies. Except in one case (3%), all proxies were partners (55%) or family members (child 26%, parent 11%, sibling 5%) of the patients. No statistically significant differences in potential predictors (age, APACHE II score, duration of ventilation) or primary outcome (Barthel Index score) were found between patients whose proxies returned the SF-36 and patients whose proxies didn't return the SF-36. Therefore, the results were considered representative of the whole study group. QoL prior to admission did not deviate from that of the general Dutch population (age and gender matched). Z-scores of the domains were between -0.32 and +0.65 (Table 2).

Table 1 Demographic and clinical patient characteristics of study patients (n=69)

Patient characteristics	Value
Median age, years (IQR)	60 (49-71)
Sex	
Male, n (%)	43 (62%)
Female, n (%)	26 (38%)
Type of admission	
Elective, n (%)	10 (14%)
Non-elective, n (%)	59 (86%)
Diagnosis at ICU admission, n (%)	
Surgical	10 (15%)
Cardiovascular	12 (17%)
Neurological (including head trauma)	6 (9%)
Gastrointestinal	3 (4%)
Trauma	
Medical	9 (13%)
Cardiovascular	6 (9%)
Neurological	17 (25%)
Respiratory	6 (9%)
Other	
Severity of illness	
APACHE II score	16 (12-20)
SAPS II score	44 (36-56)
SOFA score on admission	8 (6-11)
SOFA score on discharge	5 (3-7)
Median duration of mechanical ventilation, days (IQR)	6 (3-10)
Median length of stay in ICU, days (IQR)	7 (5-17)

Abbreviations: APACHE II, Acute Physiology and Chronic health Evaluation; ICU, Intensive Care Unit; IQR, interquartile range; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

Table 2 Quality of life in various domains before ICU admission (n = 38)

SF-36 domain*	Median score (IQR)	Median Z-score (IQR)**
Physical functioning	85 (39-96)	.09 (-1.94 - 0.58)
Physical role limitations	100 (0-100)	.65 (-2.11- 0.65)
Social functioning	88 (47-100	.16 (-1.66 - 0.71)
Emotional role limitations	100 (50-100)	.54 (-.99 – 0.54)
Bodily pain	69 (44-100)	-.24 (-1.30 - 1.07)
Mental health	76 (62-92)	-.05 (-.85 - .87)
Vitality	63 (31-84)	-.32 (-1.94 - 0.79)
General health perceptions	65 (30-85)	-.28 (-1.97- 0.69)

*Short Form 36 questionnaire: score range 0-100 (higher scores representing better functioning)
**Positive Z-scores indicate better functioning compared with the general population.
Abbreviations: IQR, interquartile range; SF-36, Short Form 36 questionnaire.

Functional status

Functional status was assessed after a median period of 4 days (range 3-7 days) after discharge from the ICU. No association was found between functional status (Barthel Index score) and the length of time between ICU discharge and assessment (r = -0.04, *P* = 0.76). Survivors had substantial ADL function limitations after discharge from the ICU, with a median Barthel Index score of 6 (interquartile range 2.5-12.5). Of the survivors, 40% were totally dependent (Barthel Index score 0-4), 36% were severely dependent (Barthel Index score 5-12), 15% were moderately dependent (Barthel Index score 6-18), 3% were slightly dependent (Barthel Index score 19), and only 6% were independent in performing basic ADL (Barthel Index score 20).[22,23] There was no difference in functional status in patients who were re-admitted to the ICU, and patients who were admitted once. Neither was there a difference between surgical and medical patients (n=31 and n=38, respectively, *P* = 0.293). As a result of the small size of subgroups based on diagnosis, differences in functional status could not be investigated.

Secondary-outcome measures could not be assessed in all the participants, due to health conditions such as reduced consciousness or the cast immobilization of an extremity. Manually measured upper-extremity and lower extremity muscle strength was slightly reduced (median Medical Research Council scale score of 4). Median grip strength in both hands was 50% lower than age-corrected and gender corrected normative data.[24,25] Sensory dysfunctions were only observed in the feet, with absent light-touch sensation in 15% of patients, and impaired vibration sense in 40% of patients. Moreover, 39% of patients were not able to walk (FAC score 0), and 34% needed physical support or

assistance with walking (FAC score 1-3). The median Mini Mental State Examination score indicated that the majority of patients were not cognitively impaired after ICU discharge. However, 15 patients (27%) had scores <24, indicating the presence of cognitive impairments.[26] Most of the errors concerned items related to concentration and short-term memory (subtracting serial 7s and recalling three objects). Secondary-outcome measures of the survivors are shown in Table 3.

Age, QoL prior to ICU admission, and severity of illness (as measured by the APACHE II) on ICU admission were not associated with functional status after ICU discharge (age and Barthel Index score, *P* = 0.77; SF-36 physical-functioning domain and Barthel Index score, *P* = 0.20; SF-36 social functioning domain and Barthel Index, *P* = 0.22; APACHE II score and Barthel Index score, *P* = 0.96). However, an association between the duration of mechanical ventilation and functional status after ICU discharge was demonstrated (r = -0.404, *P* = 0.001). Stratification of the study population, using different cut-off points for duration of ventilation, resulted in the greatest difference in the Barthel Index score between subgroups, based on a cut-off point of 6 days of ventilation. The median Barthel Index score of patients ventilated for ≥ 6 days (n=30) was 6 points lower than that of patients ventilated for < 6 days (n=39; score 4 versus 10, *P* = 0.001). This relationship is illustrated in Figure 2.

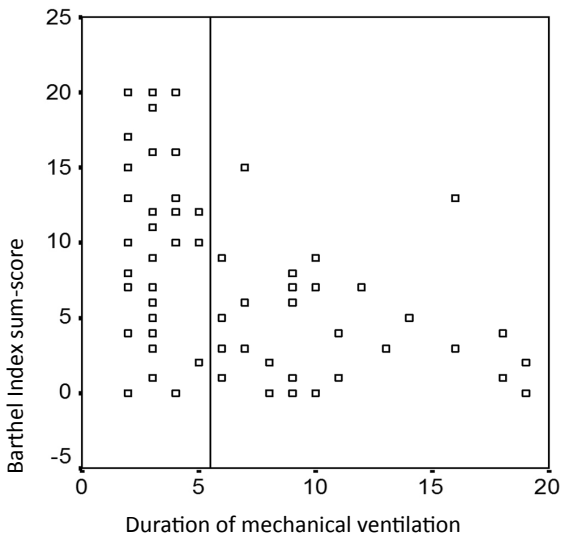

Figure 2 Association between duration of mechanical ventilation and Barthel Index score. The vertical line marks the cut-off point of 6 days.

Table 3 Patient results on secondary outcome measures

Outcome measure	Value
Median MRC scale score (scale 0-5, IQR**,** *n=55*)*	
Elbow flexion	4 (4-5)
Elbow extension	4 (4-5)
Knee extension	4 (4-5)
Ankle dorsal flexion	5 (4-5)
Median grip strength (Newton, IQR, *n=48*)	
Right hand	148 (108-227)
Left hand	130 (92-169)
Sensibility (*n=53*)	
Absent in hands, n (%)	0 (0)
Absent in feed, n (%)	8 (15)
Vibration sense in hands (*n=53*)	
Reduced in hands, n (%)	2 (4)
Reduced in feed, n (%)	21 (40)
FAC score, n (%) (*n=69*)	
0 (not able to walk or requires help from ≥ 2 people)	27 (39)
1 (requires continuous firm support from 1 person to walk)	12 (17)
2 (requires continuous or intermittent support from 1 person to walk)	5 (7)
3 (requires verbal supervision or stand-by help from one person without physical contact to walk)	7 (10)
4 (can walk independently on level ground, but requires help on stairs, slopes or uneven surfaces)	10 (14)
5 (can walk independently anywhere)	8 (11)
Median MMSE score (scale 0-30, IQR, *n=54*)	26 (23-28)

Abbreviations: FAC, Functional Ambulation Categories; IQR, interquartile range; MMSE, Mini Mental State Examination; MRC, Medical Research Council.
*Higher scores represent better functioning.

Univariate analyses showed that functional status was associated with walking ability ($P < 0.000$, $r = 0.76$), upper-extremity grip strength ($P < 0.000$, $r = 0.62$), cognitive functioning ($P = 0.032$, $r = 0.27$), and sensory dysfunction in the foot ($P = 0.035$, $r = -0.26$). Multivariate linear regression analysis identified walking ability and grip strength as independent explanatory factors of functional status ($R^2 = 0.64$). Plots of residual analysis revealed no violations of assumptions in multiple regression in terms of linearity, equality of variance, and normality. Measures of co-linearity did not reveal a high correlation between the independent variables.

DISCUSSION

The results of this study show that the majority of ICU patients who have been ventilated for at least 48 hours have substantial functional limitations in ADL immediately after ICU discharge, and that these functional limitations are associated with the duration of mechanical ventilation. Multivariate analysis showed that reduced upper-extremity strength and walking difficulties were the most important independent explanatory factors of poorer functional status. In this study, outcome was assessed between 3 and 7 days after discharge from the ICU. The timing of the outcome assessment was irrespective of the patient's health status, but depended on practical factors such as availability of the research assistants during the weekend and weekdays. With respect to a conceivable convalescence over the days following ICU discharge, one might expect that patients who were assessed earlier after ICU discharge would have a poorer functional status than would patients who were assessed at a later date. However, no association was found between functional status and the length of time between ICU discharge and assessment (r = -0.04, P = 0.76).

Contrary to reports in the literature on prognostic factors for long-term physical functioning (i.e., that advanced age and increased severity of illness on ICU admission are independently associated with a poorer functional outcome[2]), in the present study, age and severity of illness at ICU admission were not found to be associated with short-term functional status. This may seem surprising, since age and severity of illness have been found to be associated with in-hospital mortality.[27] The fact that age, a proven prognostic factor of long-term outcome, was not associated with short-term functional outcome may be surprising. Obviously, in older patients, poorer functional outcome may be explained by a limited recovery potential. However, in the early phase examined here, in which recovery has yet to occur, it seemed that this recovery potential has no effect on functional status. Furthermore, short-term functional status did not seem to be determined by the severity of illness on ICU admission. It might, however, depend on the duration of stay in the ICU, and possible complications that require ventilation for more than 48 hours (i.e., mechanical ventilation) during ICU treatment. Accordingly to our results, short-term functional outcome differs markedly from long-term functional outcome, and has different associations and determinants.

It might have been expected that functional status after ICU discharge would to a large extent be determined by physical functioning prior to ICU admission. Considering the results of the present study population on the physical domains of SF-36 before becoming critical ill, no relationship between the different domains of the SF-36 before ICU admission and functional status after ICU was found. This result could be explained by the small number of patients for which SF-36-data were available, and also by the different concepts of functioning that are measured by the SF-36 and Barthel Index.[66] The Barthel Index

measures the ability to perform basic ADL, but the SF-36 measures higher levels of functioning. Thereby, patients with a low SF-36 score could still obtain a maximum score obtain a maximum score on the Barthel Index.

In this study, ventilation for more than 48 hours was associated with poorer functional status immediately after ICU discharge. We identified a cut-off point of ≥6 days of mechanical ventilation, above which increased limitations in ADL were observed. Nearly all patients who were mechanically ventilated for at least 6 days were severely or totally dependent on others in ADL, whereas patients who were ventilated for less than 6 days were more heterogeneous in this respect, ranging from almost independent to severely dependent in basic ADL performance. The time necessary to treat the initial critical illness and possible complications during the stay in the ICU clearly has a great impact on daily functioning in the first week after ICU discharge. In this respect, age and severity of illness at ICU admission seem not to play an important role.

Potential study limitations are the small sample size and the possibility of selection bias. Although the sample consisted of a consecutive series of patients, no information on functional status could be obtained from 21 patients who were discharged from hospital before assessment and consequently excluded from the study. Therefore, it remains unknown whether the study population is an accurate representation of the population admitted to the ICU in our hospital. Another selection bias might have occurred in the data collection, regarding QoL prior to ICU admission. In the design of this study, the importance of obtaining data on pre-ICU functioning was considered. However, only 55% of the SF-36 questionnaires were returned by the patients' proxies. Unfortunately, reasons for not responding could not be further specified. Although patient age, severity of illness on ICU admission, and duration of ICU stay did not differ between patients for whom the SF-36 was returned and patients for whom it was not returned, selection bias could not fully be ruled out with respect to this outcome measure. Another consequence of the low response of the proxies was that information on QoL prior to ICU admission could only be obtained from a small population. The striking finding, which is in conflict with the literature,[2] that patient QoL prior to ICU admission of the study population did not deviate from the norm for the general population, might possibly be explained by the small sample size.

This study provides information that is important for the planning of care of critically ill patients after discharge from an ICU. After transfer from the ICU to the medium-care unit or a nursing ward, the cardiac and respiratory functioning of these critically ill patients is stable, but their physical resilience is very limited: over 75% of the patients in our study population were severely or totally dependent with regard to basic ADL. This implies that prior assessment of any care needed after discharge from the ICU is very important. Ideally,

all ICU patients who are ventilated longer than 48 hours should be discharged to specialized wards, and closely monitored in order to decide whether additional physical, mental, or psychological support is required during and after their hospital stay. These patients may need rehabilitation care, tailored to their individual needs, in order to achieve the best long-term functional outcome. The findings that walking ability and upper-extremity strength were explanatory factors for functional limitations in ADL suggest that physical impairments, rather than sensory impairments and cognitive dysfunction, contribute a great deal to the patient's functional status shortly after discharge from the ICU.

CONCLUSIONS

Within the first week of ICU discharge, the majority of patients were severely impaired and dependent on others with regard to basic ADL. Therefore, we recommend that all patients ventilated for more than 48 hours in the ICU should be closely monitored, so that rehabilitation treatment can be provided in an early stage for patients with a complicated functional recovery. More research on the course of functional recovery, and the determinants of functional status in the different stages of convalescence, is needed in order to focus on appropriate rehabilitation treatment and to achieve optimal patient outcomes after a prolonged stay in an ICU.

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CHAPTER 3

Impact of ICU-acquired weakness on post-ICU physical functioning: a follow-up study

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ABSTRACT

Introduction

ICU-acquired weakness is thought to mediate physical impairments in survivors of critical illness, but few studies have investigated this thoroughly. The purpose was to investigate differences in post-ICU mortality and physical functioning between patients with and without ICU-acquired weakness at 6 months after ICU discharge.

Method

ICU patients, mechanically ventilated ≥2 days, were included in a single-center prospective observational cohort study. ICU-acquired weakness was diagnosed when the average Medical Research Council score was <4 in awake and attentive patients. Post-ICU mortality was recorded until 6 months after ICU discharge; in surviving patients, physical functioning was assessed using the Short-Form Health Survey physical functioning domain. The independent effect of ICU-acquired weakness on post-ICU mortality was analyzed using a multivariable Cox proportional hazards model. The independent effect of ICU-acquired weakness on the physical functioning domain score was analyzed using a multivariable linear regression model.

Results

Of the 156 patients included, 80 had ICU-acquired weakness. Twenty-three patients died in the ICU (20 with ICU-acquired weakness); during 6 months follow-up after ICU discharge another 25 patients died (17 with ICU-acquired weakness). Physical functioning domain scores were available for 96 survivors (39 patients with ICU-acquired weakness). ICU-acquired weakness was independently associated with an increase in post-ICU mortality (hazard ratio 3.6, 95% confidence interval, 1.3 to 9.8; *P* = 0.01) and with a decrease in physical functioning (β: -16.7 points; 95% confidence interval, -30.2 to -3.1; *P* = 0.02).

Conclusion

ICU-acquired weakness is independently associated with higher post-ICU mortality and with clinically relevant lower physical functioning in survivors at 6 months after ICU discharge.

INTRODUCTION

After surviving critical illness, many patients suffer from its long-term consequences, which may consist of physical impairments, cognitive dysfunction, and mental health problems.[1] The relevance of physical impairments was described in acute respiratory distress syndrome survivors, who continued to suffer from physical impairments up to 5 years after resolution of critical illness.[2] It is thought that development of ICU-acquired weakness (ICU-AW) is an important mediator of physical impairments.[1] However, evidence supporting this hypothesis is limited.[3]

ICU-AW is a frequently occurring neuromuscular complication of critical illness, with an estimated incidence of 46% (95% confidence interval (CI), 43 to 49) in patients with sepsis, prolonged mechanical ventilation or multiple organ dysfunction syndrome.[4] ICU-AW is defined as clinical signs of weakness that develop after the onset of critical illness.[5,6] For diagnosing ICU-AW, muscle strength is assessed manually.[5,6] This can be done reliably when patients are awake and attentive.[7] Weakness may be caused by muscle and/or peripheral nerve dysfunction and damage.[5] If differentiation between these underlying disorders is needed, electrophysiological testing may be performed.[5] In a cohort of acute lung injury survivors, it was found that development of ICU-AW was associated with more physical impairments during follow-up.[8] However, this association was not corrected for possible confounders. Also, acute lung injury survivors represent a subgroup of critically ill patients and the association between ICU-AW and long-term physical impairments in critically ill patients in general remains to be investigated. Besides being a possible mediator of post-ICU physical impairments, ICU-AW also has a substantial impact on post-ICU mortality. ICU-AW is independently associated with increased in-hospital mortality.[9,10] Also, 1-year mortality is worsened by ICU-AW.[11] In this 6-month follow-up study, we investigated the impact of ICU-AW on the post-ICU period by comparing post-ICU mortality and physical functioning between patients with and without ICU-AW. We hypothesized that ICU-AW is independently associated with increased post-ICU mortality and that survivors with ICU-AW have decreased physical functioning at 6 months after ICU discharge.

METHODS

Study design and ethical approval

We conducted a single-center prospective observational cohort study. The institutional review board of the Academic Medical Center, Amsterdam, the Netherlands, decided that the study did not fulfill the criteria for medical research as stated in the Dutch 'Law on medical research' because the nature of the data collected for this study was judged to be non-intrusive for patients (METC 10/219) and therefore formal informed consent procedures did not apply. Still, we sought verbal and/or written approval of all surviving patients for participating in this study and using their data.

Study setting

The study was performed in the closed-format tertiary, 34-bed, mixed medical-surgical intensive care unit of the Academic Medical Center in Amsterdam, the Netherlands. As an integral part of care, all patients received early rehabilitation that was continued after transfer to the regular ward until hospital discharge.

Study population

Inclusion criteria were newly admitted ICU patients aged ≥18 years, mechanically ventilated for ≥2 days. Exclusion criteria were neuromuscular disorders (for example, Guillain-Barré syndrome), any type of stroke, and out-of-hospital cardiac arrest as reasons for admission, and quadriplegia due to a spinal cord syndrome in the medical history or as reason for admission. Additionally, we excluded patients in whom manual muscle strength could not be assessed because of prolonged delirium or failure to awake (that is, up to ICU discharge), patients who had poor functional status before admission (modified Rankin score ≥4[12]) and patients with a language barrier. Patients with pre-existing neuromuscular disorders not leading to ICU admission or a poor functional status were included in this study. Also, patients admitted because of central nervous system disorders not involving any type of stroke and being awake and alert during ICU admission (for criteria, see below) were included in this study.

Assessment of ICU-acquired weakness

ICU-AW was diagnosed using the current diagnostic reference standard.[5] As a part of routine care, physical therapists performed manual muscle strength assessments using the Medical Research Council (MRC) score as soon as patients were awake (Richmond Agitation Sedation Scale[13] between -1 and +1) and attentive (able to follow verbal commands using arms or eyelids). MRC scores of six different muscle groups were measured bilaterally; that is, wrist dorsiflexors, elbow flexors, shoulder abductors, hip flexors, knee extensors and ankle dorsiflexors. The scores of muscle groups were summated and divided by the number of muscle groups that could be assessed to obtain an average MRC score (range 0 to 5). Symmetric weakness that had developed after ICU admission with an average MRC score <4 was defined as ICU-AW.[5]

Mortality

All-cause mortality was registered during ICU admission and in the 6 months follow-up after the final ICU discharge date. Mortality of patients who were lost to follow-up was obtained by checking municipal registries.

Physical functioning

Physical functioning was assessed in patients surviving to 6 months after the final ICU discharge date using the 36-item Short-Form health survey (SF-36) physical functioning (PF) domain score.[14,15] To optimize response rate, the 36-item Short-Form health survey was assessed both by telephone interview conducted by one of the investigators and by mail.

Baseline and clinical characteristics

During admission, we scored the presence of the following disorders: sepsis[16], severe sepsis[17], septic shock[17] and acute respiratory distress syndrome.[18] Additionally, we collected the following characteristics from the electronic patient file: age, gender, body mass index (kg/m2), Charlson co-morbidity index (ranging from 0 to 24[19]), admission type, Acute Physiology and Chronic Health Evaluation (APACHE) IV score, maximal Sequential Organ Failure Assessment score during admission, days with mechanical ventilation, use of renal replacement therapy, and ICU and hospital length of stay.

Statistical analysis

The primary analyses were the independent effect of ICU-AW on post-ICU mortality and on the PF domain score. The independent effect of ICU-AW on post-ICU mortality was analyzed using a Cox proportional hazard model (hazard ratio reported with 95% CI) adjusted for confounders. Confounders were a priori defined as age, gender, Charlson co-morbidity index, presence of septic shock, APACHE IV score and maximal Sequential Organ Failure Assessment score during admission.[20,21] The independent effect of ICU-AW on the PF domain score was assessed using a multivariable linear regression model adjusted for the above mentioned confounders (regression coefficient (β) reported with 95% CI). A difference of 10 points on the PF domain score was defined as clinically relevant.[22,23] More detail on statistical methodology and the results of the regression models including the individual variables is provided in Additional file 1. The PF domain score assessed by telephone was used for analysis or, if unavailable, the PF domain score assessed by mail. Agreement between the two interview methods was assessed using the intra-class correlation coefficient (reported with 95% CI) in patients for whom both the telephone and mail PF domain scores were available.

We also analyzed differences in the number of days free from hospital and alive at 3 months after the final ICU discharge between patients with and without ICU-AW using the Wilcoxon rank-sum test. For descriptive analyses, mean values are presented with standard deviation, median values with interquartile range, and proportions with percentages and total numbers. Differences between proportions were assessed using chi-square test or Fisher's exact test. Differences between normally distributed variables were assessed using Welch's t-test; differences between non-normally distributed continuous variables were assessed using Wilcoxon rank-sum test. For correlation analyses, spearman's rho was

used in case of ordinal variables and Pearson biserial correlation in case of dichotomous variables. A *P* value less than 0.05 was considered statistically significant. Analyses were done using R (version: 3.0.1; R Foundation for Statistical Computing, Vienna, Austria).

Sample size estimation

This study was powered to detect a difference of 10 points on the PF domain score. With an alpha of 0.05, power of 80% and a common standard deviation of 10,[24] 40 patients per group would be needed. Assuming that 50% of newly admitted ICU patients would develop ICU-AW,[4] a mortality rate of 35% after 6 months follow-up,[25] and that 10% of the population would be lost to follow-up, a population of 140 patients was needed.

RESULTS

Between May 2011 and January 2013 156 patients were included, 133 of whom survived to ICU discharge. Figure 1 displays the study flowchart. Patient and admission characteristics are displayed in Table 1.

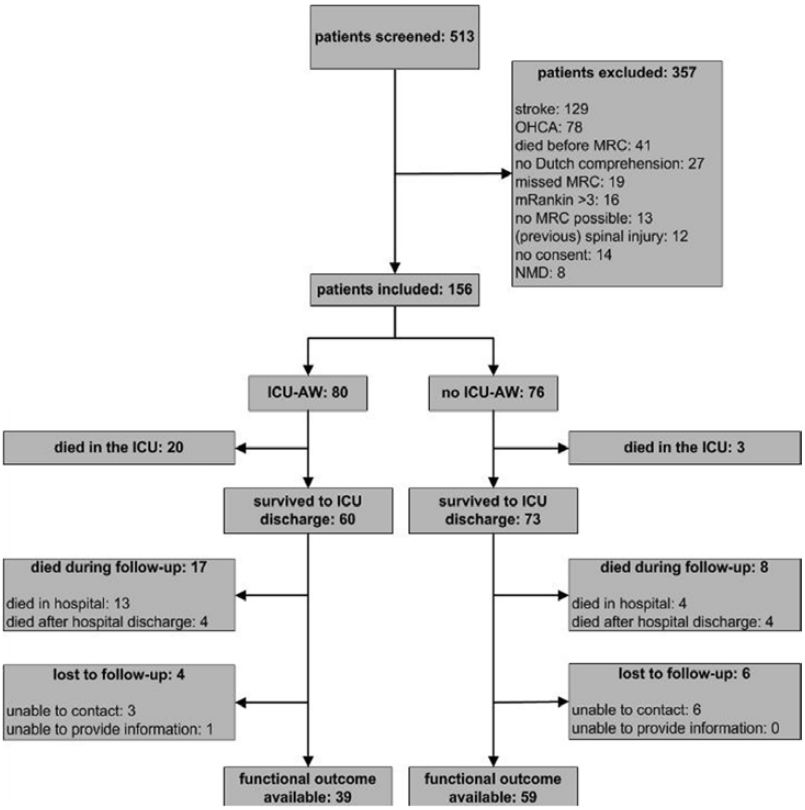

Figure 1 Flowchart of the study population.

ICU-AW, ICU-acquired weakness; OHCA, out-of-hospital cardiac arrest; MRC, muscle strength as assessed with Medical Research Council scale; mRankin, modified Rankin score; NMD, neuromuscular disorder.

Table 1 Baseline and ICU admission characteristics for patients surviving to ICU discharge

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

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; SD, standard deviation; SOFA, Sequential Organ Failure Assessment score; NA, not applicable; *, overall test for differences between groups.

Post-ICU mortality

Post-ICU mortality was higher in patients with ICU-AW (17/60 (28%) vs 8/73 (11%); *P* = 0.02). Lower average MRC scores were correlated with higher mortality (r = -0.21; *P* < 0.01). When adjusted for confounders, ICU-AW was associated with higher post-ICU mortality until 6 months after ICU discharge (hazard ratio 3.6; 95% CI, 1.3 to 9.8; *P* = 0.01; two patients excluded because of missing APACHE IV scores). Figure 2 displays the post-ICU mortality curve. Most deaths occurred during hospital admission; mortality rates after hospital discharge were not different for patients with or without ICU-AW (Table 2). The number of days free from hospital and alive at 3 months after ICU discharge was lower for patients with ICU-AW (Table 1). Overall mortality, including the period of ICU admission, was 37/80 (46%) for patients with ICU-AW and 11/76 (15%) for patients without ICU-AW (P < 0.01).

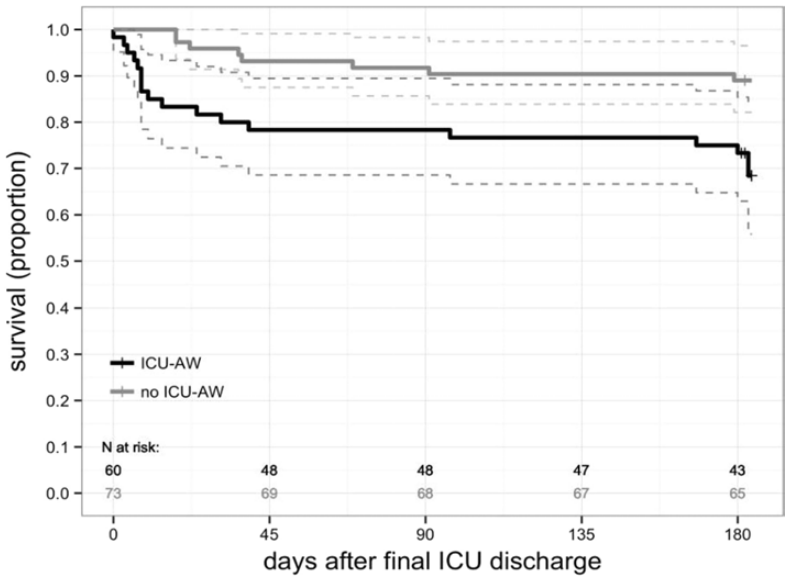

Figure 2 Post-ICU survival curves for patients with and without ICU-acquired weakness

Survival curves for patients with (black line) and without (grey line) Intensive Care Unit-acquired weakness starting at final ICU discharge until end of follow-up, i.e. 6 months after final ICU discharge. Dotted lines represent the 95% confidence interval; censored patients presented with +. ICU-AW, Intensive Care Unit-acquired weakness.

Table 2 Post-ICU outcomes for patients with or without ICU-acquired weakness

	ICU-AW	no ICU-AW	*P* value
Post-ICU mortality			
In-hospital, n/total n (%)	13/60 (22)	4/73 (5)	0.01
After hospital discharge, n/total n (%)	4/47 (9)	4/69 (6)	0.71
PF domain scores at 6 months follow-up, median (IQR; n)	45 (30-70; 39)	75 (50-90; 59)	<0.01
Patients' residence at 6 months follow-up			
Hospital, n/total n (%)	0/39 (0)	4/59 (7)	
Rehabilitation facility, n/total n (%)	4/39 (10)	0/59 (0)	0.01*
Home, n/total n (%)	35/39 (90)	55/59 (93)	

*: overall *P* value for comparison of all categories
ICU-AW: Intensive Care Unit – acquired weakness; PF: Short-Form Health Survey (SF-36) physical functioning domain score.

Physical functioning

Of the 108 patients who survived up to 6 months after ICU discharge, physical functioning was assessed in 98 patients (10 were lost to follow-up; Figure 1). Patients' place of residence when physical functioning was assessed is shown in Table 2. Sixty-six questionnaires completed via telephone and 32 by mail were used for the analyses. The intra-class correlation coefficient between the telephone-obtained and mail-obtained PF scores was 0.88 (95% CI, 0.67 to 0.95; N = 30). The physical functioning domain score was significantly lower in patients with ICU-AW (Table 2). Higher average MRC scores were correlated with higher physical functioning domain scores (rho = 0.34; $P < 0.01$). After adjusting for confounders, ICU-AW was associated with a decrease of 16.7 points on the PF domain score (95% CI, -30.2 to -3.1; $P = 0.02$; 2 patients excluded because of missing APACHE IV scores).

DISCUSSION

The results from this study show that, when assessed at 6 months after ICU discharge, ICU-AW is independently associated with higher post-ICU mortality and with clinically relevant lower physical functioning in survivors. We found no difference in mortality after hospital discharge. However, it should be noted that, up to the point of hospital discharge, 41% of patients with ICU-AW had already died and the duration of hospital admission after ICU discharge was much longer for patients with ICU-AW. Hermans and colleagues reported increased 1-year mortality in ICU-AW patients.[11] Additionally, mortality was increased during ICU stay and hospital stay in patients with ICU-AW, which has been reported before.[9,10] Ali and colleagues[9] reported a combined ICU- and in-hospital mortality of 31% in patients with ICU-AW, compared to 6% for patients without ICU-AW. Sharshar and colleagues[10] reported

similar mortality rates (31% in patients with ICU-AW; 10% in patients without ICU-AW). Compared to these studies, we found a higher combined ICU- and in-hospital mortality rate in ICU-AW patients (41%), whereas mortality in patients without ICU-AW was similar (9%). Both studies also based the diagnosis of ICU-AW on manual muscle strength with a cut-off of an average MRC score <4. The difference in mortality may be explained by differences in case-mix and inclusion and exclusion criteria. Increased mortality in ICU-AW may be explained by an increased risk of developing (nosocomial) infections, as was reported by Sharshar and colleagues.[10] The increased risk for developing (nosocomial) infections may be the result of increased durations of mechanical ventilation,[26,27] ICU admission[27] and hospital admission,[9] which we also found in our study. Alternatively, an increased risk of developing infections may be the result of immune dysfunction secondary to autonomic dysfunction that may accompany ICU-AW.[28,29] Autonomic dysfunction in general may also increase mortality, as was found in critically ill patients.[30] More research is needed to establish reasons for and prevention of mortality in ICU-AW. In surviving patients, we found that ICU-AW is independently associated with decreased physical functioning. While it was known that survivors with ICU-AW have physical impairments,[8,31-33] our study now suggests that, by comparison with critically ill patients without ICU-AW and by correcting for possible confounders, there is an independent effect of ICU-AW on the outcome of critical illness survivors. Moreover, this effect of ICU-AW seems clinically relevant, shown by the difference of more than 10 points on the PF domain score.[22,23] ICU-AW may cause post-ICU physical impairments by various mechanisms. In ICU-AW, muscle and/or nerves can be affected both on a functional and structural level.[5] Decreased excitability may cause muscle and nerve dysfunction and this may resolve quickly.[34] In contrast, structural damage may result in long-term symptoms.[34] Also, nerve involvement as compared to muscle involvement has been linked to worse outcome.[32,35,36]

Our study has some limitations. Firstly, because of the single-center design, our results may not be fully generalizable to other populations. The critically ill patients included in this study may represent a relatively healthy population, as shown by the low scores on the Charlson co-morbidity index. Secondly, we did not use electrophysiological studies and muscle biopsies to differentiate between the underlying disorders causing ICU-AW. Three disorders can cause ICU-AW; that is, critical illness polyneuropathy, critical illness myopathy, and critical illness neuromyopathy.[5] The additional diagnostic information obtained by electrophysiology and muscle biopsy is unclear because this has not been studied extensively. Three small studies described a better outcome in critical illness myopathy compared to critical illness polyneuropathy or critical illness neuromyopathy.[32,35,36] Third, our finding that mortality after hospital discharge did not differ between groups may be the result of lack of power because our study was not powered for this analysis. Fourth, due to the nature of the study design, there is the possibility of residual bias confounding

the observed association between ICU-AW and physical impairments. Fifth, we did not correct for confounders that function as an intermediate between ICU-AW and physical impairments, such as length of stay in the ICU. Because of ICU-AW, length of stay in the ICU will be longer[35] and the longer length of stay may in turn result in more physical impairments. Instead, we a priori selected confounders from the literature that may result in physical impairments in a mechanism independent of ICU-AW. Finally, we did not investigate the impact of the observed physical impairments on (health-related) quality of life of our patients. Quality of life relies on many factors other than physical functioning, such as critical illness-induced cognitive dysfunction or post-traumatic stress disorders, and general factors like age, pre-existing co-morbidities and the availability of support resources and/or caregivers.[34,37]

The results of this study have several implications. With a better understanding of the long-term impact of ICU-AW, the prognosis may be discussed more reliably with patients and families by neurologists and intensivists. More information on possibly preventable causes of death in patients with ICU-AW is needed. Furthermore, pathophysiological mechanisms leading to ICU-AW and its long-term sequelae should be clarified to enable interventions preventing or attenuating ICU-AW. Strict glycemic control and late initiation of parenteral nutrition may prevent development of ICU-AW.[38,39] Interventions attenuating the course of ICU-AW are not yet available. Early rehabilitation may be interesting as this has been shown to improve functional outcome in general ICU patients.[40]

CONCLUSIONS

We found, in patients mechanically ventilated for 2 days or more, that development of ICU-AW was independently associated with increased post-ICU mortality and clinically relevant lower physical functioning at 6 months after discharge from the ICU. These findings implicate ICU-AW as an important mediator of physical impairments in survivors of critical illness. As such, studies on prevention or treatment of ICU-AW are urgently needed.

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Competing interests

LW is supported by a personal grant from the Netherlands Organization for Health Research and Development (ZonMw–AGIKO grant (project number 40-00703-98-11636)). INvS received departmental honoraria for serving on scientific advisory boards and a steering committee for CSL-Behring. The other authors declare that they have no competing interests.

Additional file 1

1. Statistical analyses

Propensity score

Because of the sample size, all a priori defined confounders for the multivariate models were summarized into a propensity score. The propensity score was calculated using a logistic regression model with ICU-AW as the dependent variable and the confounders as the independent variables. The resulting predicted value per patient was transformed to the probability scale making the propensity score. The propensity was subsequently added as an independent variable along with ICU-AW in the multivariable analyses.

Multivariable models

Two different multivariable models were used in this study: i.e. a multivariable Cox proportional hazard model to investigate the independent effect of ICU-AW on post-ICU mortality and a multivariable linear regression model to investigate he independent effect of ICU-AW on the physical functioning (PF) domain score. For the multivariable Cox model, the time to event was first calculated from the day of ICU discharge to day of death up to six months after ICU discharge. Follow-up data for mortality was complete for all patients. Next, the propensity score and ICUAW were entered in the Cox model to obtain an adjusted hazard ratio. The proportionality of the hazard was verified. For the multivariable linear regression model, the PF domain score was used as the dependent variable. Although not truly a continuous dependent variable, model assumptions of normality were not violated. ICU-AW and the propensity score were entered as independent variables to the model. The mean predicted effect of ICU-AW on the PF domain score (the regression coefficient (β) reported with 95% confidence interval) was used for reporting.

2. Regression models

Propensity score

The following regression formula was used to calculate the propensity score *"propensity score = predict(lrm(ICUAW~ age+ gender+ CCI+ max.sofa+ apacheIV+ sep.shock), type = "fitted")"*. The following model was produced:

Variable	Regression coefficient	*P* value
intercept	- 4.736	<0.01
age	0.034	0.02
gender=female	0.409	0.28
CCI	- 0.332	<0.01
max.sofa	0.274	<0.01
apacheIV	- 0.004	0.61
sep.shock=yes	0.280	0.50
model likelihood ratio test (X^2)	**41.53 (6 df)**	**<0.01**

CCI: Charlson co-morbidty index; SOFA: Sequential Organ Failure Score; apacheIV: Acute Physiology and Chronic Health Evaluation IV score; df: degrees of freedom

Multivariable Cox proportional hazard model

The following regression formula was used to calculate the hazard ratio *"hazard ratio= coxph(surv.obj (observation time) ~ propensity score+ ICUAW)"*. The following model was produced:

Variable	Regression coefficient	*P* value
propensity score	- 0.212	0.83
ICUAW	1.292	0.01
model likelihood ratio test (X^2)	**8.62 (2 df)**	**0.01**

ICUAW: Intensive Care Unit – acquired weakness; df: degrees of freedom

Multivariable linear regression model

The following regression formula was used to calculate the hazard ratio *"regression coefficient = lm(SF36 physical functioning domain score ~ propensity score+ ICUAW)"*. The following model was produced:

Variable	Regression coefficient	*P* value
propensity score	- 6.868	0.61
ICUAW	- 16.684	0.02
F-statistic	**4.499 (2 df)**	**0.01**

ICUAW: Intensive Care Unit – acquired weakness; df: degrees of freedom

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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.[1-3] 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.[4] 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.[5,6] It can be further differentiated into critical illness polyneuropathy, critical illness myopathy, or a combination of both (critical illness neuro-myopathy).[6,7] 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.[5] Previous studies showed that ICU-AW is associated with increased physical limitations and mortality.[5,8,9] 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.[10-12] Early rehabilitation in the ICU[13] and beyond hospital discharge[14-17] 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[18] 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.[9] 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)[19] 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.[20] 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.[6,21] 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[22] 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).[6]

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.[23-25] 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.[26] 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.[27] The Dutch version of the SIP68 shows good reliability, responsiveness, and validity in different populations.[25,28,29] 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,[30] admission type, severity of illness (Acute Physiology and Chronic Health Evaluation IV score[31]), organ failure during ICU stay (maximal Sequential Organ Failure Assessment score[32]), sepsis,[33] 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 (25^{th}-75^{th} 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 X^2 or Fisher exact test, when applicable. The course of functional outcome between groups at the different time points was assessed using mixed model anayses. 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 ICUAW 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 ($P = 0.02$).

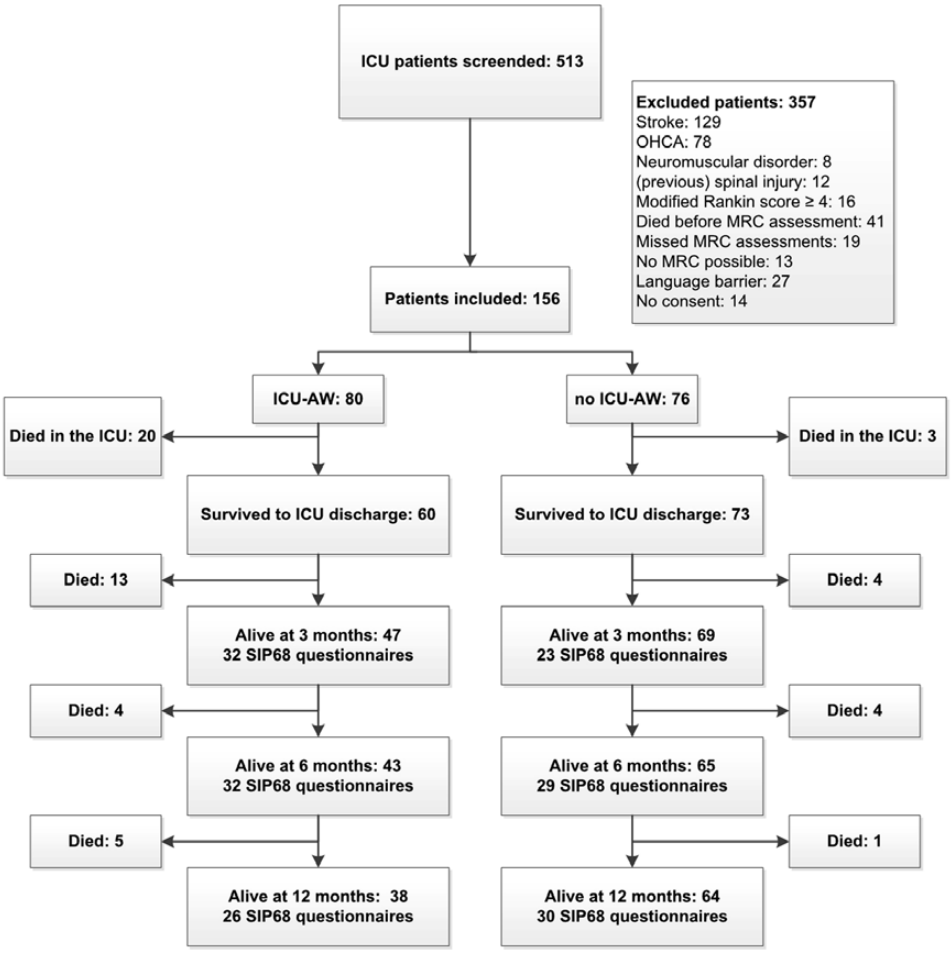

Figure 1 Flowchart of the study population

Table 1 Baseline characteristics for ICU survivors

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

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.

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

SIP68 (0-100), Median (IQR)	3 Months after ICU discharge		6 Months after ICU discharge		12 Months after ICU discharge	
	ICU-AW (n=32)	No ICU-AW (n=23)	ICU-AW (n= 32)	No ICU-AW (n=29)	ICU-AW (n=26)	No ICU-AW (n=30)
Physical dimension	**24 (7-34)[a]**	**4 (0-14)**	**12 (4-27)**	**7 (0-17)**	**10 (3-24)[b]**	**0 (0-11)**
Somatic autonomy	6 (0-12)[a]	0 (0-0)	0 (0-10)[b]	0 (0-0)	0 (0-7)[a]	0 (0-0)
Mobility control	38 (17-58)[a]	8 (0-25)	21 (8-48)	17 (0-38)	17 (0-52)	0 (0-27)
Psychological dimension	**6 (0-22)**	**0 (0-12)**	**6 (0-29)**	**6 (0-21)**	**6 (0-18)**	**6 (0-13)**
Psychol. Autonomy and communication	5 (0-25)	0 (0-9)	5 (0-36)	0 (0-27)	0 (0-27)	0 (0-18)
Emotional stability	0 (0-17)	0 (0-17)	0 (0-17)	0 (0-33)	0 (0-17)	0 (0-17)
Social dimension	**36 (23-66)**	**23 (14-41)**	**31 (9-49)**	**9 (5-57)**	**27 (9-51)**	**11 (0-32)**
Mobility range	30 (10-68)[b]	10 (0-20)	15 (0-30)	0 (0-30)	0 (0-33)[b]	0 (0-0)
Social behavior	42 (17-75)	33 (17-58)	38 (8-67)	17 (8-71)	33 (17-58)	17 (0-52)
Total score	**24 (14-38)[b]**	**10 (7-27)**	**14 (9-36)**	**10 (3-35)**	**13 (5-30)**	**6 (2-18)**

[a] $P < 0.01$.
[b] $P < 0.05$.
ADL: activities of daily living; IQR: interquartile range; SIP68: Sickness impact Profile 68, scores ranging from 0-100 with higher scores indicating poorer functioning.

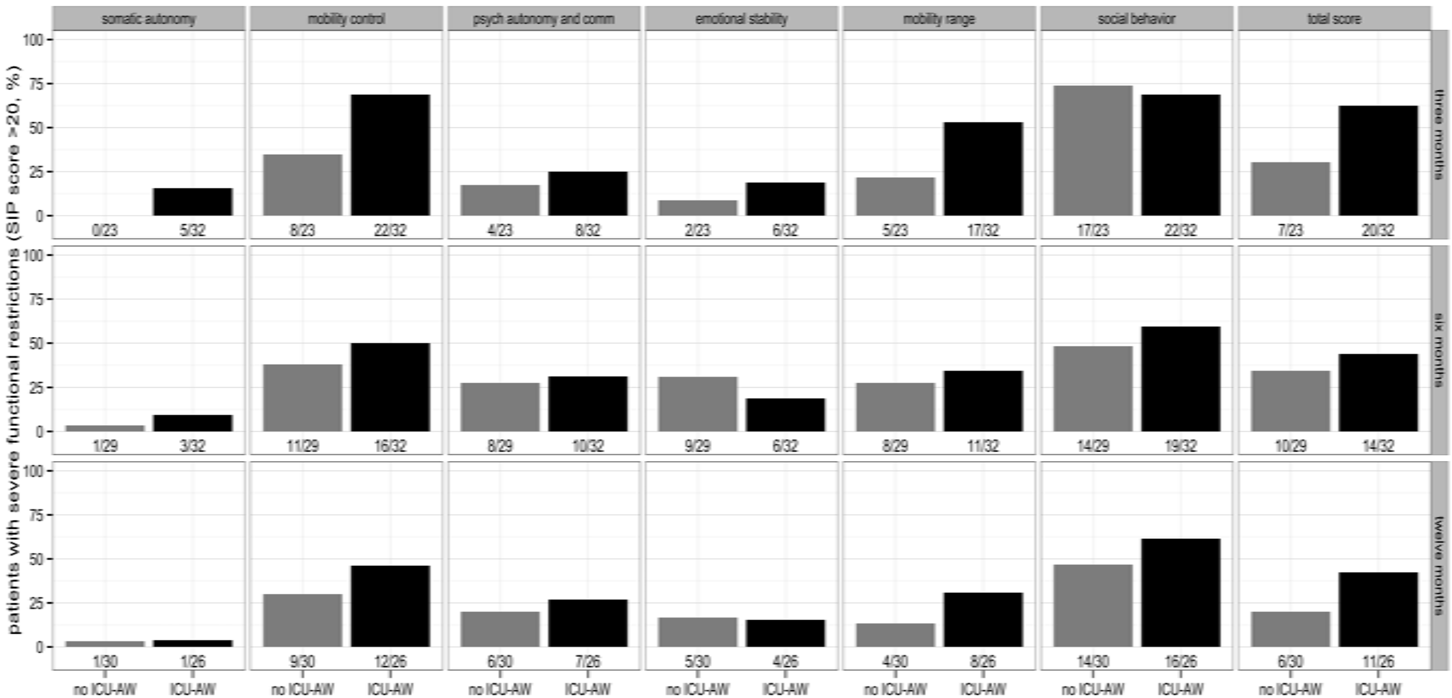

Figure 2 Number of patients with severe restrictions in performing activities of daily living (SIP score >20).

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,[34-36] 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.[1,34-36] The SF-36 is a generic measure for assessing health-related quality of life. Empirical studies have shown mixed results for its construct validity ($r > 0.6$).[37,38] 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.[28] Furthermore, the SIP68 received support for its excellent construct validity ($r = 0.94$).[24,26] The SIP68 has also been used previously to evaluate functional recovery in ICU survivors.[12] 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,[16,39,40] 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.[9] 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).[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.[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.[18] In agreement with previous studies,[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.

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Additional file 1: Baseline characteristics for ICU survivors at 3, 6 and 12 months after ICU discharge

Patient characteristics	3 months after discharge		6 months after discharge		12 months after discharge	
	ICU-AW (n=32)	**no ICU-AW (n=23)**	**ICU-AW (n= 32)**	**no ICU-AW (n=29)**	**ICU-AW (n=26)**	**no ICU-AW (n=30)**
Age, mean ± SD	61 ± 15	60 ± 13	62 ± 17	62 ± 11	61 ± 16	64 ± 11
Gender female, n (%)	19 (60)	9 (39)	18 (56)	12 (41)	14 (54)	11 (37)
BMI > 30, n (%)	8 (25)	5 (22)	8 (25)	5 (17)	5 (19)	3 (10)
Charlson co-morbidity index, median (IQR)	0 (0-2)	0 (0-2)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-2)
Admission type						
Medical, n (%)	17 (53)	17 (74)	17 (53)	19 (66)	16 (62)	19 (63)
Surgical elective, n (%)	7 (22)	3 (13)	7 (22)	5 (17)	6 (23)	5 (17)
Surgical emergency, n (%)	8 (25)	3 (13)	8 (25)	5 (17)	4 (15)	6 (20)
APACHE IV score, mean ± SD	84 ± 21	78 ± 27	81 ± 19	84 ± 32	80 ± 18	80 ± 31
Maximal SOFA score during ICU-stay, mean ± SD	13 ± 4 [b]	10 ± 4	13 ± 4 [b]	11 ± 3	13 ± 4 [b]	10 ± 3
Sepsis during ICU-stay, n (%)	30 (94) [b]	16 (70)	31 (97) [b]	23 (79)	25 (96) [b]	23 (77)
Average MRC score, median (IQR)	3 (1-3) [a]	5 (4-5)	3 (2-3) [a]	5 (4-5)	3 (2-3) [a]	5 (4-5)
Days with mechanical ventilation, median (IQR)	13 (6-19) [a]	5 (4-7)	12 (5-19) [a]	5 (4-7)	14 (8-18) [a]	6 (4-9)
Length of stay in ICU (days), median (IQR)	22 (11-36) [a]	7 (6-10)	19 (10-36) [a]	7 (6-13)	20 (11-36) [a]	8 (6-13)
Total length of stay in hospital (days), median (IQR)	62 (38-84) [a]	25 (21-35)	60 (37-84) [a]	28 (23-46)	62 (38-82) [a]	27 (23-44)
Discharge destination from hospital						
Other hospital, n (%)	12 (38)	5 (22)	11 (34)	7 (24)	10 (39)	7 (23)
Rehabilitation facility, n (%)	7 (22)	0 (0)	8 (25)	3 (10)	8 (31)	2 (7)
Home, n (%)	13 (41) [b]	18 (78)	13 (41)	19 (66)	8 (31) [b]	21 (70)

[a] $P < 0.01$.
[b] $P < 0.05$.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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CHAPTER 5

Coping style and quality of life in Dutch intensive care unit survivors

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ABSTRACT

Objective

The purpose of this study was to explore coping styles among intensive care unit (ICU) survivors and investigate the association between coping style and quality of life (QoL).

Method

In this cross-sectional multicenter study, 150 adult patients who were mechanically ventilated in an ICU for ≥ 2 days and discharged to their homes were invited to visit the post-ICU clinic 3 months after discharge. Before the post-ICU visit, the patients completed questionnaires regarding their QoL, coping style, and psychological distress. Coping style was assessed using the Coping Inventory for Stressful Situations (CISS-21), which measures task-oriented coping, emotion-oriented coping, and avoidance coping styles. QoL was assessed using the Physical Component Score (PCS) and Mental Component Score (MCS) derived from the 36-item Short Form Health Survey (SF-36). Univariate and multivariate linear regressions were performed.

Results

One hundred four patients (mean age = 59 years; 71 men, 33 women) completed the questionnaires (response rate = 69%). The highest CISS-21 subscale mean was found in the Task-Oriented subscale (21.3), followed by the Avoidance Coping subscale (18.7) and the Emotion-Oriented subscale (15.2). Emotion-oriented coping style was independently associated with reduced mental health (i.e., SF-36 MCS), but not with physical functioning (i.e., SF-36 PCS).

Conclusions

An emotion-oriented coping style is associated with worse mental health among Dutch ICU survivors. Additional research is needed in order to determine the precise role that coping style plays in the long-term recovery of ICU survivors.

INTRODUCTION

Patients who survive a critical illness are often confronted with undesirable long-lasting outcomes, including physical and cognitive impairment, emotional problems, and decreased quality of life (QoL).[1-4] The most common physical sequelae following critical illness include neuromuscular weakness, impaired walking and mobility, lack of energy, and fatigue; these symptoms can persist for years following discharge from the intensive care unit (ICU).[2,5,6] In addition to these physical complaints, many ICU survivors have paranoia-like memories regarding their time in the ICU, hospital-related phobias, and panic attacks that can lead to longer lasting anxiety, depression, and posttraumatic stress disorder (PTSD), ultimately impeding the patient's recovery and significantly reducing QoL.[7,8] After being discharged from the hospital, most ICU survivors are confronted with the challenges of restoring maximum function; adjusting to changes in their physical, emotional, and social functioning,[3] and overcoming their recent traumatic experiences. As the survival rates of patients admitted to an ICU have increased, the long-term consequences of critical illness have become increasingly recognized as an important health care issue, and QoL has become an increasingly important outcome measure in intensive care studies.[9-11] The way in which health-related QoL is perceived is generally determined by the interaction between several factors, including personal life events, lifestyle, sociodemographic factors, economic status, personal and psychological characteristics, and mechanisms for coping with stress.[12] The ability to cope effectively with the physical and emotional impact of an illness is essential for achieving long-term recovery and maintaining high QoL.[13,14]

Coping is defined as "a response aimed at diminishing the physical, emotional and psychological burden that is linked to stressful life events and daily hassles".[15] Moreover, coping can be conceptualized as being situation-dependent, as being domain-specific, or as a personality trait or style.[16] When coping is considered as a personality trait or style, three principal styles can be identified: task-oriented coping, emotion-oriented coping, and avoidance coping.[17] With task-oriented coping, the individual attempts to solve a problem using various behavioral or cognitive approaches, such as breaking down the problem before reacting or recalling how past problems were solved to help find current solutions. With emotion-oriented coping, the individual responds to a stressful situation with emotional reactions (e.g., anger, worry), directed toward oneself rather than the problem at hand. With avoidance coping, the individual uses distractions in order to avoid a particular situation rather than dealing directly with the situation. Individuals use a variety of coping styles to manage stressful situations, and oftentimes different coping styles may be used simultaneously. Most people have a preference for one particular coping style, and this preference is generally determined by his or her personality, phenotype, demographics, and environmental factors (e.g., social support, cultural factors), and by the nature of the stressful event.

The relationship between coping style and QoL has been examined in patients with chronic disease or traumatic injury, and most authors recommend taking a patient's specific coping style into account in order to optimize the outcome of rehabilitation.[18-22] For several patient populations, it has been described that an active, task-oriented coping style is associated with better QoL, whereas passive, emotion-oriented and avoidance coping styles are generally associated with lower QoL.[23-25] These associations have also been decribed in the general population.[26-28]

With respect to survivors of critical illness, the relationship between coping style and QoL has hardly been investigated to date. However, in order to develop effective rehabilitation strategies, particularly given the broad spectrum of symptoms that can develop in patients following critical illness, investigating the coping styles used by this patient population—and the association between each coping style and subsequent QoL—is highly relevant. Therefore, the aim of this study was to examine the coping styles used by ICU survivors and investigate the relationship between each coping style and QoL. We hypothesized that a task-oriented coping style will be associated with better QoL, whereas an emotion-oriented or avoidance coping style will be associated with worse QoL.

METHOD

Participants and Procedures

In this cross-sectional study, we analyzed the outcome of ICU survivors who visited the post-ICU clinics at the Academic Medical Center (Amsterdam, the Netherlands) and the Tergooi hospital (Hilversum, the Netherlands) from 2010 through 2012. The organization of these post-ICU clinics has been described in detail previously.[29] The Academic Medical Center is a university hospital with 1,000 beds, including 34 beds dedicated to mixed medical and surgical ICU care; the Tergooi hospital is a general hospital with 633 beds, including 10 beds dedicated to mixed medical and surgical ICU care. Adult (≥18 years of age) patients who had been mechanically ventilated in the ICU for ≥2 days and were subsequently discharged to their home were invited to the post-ICU clinic and were eligible for inclusion in the study. Patients who were in the ICU fewer than 2 days—which primarily includes patients who are admitted for routine post-surgical observation and are not likely to develop post-ICU physical and/or mental restrictions—were not invited to the post-ICU clinic. Patients who had insufficient knowledge of the Dutch language or any condition that might have precluded their ability to complete the questionnaires (e.g., mental retardation, a terminal disease, etc.) were excluded. The questionnaires were part of the routine care provided within the post-ICU clinics; thus, the ethics committee ruled that the Medical Research Involving Human Subjects Act (version March 1, 2006; http://www.ccmo.nl) did not apply to the current study, and official committee approval was not required for this study. The participants completed the questionnaires 3 months after they were discharged from the ICU.

Measures

Coping style was determined using the validated Dutch short version of the Coping Inventory for Stressful Situations-21.[26] This 21-item self-report instrument is used to determine which coping style an individual prefers during a specific stressful situation. The CISS-21 contains three subscales with seven items each, and these 21 items are distributed randomly throughout the form in order to investigate the presence of task-oriented, emotion-oriented, and avoidance coping styles. The Task-Oriented subscale contains items such as "analyzing the problem," "making a plan before solving the problem," and "thinking about the situation and learning from mistakes." Examples of Emotion-Oriented items include "blaming oneself for being emotional or not knowing how to handle a situation" and "being worried and/or becoming upset." The Avoidance subscale contains items such as "taking a break to distance oneself from the situation," "spending time with a special person," and "going shopping or treating oneself with sweets or snacks." Each item is scored on a 5-point Likert scale, with 1 corresponding to *not at all*, and 5 corresponding to *very much*. A total score ranging from 7 to 35 is then calculated for each subscale, with a higher score indicating a preference for a specific coping style. The Dutch version of the CISS was developed by de Ridder and van Heck (2004)[26] and has been validated in healthy adults. The CISS has good internal consistency (Cronbach's alpha = .75 to .88), the three main scales have sufficient discriminant validity ($r < .25$), and test–retest correlation is strong ($r = .78$ to $.90$).[26]

QoL was assessed using the validated Dutch version of the Medical Outcomes Study 36-item Short Form Health Survey.[30,31] The SF-36 is a reliable, validated questionnaire that has been recommended for measuring QoL in ICU survivors.[32] The Physical Component score (PCS) and Mental Component score (MCS) of the SF-36 were used as the primary outcome measures of QoL. The SF-36 contains 36 items that measure physical functioning, limitations related to physical problems, bodily pain, general health, vitality, social functioning, limitations related to emotional problems, and mental health. PCS and MCS were calculated using standard techniques.[30]

In addition, the following sociodemographic data were obtained: age, gender, civil-state/living situation (e.g., married/in a partnership, living alone, cohabiting with children/partents), and employment status (e.g., paid work, volunteer work). Disease-related factors,inclu-ding the ICU admission diagnosis, severity of illness (measured using the Acute Physiology and Chronic Health Evaluation II [APACHE II]), duration of mechanical ventilation, and length of stay in the ICU and in the hospital were retrieved electronically from the patients' medical records. We also assessed symptoms of anxiety, depression, and PTSD, as these symptoms are highly prevalent among ICU survivors.[6,33,34] Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS);[35-37] a subscale score ≥8 (from a range of 0 to 21) indicates the presence of anxiety or depression symptoms.[37,38] The 10-item Trauma Screening Questionnaire (TSQ) was used to identify patients at risk for PTSD, with a score of 6 or higher indicating the presence of PTSD symptoms.[39,40]

Statistical Analysis

Descriptive statistics were used to analyze the patient characteristics and outcomes. Respondents and non-respondents were compared with respect to age, gender, and disease-related factors using the chi-square test (in case of proportions), Student's *t* test (in case of normally distributed continuous variables), or the Mann–Whitney *U* test (in case of non-normally distributed variables or ordinal variables). Variables potentially associated with QoL (i.e., MCS and PCS) were identified using univariate analysis: for this purpose, we assessed the associations between MCS/PCS and coping style, anxiety, depression, PTSD, sociodemographic factors (age, gender, living situation, and employment status), and disease-related factors (severity of illness measured using APACHE II, duration of mechanical ventilation, and total length of hospital stay). The variables with a *P* value <0.10 in the univariate analysis were entered into two separate multiple linear regression analyses (with backward elimination of variables), using PCS and MCS as dependent variables, respectively. Model assumptions of linearity and normality were checked, and a variance inflation factor was used to test multicollinearity for each model. The level of significance was set at 0.05. All analyses were conducted using Statistical Package for Social Science (SPSS), Version 20.0 for Windows (IBM, Armonk, NY).

RESULTS

From 150 ICU survivors who were invited consecutively to visit the post-ICU clinic, 104 (69%) completed the questionnaires; the mean (±SD) interval between ICU discharge and completing the questionnaires was 12.5 ± 4.7 weeks. The baseline characteristics of the study population are summarized in Table 1. Employment status was completed by 98 patients. The non-respondents did not differ significantly from the respondents, with the exception of the reason for admission to the ICU. In the group of respondents, 73% and 27% were admitted to the ICU for medical reasons or surgery, respectively; in the group of non-respondents, 54% and 46% were admitted for medical reasons or surgery, respectively. Of all study partici-pants who completed the CISS-21, the highest subscale mean was found in the Task-Oriented subscale (21.3), followed by the Avoidance Coping subscale (18.7) and the Emotion-Oriented subscale (15.2). This result indicates that our study population had a preference for the task-oriented coping style, and less preference for emotion-oriented coping style. The primary study variables are summarized in Table 2. The TSQ was completed by only 89 ICU survivors.

Three months after discharge from the ICU, the mean (±SD) PCS and MCS scores were 38.1 ± 10.5 and 46.3 ± 10.6, respectively. Twenty-five percent of the ICU survivors endorsed clinically elevated symptoms of anxiety, and 16% endorsed clinically elevated symptoms of depression. Fourteen out of 89 patients (16%) endorsed clinically elevated symptoms of PTSD.

Table 1 Baseline characteristics of ICU survivors (n=150)

Patient characteristics	**Respondents n=104**	**Non-respondents n=46**	***P* value**
Age in years, mean ± SD	59 ± 15	57 ± 17	0.93[b]
Male gender, n (%)	71 (68)	30 (65)	0.71[c]
Civil state/living situation, n (%)			
Married/with partner	68 (65)	NA	NA
Cohabiting with >2 persons	19 (19)	NA	NA
Living alone	17 (16)	NA	NA
Employment status[a], n (%)	*n=98*		
Paid work	35 (36)	NA	NA
Volunteer work	11 (11)	NA	NA
Disease-related factors			
Admission type, n (%)			0.01[c]
Medical	76 (73)	25 (54)	
Surgical elective	11 (11)	10 (22)	
Surgical emergency	17 (16)	11 (24)	
APACHE II, mean ± SD	19 ± 7	18 ± 6	0.23[b]
Days on mechanical ventilation, median (IQR)	6 (4-9)	7 (4-11)	0.11[d]
Days in the ICU, median (IQR)	8 (5-12)	9 (6-13)	0.36[d]
Total LOS in hospital, in days, median (IQR)	22 (16-33)	21 (15-31)	0.99[d]

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; IQR, interquartile range (25th and 75th percentiles); LOS, length of stay; NA, not available.
[a] n=98
[b] Student's *t* test
[c] Chi-square test
[d] Mann-Whitney *U* test

Table 2 Coping style, Quality of Life, Anxiety/Depression, and PTSD measured 3 months after discharge from the ICU (n=104)

Variable	Mean ± SD n (%)
Coping style (CISS-21)	
Task-oriented	21.3 ± 6.7
Emotion-oriented	15.2 ± 5.9
Avoidance coping	18.7 ± 7.3
SF-36 (normative value ± SD[a])	
Physical function (77 ± 23)	54.9 ± 28.5
Social function (83 ± 23)	65.6 ± 27.1
Role physical (71 ± 39)	26.2 ± 35.3
Role emotional (82 ± 32)	62.5 ± 40.6
Mental health (76 ± 18)	73.3 ± 20.2
Vitality (69 ± 19)	54.1 ± 20.9
Bodily pain (71 ± 24)	67.5 ± 27.6
General health (65 ± 20)	48.6 ± 23.1
Physical Component Score (47 ± 10)	38.1 ± 10.5
Mental Component Score (51 ± 10)	46.3 ± 10.6
HADS subscales	
Anxiety sub-score ≥8	26 (25)
Depression sub-score ≥8	17 (16)
PTSD (TSQ ≥6)[b]	14 (16)

Abbreviations: PTSD, post-traumatic stress disorder; ICU, Intensive Care Unit; CISS-21, Coping Inventory for Stressful Situations-21; SF36, Medical Outcomes Study 36-Item Short-Form Health Survey (a higher score represents better functioning); HADS, Hospital Anxiety and Depression Scale; TSQ, Trauma Screening Questionnaire.
[a]SF-36 normative data for the age-matched general Dutch population, [b]n=89

The results of the univariate association analyses are summarized in Table 3. Of the three principal coping styles, only emotion-oriented coping was significantly associated with MCS (β = -0.53, $P < 0.01$) and PCS (β = -0.24, $P = 0.02$). Moreover, symptoms of anxiety, depression, and PTSD were correlated negatively with both MCS and PCS (see Table 3). In contrast, patient characteristics and disease-related factors were not correlated with QoL and were therefore not entered into the multivariate regression analyses. The results of the multivariate regression analyses are summarized in Table 4. After adjusting for anxiety and depression, the emotion-oriented coping style was associated independently with lower MCS scores. Together, these variables accounted for 45% of the variance in MCS. With respect to PCS, only PTSD remained in the model, indicating that emotion-oriented coping style, anxiety, and depression were not associated independently with PCS.

Table 3 Univariate associations between QoL scores and potential determinants

Potential determinants	Mental Component score				Physical Component score			
	B	*SE B*	β	*P* value	*B*	*SE B*	β	*P* value
Task-oriented coping	.04	.16	.03	.81	-.07	.16	-.04	.66
Emotion-oriented coping	-.93	.15	-.53	<.01	-.42	.17	-.24	.02
Avoidant coping	-.11	.15	-.08	.44	-.16	.14	-.11	.27
Anxiety (HADS subscale ≥8)	-13.87	2.01	-.57	<.01	-3.21	2.43	-.13	<.01
Depression (HADS subscale ≥8)	-14.67	2.40	-.53	<.01	-7.39	2.73	-.27	.01
PTSD (TSQ ≥ 6)	-8.89	2.83	-.33	<.01	-8.10	2.89	-.29	.01
Age	.08	.08	.10	.32	-.01	.08	-.02	.85
Severity of illness (APACHE II)	-.14	.15	-.07	.50	.05	.15	-.03	.76
Duration of mechanical ventilation	-.01	.14	-.01	.94	-.15	.13	-.01	.27
LOS in hospital	-.02	.06	-.03	.79	-.05	.06	-.03	.40

Abbreviations: QOL, quality of life; *SE,* standard error; HADS, Hospital Anxiety and Depression Scale; PTSD, posttraumatic stress disorder; TSQ, Trauma Screening Questionnaire; LOS, length of stay.

Table 4 Results of multivariate linear regression analyses for the association between coping style and QoL

Regression models	Mental Component Scale				Physical Component Scale			
	B	*SE B*	*P* value	Adjusted R^2 final model	*B*	*SE B*	*P* value	Adjusted R^2 final model
Model 1								
Emotion-oriented coping	-.52	.16	.00		-.23	.21	.28	
Anxiety	-6.79	2.60	.01		-1.99	3.37	.56	
Depression	-9.22	2.51	.00		-4.86	3.25	.14	
PTSD	-1.51	2.78	.54		-6.61	3.60	.07	
Model 2								
Emotion-oriented coping	-.49	.16	.00		-.19	.20	.34	
Anxiety	-6.17	2.32	.01		-4.40	3.15	.17	
Depression	-9.21	2.50	.00	.45	-5.65	3.21	.08	
Model 3								
Depression					-5.11	3.06	.10	
PTSD					-6.83	2.97	.03	.10

Abbreviations: QoL, quality of life; *SE,* standard error; PTSD, posttraumatic stress disorder.

DISCUSSION

In this explorative study, we examined various coping styles and their association with QoL in Dutch ICU survivors 3 months after discharge from the ICU. Our analysis revealed that the most prevalent and least prevalent coping styles were task-oriented and emotion-oriented, respectively. In addition, we found that the emotion-oriented coping style was associated independently with poorer mental health (measured using the SF-36 MCS), but not with physical functioning (measured using the SF-36 PCS).

This is the first study to examine the relationship between coping style and QoL in Dutch ICU survivors. Nevertheless, our findings are consistent with previous studies that reported a negative correlation between emotion-oriented coping and mental health in general populations.[26-28] Similar relationships between coping style and QoL have also been described in several patient populations with chronic disease.[19,22,24,41] Only a few studies examined coping styles used by patients following critical illness. For example, Fok, Chair, and Lopez (2005) studied 89 Chinese ICU survivors and found that "coping ability" was significantly correlated with QoL (r = .25 to .52).[42] Another Chinese study examined ICU patients following coronary bypass graft surgery and found that better QoL was associated both with problem-focused coping strategies and with lower anxiety levels.[43] These findings by Tung et al. and Fok et al. are similar to the results obtained from aforementioned studies regarding coping strategies among patients with chronic diseases, and they are consistent with our own results. However, the previous studies used different instruments to assess coping, and cultural differences likely exist between Chinese and European patients; thus, the results obtained from these studies may not be directly comparable.

Previous studies have shown that ICU survivors are at risk for developing mental health issues, including anxiety, depression, and PTSD.[6,33,34,44] In our study, 25% of ICU survivors revealed clinically elevated symptoms of anxiety, and 16% revealed clinically elevated symptoms of both anxiety and PTSD. Moreover, symptoms of anxiety and depression—together with an emotion-oriented coping style—were associated independently with decreased MCS, and these factors explained 45% of the variance in this score. In addition, symptoms of PTSD were significantly correlated with lower PCS scores.

The HADS depression subscale is reported to be correlated positively with the Emotion-Oriented subscale of the CISS (r = .50 to .61) but negatively with the Task-Oriented subscale (r = -.20 to -.43).[27,28] In addition, anxiety is reported to be correlated with the Emotion-Oriented CISS subscale. Given the partial overlap between questions in the TSQ and the anxiety subscale of the HADS, it is reasonable to expect that the emotion-oriented coping style would also be correlated with symptoms of PTSD. Negative associations between psychological symptoms and QoL, as well as the relationship between emotion-oriented coping and psychological distress, have been described in several populations;[28,45,46] however, the underlying cause of the latter association remains unclear, as high anxiety

levels can result from ineffective coping, and coping can be affected by anxiety.[47] In this context, it should also be mentioned that we had no access to data regarding delirium in our patient group, although delirium can be a major problem in ICU patients, affecting up to 80% of patients on mechanical ventilation.[48] Besides being a risk factor for mortality,[49] delirium is also associated with the development of cognitive impairment, which in turn is associated with long-term psychological morbidity.[50] In the current study, we were unable to distinguish between patients with and without delirium, but in future studies, the presence of delirium should be assessed as a potential risk factor for impaired mental health outcome.

Sociodemographic factors are known to play an important role in mediating QoL.[51,52] In our study, we found no significant association between age, gender, or living situation (i.e., living alone) and QoL 3 months after ICU discharge. We also found no associations between QoL and medical characteristics such as severity of illness (measured using the APACHE II tool), duration of mechanical ventilation, and length of hospital stay, although these factors can contribute to the development of physical, emotional, and cognitive impairments.[3] A possible explanation for this observation is the relatively low number of participants and/or the rather restrictive inclusion criteria, which might have led to selection bias, thereby yielding findings that may differ from previous studies. With respect to the missing data regarding the employment status and the TSQ, we assume that due to the extent of the double-sided questionnaires, some patients may have failed to notice and complete all questions. However, both measures were not required for the primary purpose of our study and therefore have had no substantially affect on the outcome.

We used the CISS-21 to examine coping styles in ICU survivors because this instrument has been used widely in several populations and was developed in order to identify and compare the basic coping strategies used by individuals in a variety of situations.[27] The CISS-21 has been validated in several populations and has good psychometric properties;[16,26] however, this instrument has not been validated for use specifically in ICU survivors. The internal consistency of the CISS-21 in our study, as measured with the Cronbach's alpha, was 0.83 for the Task-Oriented subscale, 0.80 for the Emotion-Oriented subscale, and 0.83 for the Avoidance subscale, indicating good internal consistency.

Implications

For most individuals, receiving care in an ICU for a life-threatening condition can be an extremely stressful and traumatic experience.[53] The complexity and magnitude of the ICU-related consequences require comprehensive multidisciplinary care. However, many ICU survivors experience inadequate and disjointed multidisciplinary care after hospital discharge, with inconsistent service provision,[1] and, to date, structured rehabilitation programs do not exist for survivors of critical illness. Given the generally low QoL and long-

lasting restrictions in physical, emotional, and cognitive functioning in ICU survivors,[9-11] the development of interdisciplinary rehabilitation interventions is urgently warranted. These interventions should consist of combined physical, occupational, and psychological therapies, and should be tailored to patients individual needs. Moreover, understanding a patient's coping style and psychological resiliency will enable rehabilitation professionals to optimize the treatment plan to match the patient's needs and situation. In other patient populations, psycho-educational interventions (e.g., motivational interviewing, cognitive–behavioral therapy) and self-management strategies have been found to be effective to improve "self-efficacy".[54-57] In addition, other interventions that address coping style, such as coping skills training and problem-solving therapy, are promising interventions that can help a patient in using appropriate coping strategies and reduce psychological distress.[58,59] These approaches could also be offered to ICU survivors with preference for an emotion-oriented coping style in order to facilitate recovery.

Limitations

Some limitations of our study should be considered with respect to the interpretation of the results. First, because we examined Dutch ICU survivors and focused on ICU patients who were mechanically ventilated for ≥2 days and were subsequently discharged to their homes, the results may not be applicable to other ICU populations. Second, our study population was limited to patients who completed the questionnaires within the framework of our post-ICU aftercare clinic, which resulted in a relatively small sample size. Although the characteristics of the responding participants did not differ significantly from non-respondents, we were unable to determine whether their coping styles were similar. Nevertheless, it is reasonable to assume that non-respondents likely exhibit an avoidance and/or emotion-oriented style of coping, and would therefore avoid contact with the hospital. Moreover, patients who use a task-oriented coping style may actively seek to participate in research. Together, these factors might have led to selection bias, which might limit the external validity of this study. Third, the participants were assessed at a single time point only. Thus, our results represent a single snapshot during a dynamic recovery process following a critical illness. Finally, the cross-sectional design of the study precludes drawing any conclusions regarding causality.

Future Research

With respect to future research, it would be interesting to investigate the relationships between QoL and coping patterns, symptoms of anxiety/depression, and/or PTSD in ICU survivors by performing a longitudinal study, for example with measurements 3, 6, and 12 months after ICU discharge. Gaining further insight into the possible changes in psychological distress, coping style, and/or QoL over time can help elucidate the specific role that coping style plays in the long-term recovery of ICU survivors.

CONCLUSIONS

The present study shows that an emotion-oriented coping style is associated with worse mental health among Dutch ICU survivors. Further research should be designed to clarify the specific long-term role of each coping style in post-ICU outcome and to investigate whether a coping-oriented rehabilitation intervention can improve QoL in these patients.

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CHAPTER 6

Feasibility of Post-Intensive Care Unit Clinics:

an observational cohort study of two different approaches

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ABSTRACT

Background

Post-ICU clinics have been advocated to reduce long-term physical and psychological impairments among ICU survivors. A format for optimal structure, timing, and care content has not yet been established. We developed and implemented two post-ICU clinics in different hospital settings and evaluated the feasibility.

Methods

In this prospective cohort study ICU survivors of a university hospital (AMC) and a general hospital (TG), who were mechanically ventilated ≥2 days and discharged to their homes, were invited to the post-ICU clinic one month after hospital discharge (AMC) or three months after ICU discharge (TG). Feasibility was evaluated as 1) the number of eligible ICU survivors and the proportion that attended; 2) the prevalence of ICU-related abnormalities, that required referral for further treatment; and 3) patient satisfaction.

Results

Forty-five of 629 AMC-patients and 70 of 142 TG-patients were eligible for the post-ICU clinic. Of these, 49% and 67% respectively, visited the outpatient clinic (P = 0.026). The majority of all screened patients had functional restrictions, and 68% required referral for further diagnosis and treatment. Patient satisfaction was high.

Conclusion

This study provides valuable information to support the implementation of post-ICU clinics. The use of validated screening instruments facilitates the identification of patients with need for further treatment. Early in-hospital screening and recruiting patients at highest risk for adverse outcome could be a more targeted approach to achieve greater benefit.

INTRODUCTION

Each year about 80,000 adults are admitted to intensive care units (ICUs) in the Netherlands and, due to progress in critical care, survival rates have increased. A significant proportion of survivors have long-term physical, psychological, and cognitive impairments that negatively affect daily function, employment, and health related quality of life (HRQoL).[1-5] The com-plexity and magnitude of these ICU-related consequences, recently denoted as Post Intensive Care Syndrome (PICS), require comprehensive multidisciplinary care.[6] However, ICU survivors experience inadequate and disjointed multidisciplinary care after hospital discharge, with inconsistent service provision.[7] Particularly for ICU survivors who are discharged to their homes, PICS may not be reliably and promptly recognized, resulting in incomplete or late referral to the appropriate care.

Post-ICU clinics have been advocated to manage ICU-related problems in survivors,[8-10] but to date such clinics are scarce, their organization varies, and their optimal structure, timing, and care content has not been established yet. Furthermore, there is no direction or consensus on how to implement it. We developed and implemented a post-ICU clinic in a large tertiary university hospital and in a general hospital in the Netherlands, based on the recommendations from the National Institute for Health and Clinical Excellence (NICE) guidelines.[11] The aim of this post-ICU clinic according to the NICE guideline, is to 'screen and detect' patients "that recover at a slower rate than anticipated, and to identify patients that has developed new physical and/or psychological morbidity, that was not previously identified", and to initiate tailored treatment, if required. We assumed that patients of a university hospital would have more complex and serious illnesses, resulting in longer ICU and hospital stays and a greater need for the post-ICU clinic than ICU survivors of a general hospital would have. Also, we expected that the programmatic evaluation of both approaches would provide important practical information for further improvement of post-ICU clinics.

The purpose of this study was to evaluate the feasibility of the post-ICU clinic in each hospital setting by determining: 1) the number of eligible ICU survivors and the proportion that attends the post-ICU clinic; 2) the prevalence of physical and psychological impairments and functional restrictions that require referral for further diagnosis and treatment; and 3) the level of patient satisfaction with the post-ICU clinic.

MATERIALS AND METHODS

Study design, setting and participants

This prospective cohort study was undertaken in the Academic Medical Center (AMC) in Amsterdam and the Tergooi (TG) in Hilversum. The AMC is a 1,000-bed university hospital with a 34-bed mixed medical and surgical closed-format ICU and TG is a 633-bed general hospital with a 10-bed mixed medical and surgical closed-format ICU.

All consecutive adult (age ≥18 years) ICU patients admitted in a 20 months period (2010-

2012) in the AMC and TG were screened for participation in the study. Critically ill patients mechanically ventilated for ≥2 days and discharged to their homes from the hospital were considered eligible. Patients with insufficient knowledge of the Dutch language or co-morbidity that would impair completing questionnaires or visiting the outpatient clinic (e.g., mental retardation, mechanical ventilation at home, terminal disease, etc.) were excluded. Considering their limited physical resilience and mobility range, AMC patients living beyond the service area of the hospital (a travel distance of more than 15 km) were also excluded. The Ethical Review Board of the AMC waived the need for informed consent because of the non-interventional nature of this study.

Description of the Post-ICU clinics

The main purposes of our post-ICU clinics were (1) to screen patients for physical and psychological impairments, functional restrictions, and HRQoL; (2) to identify care giver strain and symptoms of post-traumatic stress disorder (PTSD) in close relatives; (3) to refer patients or close relatives with unanticipated ICU-related sequelae for further treatment; and (4) to inform patients and their close relatives about short and long-term ICU-related consequences. As part of the standard clinical care, in both hospitals physical therapy interventions started early on the ICU, and were continued on the wards until hospital discharge. Although the purposes of the post-ICU clinic were similar in the two hospitals, the approach differed with respect to the involved professionals, the timing, and the used satisfaction questionnaires because of the differences in existing care approaches.

In the AMC, the post-ICU clinic was implemented in May 2010 by the department of rehabilitation medicine and carried out by a senior physical therapist specialized in critical care. Patients and relatives were invited one month after hospital discharge to enable early identification of ICU-related problems and referral to other practitioners. In October 2010, a similar post-ICU clinic was implemented in the general hospital under the responsibility of the ICU, led by nursing staff. Patients and their relatives were invited three months after ICU discharge to evaluate recovery and initiate additional care if necessary. In both hospitals, two weeks prior to the visit to the post-ICU clinic, patients completed the Dutch-translated and validated versions of the following questionnaires:

1) The Medical Outcomes Study 36-item Short Form Health Survey (SF-36) was used to measure HRQoL.[12,13] The domains “physical function” and “role limitation due to physical problems” were used to screen patients for physical impairments and functional restrictions.

2) The Hospital Anxiety and Depression Scale (HADS) was uses to assess symptoms of anxiety and depression.[14-16] Sub-scale scores (0-21) of ≥8 indicate anxiety or depressive symptoms.[16,17]

3) The 10-item Trauma Screening Questionnaire (TSQ) was used to identify patients at risk for PTSD. A cut-off score of 6 has found to be optimal.[18,19]

4) Health care utilization, a self-composed list on which patients had to mark all health

care professionals that they received care from.
Information on socio-demographics (age, height, body weight, living situation, and employment [number of working hours] before and after the ICU admission) was recorded, and clinical data were retrieved from medical records.
In close relatives, PTSD and potential care giving concerns were assessed before their visit to the post-ICU clinic, using the TSQ and Caregiver Strain Index (CSI). The CSI is a validated 13 item questionnaire with a score of >7 indicating a higher risk for strain.[20] In addition, socio-demographic characteristics (age, gender, relationship to the patient, work situation before and after patient's hospital admission) were recorded.

At the post-ICU clinic, a shortened version of the International Classification of Functioning, Disability, and Health (ICF) checklist (Part 1a: impairments of body functions and Part 2: activity limitations and participation restrictions), and the Malnutrition Universal Screening Tool (MUST) were completed for the screening of ICU-related impairments or functional restrictions. The ICF checklist of the World Health Organization is a practical tool to identify and classify information on the functioning and disability of an individual.[21] The MUST is used in hospitals to identify patients at risk for undernourishment.[22] A MUST score of 2 implies a high risk of malnutrition.[23]
Patients with clinically meaningful ICU-related physical or psychological impairments according to the questionnaires and screening tools were referred for further treatment. Close relatives with high burden of care and/or symptoms of PTSD were advised to contact their general practitioner for support or additional care. AMC patients were asked to rate their satisfaction with the post-ICU clinic on an ordinal 5-item scale (4=very satisfied, 3=satisfied, 2=nor satisfied/nor dissatisfied, 1=dissatisfied, 0=very dissatisfied). At TG, a 10-point scale, with higher scores indicating more satisfaction (1=very dissatisfied, 10=very satisfied) was used. ICU survivors who declined the invitation to visit the post-ICU clinic were contacted by phone to ascertain their reasons for not attending.

Feasibility

The feasibility of each post-ICU clinic was evaluated as: (1) the number of eligible ICU survivors and the proportion that attended one month after hospital discharge for AMC, and three months after ICU discharge for TG; (2) the prevalence of physical and psychological impairments, and functional restrictions that required referral for further diagnosis and treatment; and (3) patient satisfaction.

Statistical analysis

Demographic and clinical data of ICU patients, including age, gender, Body Mass Index (BMI), Acute Physiology and Chronic Health Evaluation II (APACHE II), ICU admission diagnosis, duration of mechanical ventilation, length of ICU and hospital stay, and working hours prior

to ICU admission, were compared both between the two hospital settings, and between patients that attended the post-ICU clinic and patients who declined or who were lived beyond the service area of the hospital. Also, physical and psychological impairments, and functional restrictions after hospital discharge were compared between the two hospitals, as well as the demographic data of close relatives, care giver strain, and post traumatic stress. Comparisons were performed with the independent *t*-test (continuous data), the Mann-Whitney *U*-test (ordinal data), and the Chi-square test (categorical and dichotomous data) or Fisher's exact test. A *P* value less than 0.05 was considered statistically significant. For descriptive analysis, mean values were presented with standard deviation (±SD), median values with interquartile range (IQR) and proportions with percentages and total numbers. All analyses were performed in IBM SPSS Statistics 19.0 (SPSS Inc., Chicago, USA).

RESULTS

Number of eligible patients

Of the patients who were mechanically ventilated ≥2 days (AMC: N=629, TG: N=142), 45 patients from the AMC and 70 from TG met the inclusion criteria and were discharged home (Figure 1). The baseline characteristics of the 60 AMC-patients who were excluded because of travel distance >15 km, did not differ from those of included AMC-patients, except for age (median [IQR] age 57 [42-66.8] in excluded patients vs. 61 [54-69.5] in included patients, *P* = .041). Of all eligible patients, 22 AMC patients (49%) and 47 TG patients (67%) visited the post-ICU clinic (*P* = 0.026). AMC patients visited the outpatient clinic at a mean of 5.5 weeks (SD 2.6) after hospital discharge and TG patients at 12.1 weeks (SD 3.7) after ICU discharge. Reasons for not attending (n=23) the post-ICU clinic in the AMC were: good health (n=2) or participation in a cardiac rehabilitation program (n=8), no need (n=6), health-related difficulties (n=4), and re-admission to the hospital (n=2); one patient could not be traced. At TG, the reasons for not attending (n=23) were: impossible to contact (n=12), health-related difficulties (n=6), and no need (n=5). The demographic and clinical data of the study participants in the two hospitals were comparable (Table 1), except for gender (42% men in AMC vs. 76% in TG, *P* = 0.008). Patient characteristics between ICU survivors who visited the post-ICU clinic and who declined did not differ (*P* > 0.05) (Table 2). Three AMC patients and one TG patient were excluded from the analysis because of incomplete questionnaires (Figure 1).

Table1 Demographic and clinical data of intensive care unit aftercare patients

Patient characteristics	AMC	Tergooi	*P*
N of patients	19	46	
Age (years), mean (SD)	58.1 (14.2)	63.4 (11.5)	.118
Gender (male), n (%)	8 (42.1)	35 (76.1)	.008
BMI, median (IQR)	24.9 (22.5-31.2)	27.4 (23.5-29.8)	.478
Obesity (BMI > 30), n (%)	5 (26.3)	10 (21.7)	
ICU admission diagnosis, n (%)			.077
Medical	16 (84.2)	36 (78.3)	
Elective surgery	1 (5.3)	4 (8.7)	
Non-elective surgery	2 (10.5)	6 (13)	
APACHE II score, median (IQR)	21 (16-24)	18 (15-24.5)	.891
Duration of mechanical ventilation (days), median (IQR)	6 (4-7)	4.15 (2.9-7.3)	.155
LOS in ICU (days), median (IQR)	7 (5-8)	6.85 (5-10)	.840
LOS in hospital after ICU discharge (days), median (IQR)	11 (8-14)	12 (6.8-17.3)	.817
Remunerative employment, n (%)	6 (31.6)	13 (28.3)	.160
Working hours per week, median (IQR)	36 (27-40)	36 (31-39)	
Voluntary work, n (%)	2 (10.5)	8 (17.4)	.485
Hours per week, range	3-5	2-20	

Abbreviations: IQR, interquartile range (25th and 75th percentile); N, number; BMI, Body Mass Index (kg/m^2); ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation; LOS, length of stay.

Table 2 Comparison of patient characteristics between intensive care unit survivors who visited the post-ICU clinic, and who did not

Patient characteristics	Participants post-ICU clinic	Non-participants post-ICU clinic	*P*
N of patients	65	46	
Age (years), mean (SD)	64.8 (14.7)	61.8 (12.5)	.247
Gender (male), n (%)	43 (66.2)	27 (58.7)	.423
BMI, median (IQR)	26.8 (23.3-30.2)	28.4 (25.3-23.9)	.151
ICU admission diagnosis, n (%)			.799
Medical	52 (80.0)	35 (76.1)	
Elective surgery	5 (7.7)	3 (6.5)	
Non-elective surgery	8 (12.3)	8 (17.4)	
APACHE II score, median (IQR)	18 (15.5-24)	19 (15-23.25)	.838
Duration of mechanical ventilation (days), median (IQR)	5 (3-7)	8 (3-10)	.078
LOS in ICU (days), median (IQR)	6.9 (5-10)	8.6 (4.7-12.4)	.481
LOS in hospital after ICU discharge (days), median (IQR)	12 (7.5-16.5)	11 (6-20)	.808
Remunerative employment, n (%)	22 (33.8)	NA	-
Working hours per week, median (IQR)	36 (29.5-40)		
Voluntary work, n (%)	10 (15.4)	NA	-
Hours per week, range	2-20		

Abbreviations: IQR, interquartile range (25th and 75th percentile); N, number; BMI, Body Mass Index (kg/m^2); ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation; LOS, length of stay; NA, not available.

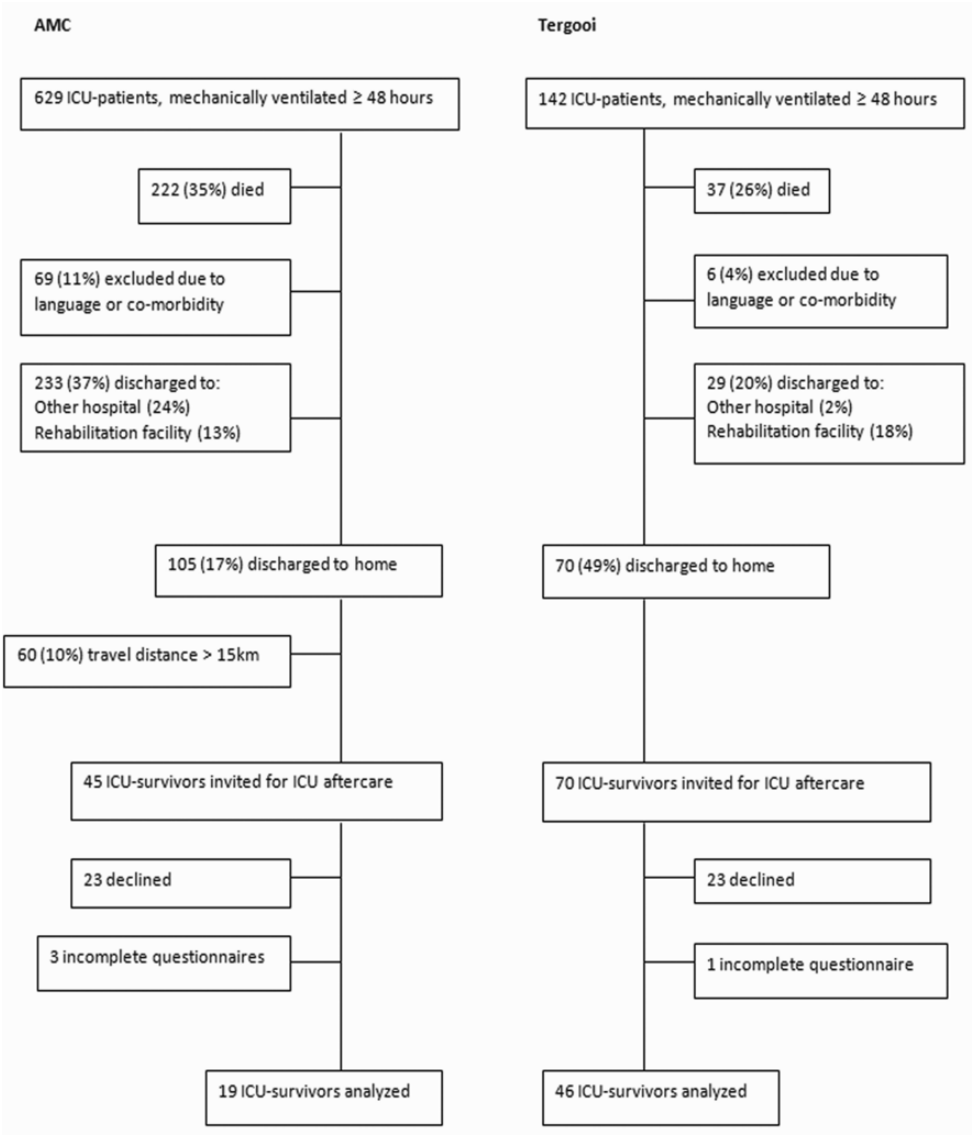

Figure 1 Study patient recruitment diagram

Functional status and referral

There were no statistical differences in functional status of ICU survivors in the two hospitals (Table 3). Out of all SF-36 domain scores, only 'bodily pain' and 'mental health' scores were comparable to the normative values of the general Dutch population. All other SF-36 domain scores were lower in our study population. Figure 2 shows the ten most frequently reported impairments and restrictions according to the ICF checklist. For these, predominantly physical impairments, 47% of the AMC patients and 54% of the TG patients received physical therapy. Signs of PTSD were found in 19% of the 65 participants and symptoms of anxiety and depression were present in 29% and 20%, respectively. Of the patients with psychological symptoms, 41% received treatment from a psychologist, psychiatrist, or social worker. Thirty-seven percent of all patients had signs of malnutrition of which 16% received treatment from a dietician. No patient had returned to paid work, but four out of ten patients had resumed the volunteer work they did prior to ICU admission.

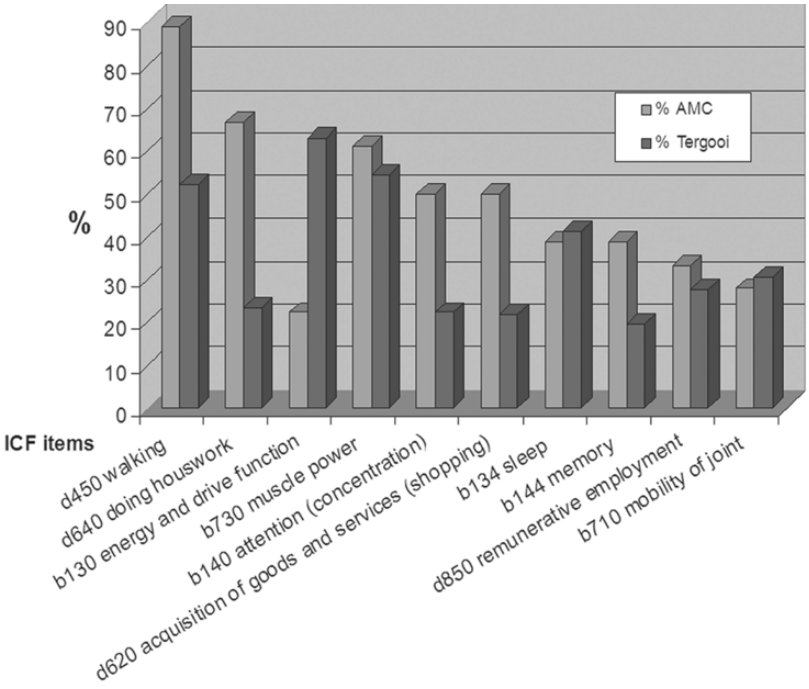

Figure 2 Ten most reported impairments and restrictions on the International Classification of Functioning, Disability and Health (ICF) checklist (AMC n=19 / TG n=46)

Table 3 Functional status at 4 weeks after hospital discharge and 3 months after intensive care unit discharge

Screening instrument	AMC (n= 19)	Tergooi (n=46)	*P*
SF36 (range 0-100, normative value)[a], median (IQR)			
Physical function (76.8)	30 (18.8-56.3)	50 (25-75)	.131
Role physical (70.8)	12.5 (0-25)	0 (0-25)	.772
Bodily pain (70.8)	67.3 (55.1-100)	67.3 (44.9-81.6)	.455
General health (65)	55 (20-67.5)	50 (35-61.3)	.822
Vitality (69)	40 (33.8-61.3)	55 (35-66.3)	.308
Social function (82.7)	62.5 (37.5-78.1)	62.5 (37.5-87.5)	.635
Role emotional (82.4)	66.7 (25-100)	66.6 (33.3-100)	.987
Mental health (75.6)	76 (59-84)	76 (55-88)	.811
TSQ (0-10)			
Patients with risk for PTSD (sum score ≥ 6)	3 (15.8%)	9 (19.6%)	.196
HADS sub-scale scores (0-21)			
Patients with indication for anxiety (score ≥ 8)	6 (31.6%)	13 (28.3%)	.080
Patients with indication for depression (score ≥ 8)	5 (26.3%)	8 (17.4%)	.493
Patients with signs of malnutrition (MUST ≥ 2)	9 (42.1%)	15 (32.6%)	.680
Returned to work	0 of 6	0 of 13	1.000
Resumed voluntary work	1 (5.3%)	3 (6.5%)	.848
Hours per week, range	5	4-5	

Abbreviations: SF36, Medical Outcomes Study 36-Item Short-Form Health Survey; IQR, interquartile range; TSQ, Trauma Screening Questionnaire; PTSD, Post-Traumatic Stress Disorder; HADS, Hospital Anxiety and Depression Scale; MUST, Malnutrition Universal Screening Tool.
[a]Higher scores representing better functioning; SF-36 normative data for the general Dutch population

In the AMC post-ICU clinic, 15 patients were referred to other specialties: physical therapist (n=6), psychologist/psychiatrist (n=3), and dietician (n=8). In addition, 2 patients with physical impairments were referred back to their physical therapist with specific training instructions. In TG, 27 patients were referred to a physical therapist (n=8), psychologist/psychiatrist (n=7), and dietician (n=12), and 12 patients were referred back to their physical therapist with additional training instructions.

Close relatives

In the AMC 11 and in TG 41 close relatives completed the questionnaires. The median age of the close relatives and the reported hours per week spent on care were significantly higher for the TG than for the AMC patients (median age: 58 vs. 63 [*P* = 0.023]; care assignment: 3.8 vs. 10 hours per week [*P* = 0.025]). Burden of care was high (CSI ≥7) in 9% of the close relatives in the AMC and 18% in the TG. Signs of PTSD were not found in the AMC population, but were present in 16% of close relatives of TG patients. High scores on TSQ and CSI were particularly found in partners and children.

Patient satisfaction

AMC patients were "very satisfied" (65%) or "satisfied" (35%) with the post-ICU clinic. For the TG patients, the median (IQR) satisfaction score was 8 (8-9).

Table 4 Demographic data of close relatives

Demographic characteristics	AMC	Tergooi	*P*
N of close relatives	11	41	
Age (years), median (IQR)	58 (52-59)	63 (57-69)	.023
Gender (female), n (%)	7 (63.6)	30 (73.2)	.535
Relationship to patient, n (%)			.576
Partner	9 (81.8)	32 (78)	
Family (other than partner)	1 (9.1)	7 (17.1)	
No family	1 (9.1)	2 (4.9)	
Remunerative employment, n (%)	5 (45.5)	15 (36.6)	.436
Working hours/week baseline , median (IQR)	36 (26-40)	32 (21.3-40)	.158
Working hours/week after ICU discharge, median (IQR)	32 (10-40)	29 (16-40)	.329
Relatives working less hours after ICU, n (%)	1 (9.1)	4 (26.7)	.781
Care assignment, n (%)	8 (72.7)	19 (55.8)	
Hours/week, median (IQR)	3.8 (1-5)	10 (3-18)	.025
CSI ≥ 7	1 (9.1)	7 (17.9) *n=39*	.666
TSQ ≥ 6	0	6 (15.8) *n=38*	.529

Abbreviations: CSI, Caregiver Strain Index (sum score ≥ 7 indicating higher risk for strain); IQR, interquartile range; no, number; TSQ, Trauma Screening Questionnaire (sum score ≥ 6 indicating risk for post-traumatic stress disease)

DISCUSSION

The results of our study show that post-ICU clinics are useful in identifying potential problems in daily functioning in survivors of critical illness. Although, the number of eligible patients and the follow-up rates of ICU survivors were limited in our study, the programmatic evaluation of the two post-ICU clinics in a university and a general hospital provides important information on different formats of post-ICU clinics.

We found that a limited proportion of the AMC survivors were discharged to their homes, 17%, versus 49% of the TG survivors. This can be explained by the fact that a tertiary university hospital has a large catchment area and many patients were transferred back to a general hospital near their residential area early after specialized medical treatment. Additionally, the majority of AMC-patients lived beyond the service area of the hospital, which resulted also in a small number of eligible patients for the post-ICU clinic. Of all eligible patients 49% of the AMC and 67% of the TG patients visited the outpatient clinic. This result was in line with comparable studies from Schandl[9] and Cutler[24] with attendance rates of 66% and 32% three months after ICU discharge. Ten eligible AMC patients (22%) did not attend the post-ICU clinic, because they had no complaints, or were already involved in a rehabilitation program. These patients may be assumed to have received care tailored to their individual needs. However, of greater concern was the group of eligible patients (13% at AMC and 23% at TG) that reported no need for ICU follow-up, because these patients may be suffering serious psychological problems, such as anxiety or PTSD, and consequently avoiding hospital contact.

With respect to the limited physical and psychological resilience of ICU survivors, also the timing of the post-ICU clinic seems important. One month after hospital discharge, 29% of the eligible AMC patients were not able to visit the outpatient clinic due to poor health. For that reason, 16% of the AMC patients visited the post-ICU clinic later, between 5 and 12 weeks after hospital discharge. Of the TG patients, only 9% did not attend the post-ICU clinic at three months after ICU discharge because of poor health. Based on these findings, we suppose that a post-ICU clinic three months after ICU discharge would be more feasible for ICU survivors. With the purpose of screening in mind, this timing enables patients to reflect on their recovery process and to determine any physical, mental or cognitive impairments, that were not present during hospital stay. This is also in line with the recommendation in the NICE guideline.[11,25] However, early identification of functional impairments is essential to initiate rehabilitation treatment as soon as possible, to improve recovery and to prevent chronic complaints.[1,19,26] In addition, several studies emphasize the importance of early support because of the many difficulties patients face shortly after hospital discharge.[27,28] Therefore, early in-hospital screening and risk stratification, followed by an assessment in a post-ICU clinic could be a more targeted approach to identify ICU patients at highest risk for adverse outcome.

We expected that patients of a university hospital (AMC) would have more complex and serious illnesses, resulting in longer ICU and hospital stays and a greater need for the post-ICU clinic than ICU survivors of a general hospital (TG). However, we found no significant differences between patient and clinical characteristics, functional status, and indications for referral between the two hospitals. These results should be taken cautiously, given the small study-population and the several differences in approach of the post-ICU clinics. Given the fact that TG patients visited the clinic two months later than AMC patients, we expected that they would have been further in their recovery process and perceive better HRQoL. Nevertheless, this was not the case in our study. Although, it is not possible to draw firm conclusions on the basis of the small numbers involved, these results show that patients experienced similar restrictions and HRQoL, regardless of type of ICU, severity of illness, demographic characteristics and time after ICU discharge. Despite the exclusion of patients who were transferred to a long-term care facility, we found severe physical and psychological impairments and functional restrictions in the majority of screened patients, both one month and three months after ICU discharge. This finding is in line with previous studies[2,8,10,29,30] and underlines the importance of a continued chain of care for ICU survivors who are discharged home.

As expected, our study also demonstrated that close relatives, such as the partners and children of ICU survivors, were at risk for PTSD or a high burden of care, which is in line with other studies that found a high prevalence of anxiety and depressive conditions.[31,32] Therefore, we recommend the assessment of close relatives for symptoms of stress, anxiety, depression, and care giver strain as a regular part of the post-ICU clinic.

With the screening instruments used in this study, problems in different health domains were identified. Subsequently, patients were referred to different health care providers based on the available cut-off scores. The validity of these criteria for referral purposes was not assessed in this study and should be evaluated in future research.

Besides the identification of ICU-related problems and referral to other professionals, providing information about the ICU period and the physical and psychological recovery was an integral part of the post-ICU clinic. A better understanding of what had happened and how to recognize and to deal with ICU-related consequences appears to be very valuable for patients and their close relatives, and contributed to an overall high satisfaction with the post-ICU clinic. It is not convincing that the use of different questionnaires has affected this result, because on both instruments the responses ranged between the highest scores. Nevertheless, the 5-item scale might be more feasible, because 5 different response options are more easily to rate than 10.

Our study has some limitations that should be considered in the interpretation of the results. Due to the small number of patients and the selection of ICU survivors who were discharged to their homes, our study results might be biased and not generalizable to other ICU survivors. Furthermore, a significant proportion of eligible patients was unable or not willing to participate in follow-up. Developing strategies to offer post-ICU clinics to all ICU survivors who might benefit, would be an important improvement in this. Additionally, an appropriate comparison between the two post-ICU clinic approaches was limited, because of the differences in hospital settings. Finally, this study does not provide long-term outcome data of the patients to control for efficacy and treatment success. In future work, patient relevant outcome data should be collected in longitudinal studies to evaluate the effectiveness of post-ICU clinics and to further improve the care of ICU survivors after hospital discharge. Despite the restrictions of this study, it provides useful information to support the implementation of post-ICU clinics.

Based on the results of this study and current developments we recommend the following longitudinal approach to improve the care for ICU survivors. First of all, a systematic early screening for patients at risk for post ICU physical and psychological impairments should be performed repeatedly during hospital admission. With this, patients can be referred directly to outpatient rehabilitation services or be scheduled for a follow-up in a post-ICU clinic. Three months after ICU discharge, patients and their next relatives should be invited to administer questionnaires, to screen for remaining or new ICU-related problems in daily functioning, and to evaluate whether the offered care is sufficient or that additional care is needed. The use of computerized questionnaires and tele-medicine applications could be useful to facilitate this process. With the use of electronic surveys, it would be possible to assess more patients, also those who are physically or practically unable to return to a clinic, or those with avoidant behaviors. We assume that this could improve the recruitment of ICU survivors. Furthermore, appropriate use of technology may also enhance the cost-effectiveness of post-ICU clinics, another concern of post-ICU clinics. Tele-medicine as an alternative to face-to-face consultation serves clients, clinicians, and systems by minimizing the barriers of distance, time, and costs.[33,34] Based on this 'electronic' reassessment, patients and relatives with symptoms of PICS could be invited for a post-ICU clinic visit or could be directly referred for further diagnosis and targeted treatment. Additionally, we suppose that the development of a network with predefined arrangements with other allied health and medical specialists will improve the continuity of care. With such an integrated, stepped care program, the continuum of care for the transition from the hospital can be ensured for critically ill patients at risk for PICS.

CONCLUSIONS

Post-ICU clinics are important to facilitate the continuity of care for critically ill patients who are discharged to their homes. Validated screening instruments should be used for the identification of physical and psychological impairments and for referral to medical and allied health professionals. To increase the proportion of patients that can take advantage of post-ICU services, an early in-hospital screening to identify patients at risk for long-term ICU-related sequelae would be a more targeted approach. In addition, future research should investigate the feasibility of computerized screening and tele-medicine interventions to improve the benefit of post-ICU clinics.

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CHAPTER 7

General discussion

Each year, about 28.000 individuals are discharged from intensive care units (ICUs) encountering physical, mental and/or cognitive disorders as part of the post-intensive care syndrome (PICS). The general aim of this thesis was to explore the course and prognosis of functioning in ICU survivors during the first year after ICU discharge, and to investigate means for early identification of PICS. The studies included in this thesis focused on adult ICU-patients, who were mechanically ventilated more than 48 hours in a closed format mixed medical-surgical ICU. In this chapter the main findings and methodological issues of the presented studies are reviewed, implications for clinical practice are discussed, and recommendations for rehabilitation care as well as for future research are provided.

MAIN FINDINGS

Course and prognosis of functioning in ICU survivors

The prevalence of impairments in body functions, limitations in activities and restrictions in participation was high during the first year following ICU discharge. Especially physical functioning was severely impaired and predominated the course of recovery in ICU survivors.

Functioning immediately after ICU discharge

We found that in the first week after discharge from the ICU, three quarter of the patients were severely dependent on others in performing basic activities of daily living (ADL) such as personal care, toileting, dressing, eating, mobility, etc. (chapter 2). Grip strength was less than half of normative data and three quarter of the patients were unable to walk independently. Besides physical limitations, one third of the patients had impaired cognitive function comparable to mild dementia. Reduced grip strength and walking ability predominantly accounted for poorer functional in the first days after discharge from ICU (chapter 2).

Severity of illness at ICU admission, age, female gender, preexisting poor functional status and patients' personality have been described as prognostic factors associated with long-term functional outcome in ICU survivors.[1-5] We assumed that these factors would also be associated with functional status shortly after ICU discharge. However, we did not find an association between these factors and functional status immediately after discharge from the ICU (chapter 2). Instead, we found that disabilities within the first week after ICU discharge were more severe in patients with prolonged mechanical ventilation (≥6 days). Apparently, a longer duration of mechanical ventilation and the longer ICU stay, often due to medical complications, negatively impacted on short-term functional status.

Impact of ICU-AW on functioning

In search of risk factors for poor functional status in the first year after ICU discharge we investigated the impact of ICU-acquired weakness (ICU-AW) on functional recovery by comparing ICU survivors with and without ICU-AW (chapter 3 and 4). ICU-AW is a frequent neuromuscular complication in ICU-patients that occurs after the onset of critical illness. While it was known that ICU-AW is associated with long-term physical impairments,[6-9] our studies showed – by correcting for covariates and using a control group – that ICU-AW was an independent risk factor for poor physical functioning during the first year after ICU discharge (chapter 3 and 4). At hospital discharge, patients with ICU-AW were less likely to be discharged home compared to patients without ICU-AW. At 3, 6 and 12 months after ICU discharge, physical functioning was significantly more impaired in patients with ICU-AW compared to critically ill patients without ICU-AW patients (chapter 3 and 4). Furthermore, ICU-AW was associated with increased post-ICU mortality at 6 months after discharge from ICU (chapter 3). Interestingly, social functioning remained severely restricted in the majority of ICU survivors, independent from ICU-AW, during the first year after discharge (chapter 4). The underlying mechanisms to long-term decreased physical functioning in patients with ICU-AW have not been fully elucidated yet. Two studies found that patients with critical illness polyneuropathy (CIP) or combined neuro-myopathy (CINM) had slower or incomplete recovery compared to patients with critical illness myopathy (CIM).[7,10] An explanation for this could be slow and incomplete axonal regeneration.[10] Another explanation for delayed functional recovery could be limited endurance capacity and respiratory muscle weakness.[11]

Coping with the consequences of critical illness

Several studies showed that surviving critical illness is associated with reduced quality of life (QoL).[2,3,12-14] Achieving long-term recovery and maintaining high QoL is dependent on the ability to cope effectively with the physical and emotional impact of illness.[15,16] We hypothesized that personal coping style might be associated with QoL in survivors of critical illness, as was found in various patient groups with chronic disease or traumatic injury.[17-23] In chapter 5, we explored the relationship between coping styles and health-related quality of life (HRQoL) in ICU survivors, and found that an emotion-oriented coping style was associated with worse mental health status, 3 months after ICU discharge. Therefore, ICU survivors with emotion-oriented coping style may have the greatest need for targeted psychoeducational interventions, such as coping skills training and problem solving therapy, in order to facilitate recovery.

Means for early identification of PICS

Post-Intensive Care Unit clinics

Ideally, ICU-patients at risk for poor functional outcome should be identified early (during hospital stay), in order to initiate targeted rehabilitation care. Additionally, there is a need to monitor the recovery process after hospital discharge, and to manage the long-term ICU-related problems among survivors. For this purpose, post-ICU clinics have been advocated,[24-27] but such clinics are scarce, their organization varies, and their optimal structure, timing, and care content have not been established yet. In order to improve aftercare for ICU survivors, we developed and implemented two post-ICU clinic in different hospital settings (chapter 6). The goals of these post-ICU clinics were: (1) to screen patients for physical and psychological impairments, functional restrictions, and QoL; (2) to identify care giver strain and symptoms of post-traumatic stress disorder (PTSD) in close relatives; (3) to refer patients or close relatives with unanticipated ICU-related sequelae for tailored treatment; and (4) to inform patients and their close relatives about short- and long-term ICU-related consequences.

We found that at 1 to 3 months after discharge from the ICU the ten most frequently reported impairments and functional restrictions in ICU survivors were: decreased muscle strength and joint mobility, reduced walking capacity, fatigue, sleep disturbances, impaired attention, concentration and memory, doing housework, going shopping, and returning to work. More than one third of former ICU-patients also showed signs of malnutrition. Additionally, more than a quarter of the ICU survivors had symptoms of anxiety, and up to one fifth had symptoms of depression and post-traumatic stress disorder (PTSD). None of the patients had returned to their previous job. Only half of the patients with physical impairments, less than half of the patients with severe psychological complaints, and only one sixth of the patients with signs of malnutrition received treatment from a rehabilitation professional specialized in that specific area. Based on the comprehensive assessment at the post-ICU clinic, two third of the patients were referred to medical or allied health care professionals for further diagnosis and treatment. These alarming findings imply that many ICU survivors are undertreated after discharge from the hospital.

Besides the high prevalence of symptoms of PICS in ICU survivors, we also found a high burden of care and psychological distress in close relatives (PICS-F), 1 to 3 months after ICU discharge. Up to one fifth of the partners and children of ICU survivors reported a high burden of care, whereby items such as 'other demands on time, changes in personal plans, and family adjustments' were mentioned most frequently. Sixteen percent of the close relatives had symptoms of PTSD (chapter 6). Also, in more recent studies high occurrence rates of psychosocial symptoms (e.g., depression, anxiety, post-traumatic stress), and decreased HRQoL has been reported.[28-30] These findings underscore the importance to pay attention to close relatives of ICU survivors in the recovery process.

The use of validated screening instruments, such as the Short Form Health Survey (SF-36), Hospital Anxiety and Depression Scale (HADS), Trauma Screening Questionnaire (TSQ), Malnutrition Universal Screening Tool (MUST), and Caregiver Strain Index (CSI) with pre-defined cut-off points enabled the identification of ICU survivors and their close relatives with symptoms of PICS. In addition, patients and close relatives highly appreciated the provision of information about ICU-related problems in daily functioning and the recovery process. We concluded that our post-ICU clinic was feasible to identify symptoms of PICS in former ICU-patients and their close relatives, and to facilitate referral for further treatment, in order to support the continuity of care after hospital discharge.

With regard to the organization and implementation of the post-ICU clinic, we found that a significant proportion of the eligible patients did not visit the post-ICU clinic because this was too burdensome, or because they had 'no need' for contact with the hospital. We also found that at 1 month after hospital discharge fewer patients were able to visit the post-ICU clinic due to health-related problems than at 3 months post ICU discharge. Based on these findings we concluded that those patients who visited the post-ICU clinic were in relative good health. Probably, patients with worse health and most in need for rehabilitation care were insufficiently reached with a post-ICU clinic. Therefore, we propose timing the first visit to a post-ICU clinic to be scheduled at 3 months after discharge. Additionally, the use of tele-medicine or e-health techniques as an alternative to face-to-face consultation could be a solution for patients who are unable to visit the post-ICU clinic, by minimizing the barriers of distance, time, and costs. Based on an early remote assessment at 1 month after hospital discharge, patients and close relatives with symptoms of PICS could be directly referred to medical, rehabilitation and allied health professionals for further diagnosis and targeted treatment. Then, at 3 months patients should visit the post-ICU clinic for a more comprehensive assessment.

METHODOLOGICAL CONSIDERATIONS

Study population

The studies in this thesis have limited sample sizes due to several reasons. Inherent to longitudinal studies of ICU survivors, we were confronted with a low follow-up rate due to high post-ICU morbidity and mortality. The logistic effort to follow patients after discharge from the hospital, to limit loss to follow-up was extensive, but unfortunately, could not prevent low attendance rates and limited sample size.

We also found that patients, who completed the questionnaires and visited the post-ICU clinic for measurements, were patients in relatively good health (chapter 3, 4, 5, 6). To improve external validity, we compared the baseline characteristic of study participants and non-respondents (chapter 3, 5), and between patients on different follow-up moments (chapter 4). Because no differences were found, we assume that bias due to selection of patients was limited.

Study design

The prospective observational design of our studies allowed us to gain insight into the recovery process of ICU survivors from shortly after ICU discharge up to 1 year thereafter. However, in our longitudinal study comparing patients with and without ICU-AW (chapter 4), the population evaluated at 3, 6 and 12 months consisted of different subgroups as a result of death and loss to follow-up. Due to skewed data, mixed model analyses were not attainable to analyze the course of functional recovery at different time points.

Another methodological shortcoming is that in chapter 3 and 4 we did not collect information on all potential confounders such as functioning prior to ICU admission, medical complications and rehabilitation treatment that might have affected the course of recovery after hospital discharge. Furthermore, we did not correct for covariates as intermediate between ICU-AW and physical impairments, such as length of stay in the ICU. This might have resulted in residual bias. However, we assume that this had only little effect on the observed association between ICU-AW and physical impairments, because we included a control group and adjusted for a priori selected covariates derived from the literature such as age, gender, co-morbidity, presence of septic shock, APACHE IV score and maximal SOFA score during admission.

Outcome measures

In most of our studies we used self-reported questionnaires, to assess functional status in ICU survivors. Although, these have good psychometric properties and pre-defined cut-off scores, important outcomes such as functional capacity in terms of muscle strength, walking endurance or cognitive functioning cannot be assessed with questionnaires. Because physical examinations are time consuming and require extensive resources, which can be an obstacle for participation, these methods were only included in some of our studies (chapter 2, 4 and 6). However, due to limited and incomplete data, we did not report on these outcomes. To monitor the recovery of impairments and limitations in activities over time, objective measures of functional capacity should be used in future studies to obtain important information, additionally to patient-reported outcomes.

Generalizability

The generalizability of our findings might be limited as most of the studies included in this thesis were conducted in only one university medical center in the Netherlands. Also, in most studies, participants were assessed at a single time point only. However, since the patient characteristics of the cohorts in this thesis were comparable to other cohort-studies in ICU survivors in the Netherlands[31-33] and other Western countries,[6,13,34,35] our findings can be considered representative for ICU survivors, who have been mechanically ventilated for more than 48 hours. In our post-ICU- and coping study (chapter 5 and 6), patients with neurological disease as admission diagnosis, and patients who were transferred

to rehabilitation facilities were excluded, potentially limiting the generalizability of our findings. We hypothesize that the prevalence and severity of impairments, limitations and restrictions might be even higher in those patients who were transferred to a rehabilitation facility. We recommend that this assumption should be investigated in future research.

CLINICAL IMPLICATIONS

The studies in this thesis provide important information about the impact of ICU-stay on functioning in survivors of critical illness. Many ICU survivors have short- and long-term functional impairments, limitations in activities and restrictions in participation as part of PICS, which in turn results in a higher burden of care for close relatives. Additionally, a majority of ICU survivors do not receive adequate rehabilitation treatment after discharge from the hospital.

Much research on outcome after critical illness has been published the last five years illustrating an increase in scientific interest in this area. Our findings add important information to current knowledge regarding the nature and complexity of physical, mental and cognitive consequences of ICU stay in survivors and their families. To show the impact of ICU-stay on daily functioning and disability, and to give directions for targeted rehabilitation interventions, we have categorized the frequently occurring symptoms of PICS according to the World Health Organization's (WHO) International Classification of Functioning, disability and health (ICF) (Figure 7.1).

Although clear criteria for the early identification of ICU survivors at risk for poor functional outcome are lacking in literature, we found that patients with prolonged ICU-stay, longer duration of mechanical ventilation, and/or ICU-AW, have a higher risk of short- and long-term functional impairments, limitations in activities and restrictions in participation. These findings imply that such patients should be closely monitored after discharge from the ICU to initiate adequate rehabilitation treatment in time to optimally support their recovery process. Patients with an emotion-oriented coping style may have the greatest need for targeted psycho-educational interventions and should be identified early after discharge from hospital to facilitate their recovery. Post-ICU clinics are useful to identify symptoms of PICS, and to monitor the long-term recovery process after hospital discharge, using standardized comprehensive assessments. Early in-hospital risk stratification followed by a post-ICU clinic evaluation 1 to 3 months after hospital discharge is a beneficial approach to improve the continuum of targeted care after critical illness.

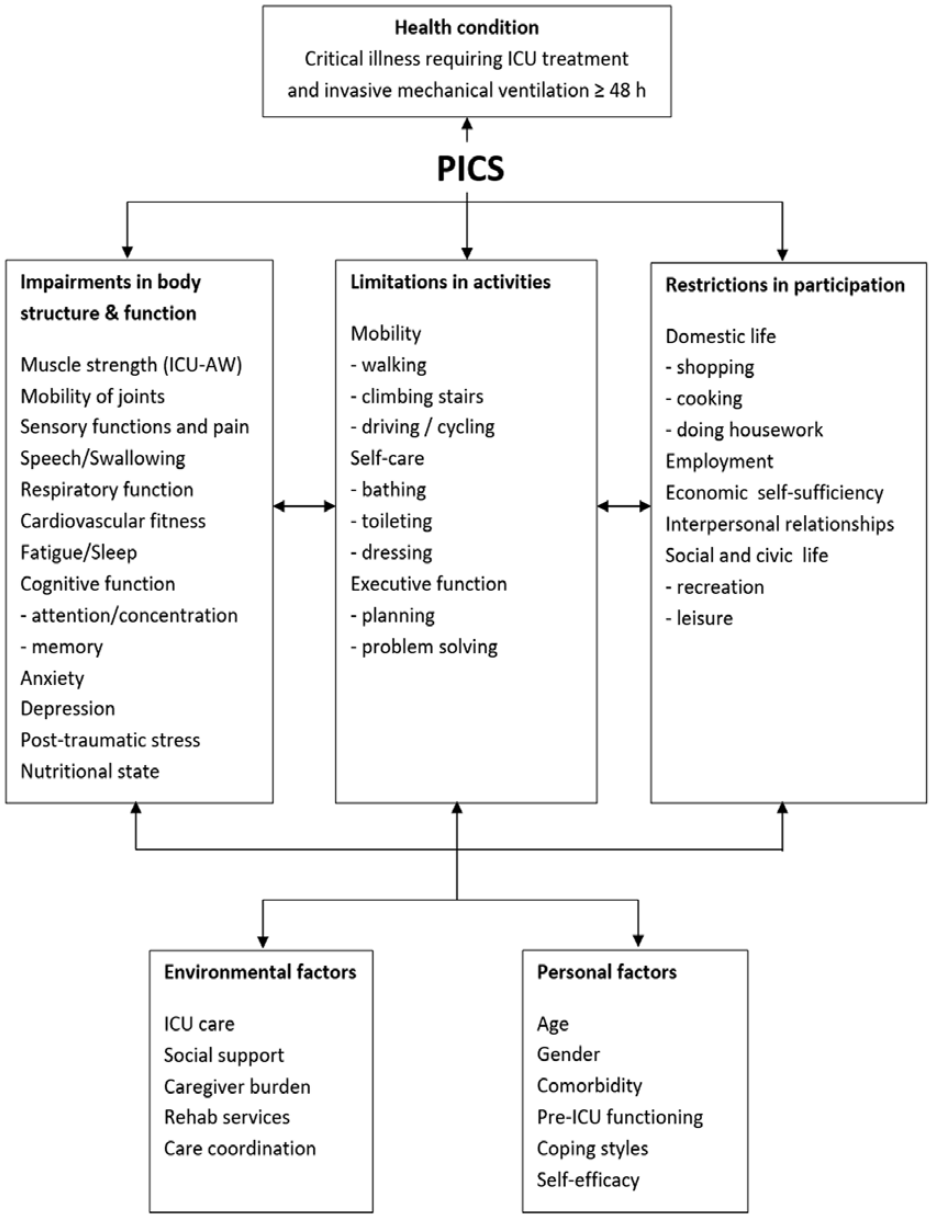

Figure 7.1 Categorization of components of PICS according to the ICF framework

Strategies to improve outcome

To achieve the best long-term functional outcome in ICU survivors with symptoms of PICS, two valuable strategies can be distinguished: prevention and treatment. Interventions that address prevention or mitigation of ICU-related symptoms particularly focus on the reduction of risk factors, such as immobilization, sedation, medication, delirium, sepsis, multi-organ failure, ARDS, hypoglycemia, hypoxia, length of mechanical ventilation, and length of stay in the ICU.[4,36,37] To minimize the likelihood of developing PICS, the application of the ABCDEFGH bundle has been promoted,[38-41] which addresses different aspects of risk reduction and treatment options, such as *A*irway management, *B*reathing trials, *C*oordination of care, *D*elirium assessment, *E*arly mobilization and rehabilitation, *F*amily involvement, *F*ollow-up referrals and *F*unctional reconciliation, *G*ood handoff communication and *H*andout materials on PICS and PICS-F. Early ambulation and early physical and occupational rehabilitation are beneficial to improve physical functioning and decrease cognitive impairments and psychiatric morbidity.[42-47] However, rehabilitation care should also be intensively continued after discharge from ICU. Therefore, we propose a structured, stepped care rehabilitation approach, which should start as soon as clinically possible within the ICU, and be continued throughout the recovery process.[25] Such an approach requires an interdisciplinary team of health care professionals with the appropriate competencies to coordinate the patients' rehabilitation care pathway: doctors, nurses, rehabilitation physicians, physical therapists, occupational therapists, psychologists, social workers, speech therapists, and dieticians.

Given the fact that this thesis focuses on functioning after ICU discharge, and that early rehabilitation interventions in the ICU have been extensively described in the literature,[38,39,48] our recommendations for a rehabilitation care pathway for ICU survivors target the period *after* discharge from the ICU. Figure 7.2 illustrates the proposed stepped care rehabilitation pathway.

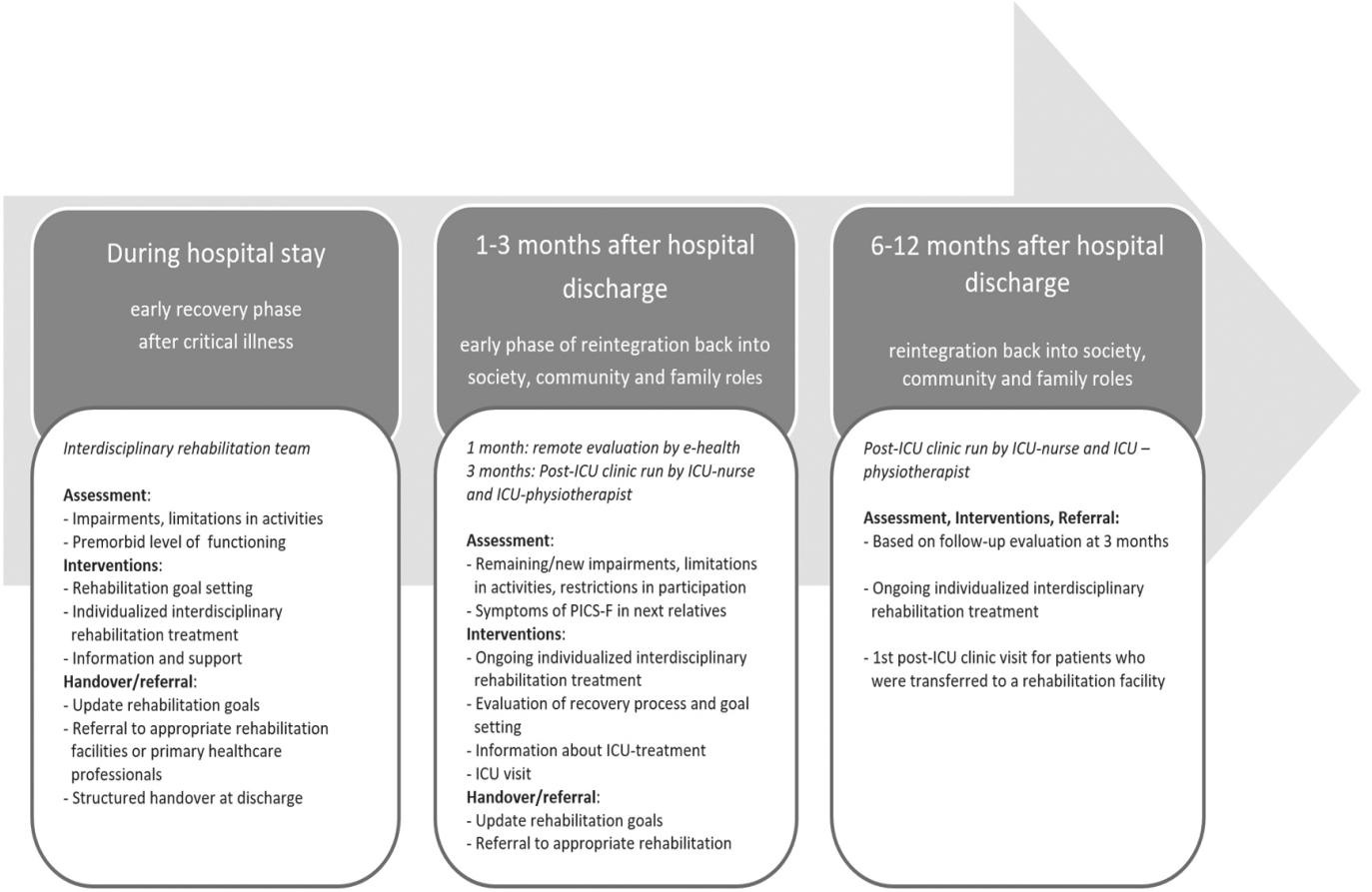

Figure 7.2 Interdisciplinary stepped care rehabilitation pathway for ICU survivors

Recommendations for an interdisciplinary stepped care rehabilitation pathway for ICU-survivors after discharge from ICU

During hospital stay

Ideally, all ICU survivors who have been ventilated for more than 48 hours are assessed after discharge from ICU to identify patients with rehabilitation needs. The shortened version of the ICF-checklist (Part 1a: impairments of body functions and Part 2: activity limitations and participation restrictions) could be useful for the primary screening. On indication, patients with multiple or more severe impairments and functional limitations are assessed more comprehensively. For that purpose, we suggest the use of the valid screening instruments with pre-defined cut-off points used in our post-ICU clinic study. Although, we did not investigate the psychometric properties of the measurement instruments, we found that these instruments were suitable in clinical practice to detect symptoms of PICS in ICU survivors and their close relatives during the first year after discharge from ICU.

Given that more than three-quarter of the patients in our study population were severely or totally dependent in basic ADL in the first week after ICU discharge, rehabilitation treatment should target gaining independence in performing daily activities, such as self-care, eating/ drinking, mobilizing out of bed, and ambulation. Physical therapy should focus on muscle strengthening, maintaining or improving joint mobility, improving walking ability, and improving cardio-pulmonary endurance. Based on the evidence-based recommendations for physical therapy in intensive care units by Sommers et al. (2014),[48] and our study experiences, we suggest the following instruments to assess physical functioning during the entire course of recovery: Medical Research Council sum score (MRC-SS) and hand grip strength dynamometry (Jamar) to assess muscle strength, range of motion (ROM) assessment to assess mobility of joints, the (Modified) Nottingham Sensory Assessment (NSA) for sensory functions, Numeric Rating Scale (NRS) to assess pain, Modified Fatigue Inventory (MFI) for fatigue, and the DE Morton Mobility Index (DEMMI) to assess activities such as transfers, sitting balance, standing, walking, and jumping. In patients who are not able to walk independently, the Functional Ambulation Categories (FAC) should be used. In patients who can walk independently with a walking aid (FAC 3), the two or six Minute Walk-Test (2 MWT/ 6MWT), and 30 seconds chair stand test are valuable measures to assess and monitor changes in walking capacity and set rehabilitation goals.[49,50] Besides the focus on limb muscle function, also respiratory muscles should be addressed during the rehabilitation program. Respiratory muscle dysfunction is observed in 80% of the patients with ICU-AW,[51] but to date little attention has been given to specific interventions to enhance strength and endurance of the respiratory muscles.[52] Inspiratory muscle training (IMT) might be a promising intervention to improve respiratory muscle function in patients with ICU-AW.[11,53]

In order to set individual rehabilitation goals, it is also important to inventory, retrospectively or by proxy, the patient's premorbid (physical, mental, cognitive) functional status. Previous studies showed that health status prior to ICU-admission has a fundamental impact on overall post-ICU quality of life.[54,55] The Katz-ADL[56] has shown to be useful to investigate the functional status prior to ICU-admission.[57] The Katz ADL should also be used during hospital stay, to monitor the recovery process. In comparison with the Barthel Index, which has been developed for stroke patients, the Katz ADL is broader applicable for general hospital patients. Limitations in basic and instrumental (I)ADL should be treated by occupational therapists. Patients with speech and/or swallowing difficulties should be further assessed and treated by speech therapists. Dieticians should be involved for patients at risk for undernourishment. The Malnutrition Universal Screening Tool (MUST) is feasible to identify patients at risk.

The high incidence of cognitive impairments (e.g., problems with concentration, attention, and short memory deficits) within the first week after ICU discharge implies, that cognitive training by an occupational therapist should also be started early to improve the recovery process. The Mini-Mental State Examination (MMSE) is a commonly used screening test in both clinical practice and research to identify cognitive deficits.[58-61]
In patients with signs of mood disturbances, the Hospital Anxiety and Depression Scale (HADS) can be used to identify mental health problems (i.e., anxiety and/or depression). This self-reported questionnaire can be administered by nurses or physical/occupational therapists. Patients with symptoms of anxiety and/or depression (HADS domain score ≥8) should be referred to a psychologist, psychiatrist or social worker for further diagnosis and treatment. Cognitive and psychological sequelae can impact survivors' capacities to re-integrate into traditional family and societal roles as well as actively engaging in their recovery.
Besides targeted psychological methods to address mental health problems (e.g., psycho-educational interventions and self-management strategies), the use of positive suggestion techniques and actively engaging ICU patients in their treatment as early as possible, have been recommended.[62] Additionally, providing information about PICS, using ICU diaries, offering self-directed rehabilitation manuals, and involving family members in the care process will help in accepting and anticipating the long-term course of recovery and reducing the risk of PICS-F. In that context, close relatives should be observed carefully, and be screened for mental health problems (HADS), in order to identify PICS-F and to facilitate support or treatment.

During hospital stay, ICU survivors should be closely monitored by the members of the interdisciplinary rehabilitation team, to evaluate the short-term recovery process and to set individual rehabilitation goals.

Before discharge from the hospital

Before hospital discharge, the clinical assessment (physical, mental, cognitive) should be repeated by the interdisciplinary rehabilitation team, and individual rehabilitation goals should be reviewed and updated in order to decide which treatment should be continued after hospital discharge. Patients with solely motor, cognitive or mental impairments could be referred to primary healthcare professionals. Patients with multiple or complex rehabilitation needs (e.g., patients with ICU-AW in combination with cognitive or mental problems) must be referred to multidisciplinary rehabilitation facilities (e.g., rehabilitation center, nursing home) or outpatient rehabilitation services.

At 1-3 months after hospital discharge

One month after hospital discharge, ICU survivors should be contacted by telephone or e-health applications for screening of remaining or new ICU-related problems in daily functioning, and to evaluate whether the offered care is sufficient or that referral for additional rehabilitation care is needed. Three months after hospital discharge, ICU survivors and their close relatives should be invited for follow-up in a post-ICU clinic for a comprehensive assessment. This timing is in accordance with recommendations from the literature,[25,63] and enables patients to reflect on their recovery process, and to determine any physical, mental of cognitive impairments that were not present or recognized during hospital stay. Also, questions about the stay in ICU should be discussed, and there should be the possibility to visit the ICU for the mental processing of the ICU-experience.

The post-ICU clinic should be run by an ICU-nurse and a senior physical therapist working in the ICU in order to evaluate both the treatment period in the ICU and the ongoing recovery process. In addition to the clinical assessment during hospital stay, at 3 months after ICU discharge, post-traumatic stress, coping style, daily functioning, and quality of life should be assessed. The Trauma Screening Questionnaire (TSQ), Coping Inventory for Stressful Situations (CISS-21), Sickness Impact Profile (SIP68), and Short-Form Health Survey (SF-36) could be used for this purpose. Moreover, employment and participation issues (e.g., return to work, recreation and leisure) should be evaluated. Functional capacity in terms of muscle strength, walking endurance and cognitive functioning should be measured with the same instruments as during hospital stay, in order to evaluate the recovery progress. While the rehabilitation treatment in hospital is primary focused on impairments in body functions and limitations in activities, in the early period after hospital discharge, the rehabilitation care should shift more towards activity limitations and restrictions in participation.

In close relatives mental health, caregiver burden, and issues regarding employment and social life should be addressed to identify symptoms of PICS-F and to facilitate appropriate support. The HADS, TSQ, Caregiver Strain Index (CSI), and further anamnestic questions should be used for this purpose, respectively.

Table 7.1 Proposed screening instruments and treatment for symptoms of PICS/PICS-F within the stepped care rehabilitation pathway for ICU survivors

ICF	Symptoms of PICS	Screening instruments	Treatment
BODY FUNCTION	Muscle strength (ICU-AW) Mobility of joints Sensory functions & pain Speech/swallowing Nutritional state Fatigue Cognitive function Mental health (anxiety/depression) PTSS Coping style	MRC-SS (<48) & Grip strength ROM NSA & NPRS Speech and dysphagia assessment MUST (>2) MFI-20 MMSE (<24) HADS (sub score ≥8) TSQ (≥6) CISS-21	Muscle strengthening exercises (PT) Functional exercises / ROM (PT) Functional exercises (PT / OT) Speech therapy, swallow training (ST) Nutritional/dietary advice (D) Structured day program (interdisciplinary) Cognitive training (OT) Psychoeducational interventions, self-management strategies, positive suggestion techniques (PS) Psychoeducational interventions, self-management strategies, positive suggestion techniques (PS) Coping skills training, problem solving therapy (PS)
ACTIVITY	Walking ability Walking endurance ADL function	FAC / DEMMI 2 or 6MWT / 30s chair stand test Katz-ADL	Balance training, walking exercises (PT) Interval / endurance training (PT) ADL training (OT)
PARTICIPATION	Domestic life / Social life Employment (return to work)	SIP 68 Anamnestic	ADL training (OT) Information/ support about economic self-sufficiency (SW)
QOL	Quality of life	SF-36	Rehabilitation goal setting / care coordination (interdisciplinary/RP)
PICS-F	Mental health (anxiety/depression) PTSS Burden of care Employment / Social life	HADS (sub score ≥8) TSQ (≥6) CSI (>7) Anamnestic	Psychoeducational interventions, self-management strategies (PS) Psychoeducational interventions, self-management strategies (PS) Information, support, social/home care (SW, RP) Information/support (SW)

Abbreviations: CISS-21, Coping Inventory for Stressful Situations; CSI, Caregiver Strain Index; D, dietician; DEMMI, De Morton Mobility Index; FAC, Functional Ambulation Categories; HADS, Hospital Anxiety and Depression Scale; ICU-AW, Intensive Care Unit acquired weakness; MFI-20, Multidimensional Fatigue Inventory; MMSE, Mini-Mental State Examination; MRC-SS, Medical Research Council sum score; MUST, Malnutrition Universal Screening Tool; 2 or 6 MWT, 2 or 6 Minute Walk-Test; NSA, Nottingham Sensory Assessment; NPRS, Numeric Pain Rating Scale; OT, occupational therapist; PS, psychologist; PT, physical therapist; ROM, Range of Motion; RP, rehabilitation physician; SF-36, Short-Form (36) Health Survey; SIP 68, Sickness Impact Profile; ST, speech therapist; SW, social worker; TSQ, Trauma Screening Questionnaire.

At 6-12 months after hospital discharge

Between 6 and 12 months after discharge from ICU, the post-ICU clinic screening should be repeated in order to evaluate the long-term functional recovery process, update rehabilitation goals, and to refer patients for appropriate care, if necessary. Also, patients who were transferred to a rehabilitation facility, and who were not able to visit the post-ICU clinic at 3 months, should be scheduled for a post-ICU screening after they have been discharged home, in order to identify unanticipated physical, mental or cognitive morbidity related to their ICU-stay. This reassessment should be based on the functional assessment at 3 months. In this phase of recovery, rehabilitation treatment should focus on restrictions in participation, such as return to work, and social life (e.g., recreation and leisure). In table 7.1, all symptoms, the proposed screening instruments, and treatment are summarized.

Barriers to an interdisciplinary stepped care rehabilitation pathway

Based on the findings in this thesis, we propose a structured stepped care rehabilitation pathway to improve long-term functional outcome. For the implementation of such a stepped care rehabilitation pathway in the Netherlands, the following issues should be considered:

- There is no evidence available on the cost-effectiveness of stepped care rehabilitation for ICU survivors after discharge from ICU; also, there is a lack of evidence about the appropriate type, timing, intensity, location, and length of post-ICU rehabilitation interventions;
- Post-ICU care is not funded within the existing regular health care system. Barriers for regular funding are that outpatient care is not covered within ICU medicine, and that PICS is not a clinical diagnosis according to the ICD;
- There is a general unawareness of PICS among health care professionals, as a result of which symptoms of PICS are not recognized and patients are not referred and adequately treated;
- There is a lack of formalized handover information to use in in the transition of care from hospital to primary care setting;
- It is difficult to reach patients with very poor functional status: patients who are most in need for rehabilitation after hospital discharge are not able to visit the outpatient clinic, because of physical complaints or because of serious psychological problems (e.g., anxiety or PTSS), and are consequently avoiding hospital contact.

Therefore, strategies should be developed and investigated to facilitate the delivery of such rehabilitation pathway. The principles (with regard to organization and content) that are used in recognized rehabilitation programs for patients after stroke, patients with cancer or patients with Parkinson disease (ParkinsonNet) might be useful for the development

of a rehabilitation pathway for ICU survivors. We expect that a network of medical specialists and allied health professionals in the hospital and primary care sector, specialized in the treatment of patients with PICS, will improve the continuity of care. In the primary care setting, there is limited knowledge of the impact of long-term consequences of PICS on daily functioning and how this should be treated among health care professions. Therefore, collaborating healthcare professionals should be trained in identifying and treating PICS/ PICS-F. The use of computerized questionnaires and telemedicine applications could be a solution to assess the need for rehabilitation in those patients and close relatives with symptoms of PICS, who are not able to visit a post-ICU clinic. Additionally, a refinement of the clinical screening will facilitate the identification of patients at low and high risk of ICU-related physical, mental and cognitive sequelae. With regard to the appropriate content, timing, intensity, location and length of rehabilitation programs for survivors of critical illness, research is still in progress.[43,64-67]

SUGGESTIONS FOR FUTURE RESEARCH

Based on the findings of this thesis, the methodological and clinical considerations, and our recommendations for rehabilitation care, the following suggestions for future research can be made.

Continuing large longitudinal observational studies

A thorough understanding of the course of symptoms associated with PICS and its potential determinants is still needed, in order to identify ICU survivors with highest risk for poor functional recovery and to develop targeted long-term rehabilitation interventions. Studying the various "phenotypes" of recovery trajectories of ICU survivors may enable a better understanding of prognosis and risk and targeted interventions both during the ICU-stay, and later on during the fragile recovery period.[68] Therefore, large observational cohort studies should be undertaken to identify additional risk factors for PICS and determinants for long-term functional outcome. Moreover, comprehensive longitudinal data collection, with standardized measurements of patient characteristics, ICU-treatment and follow-up information regarding the recovery process might enhance the possibility of identifying and predict functional outcome.

Need for intervention studies

More insight in the prevention of ICU-related problems is urgently needed to minimize physical, mental and cognitive problems. In this context, RCT's should be conducted to test the effect of early intensive rehabilitation on the prevention and recovery of PICS.

To successfully implement a structured stepped care rehabilitation pathway, there is a need to further develop and evaluate such approach, according to the new Medical

Research Council guidance.[69] First, the specific rehabilitation interventions addressing the different components of PICS in the early and late phases of recovery should be investigated for their effect on long-term functioning. With this information, evidence-based guidelines could be developed to support the delivery of structured post-ICU rehabilitation programs. Furthermore, the early identification and triage of ICU survivors at risk for poor functional recovery need further investigation. Recommendations about the appropriate timing of triage, the use of screening tools and measurement instruments are urgently needed.
Overall, there is a need to further investigate and improve the stepped care rehabilitation approach across the continuum of care, with regard to organizational aspects (e.g., set up collaborating networks, communication and education), and care environments (outpatient rehabilitation in the hospital versus treatment in primary care). Also, more qualitative studies should be conducted to investigate expectations and experiences of patients and close relatives regarding interdisciplinary rehabilitation care for ICU-patients. This would provide more insight in patient preferences and needs, barriers and facilitators, in order to develop adequate rehabilitation strategies, and could also serve as important starting point for a better organization of care.

Development of a core set for ICU patients

Currently there is no consensus on the most important outcomes and measurement instruments to assess ICU survivors with PICS.[70-72] A standardized core set of outcome measures in this population will facilitate the comparison of results across the growing number of studies in this field. Projects currently registered with the Core Outcome Measures in Effectiveness Trials (COMET) initiative (http://www.comet-initiative.org/) aim to obtain consensus on core outcomes sets (COS) for clinical trials. However, published results are limited.[50,73,74] Further research to obtain consensus on a COS of valid, reliable, and feasible measures is necessary to advance research, in order to improve the outcomes of survivors of critical illness.

GENERAL CONCLUSION

Given the frequent, complex and severe physical, mental and cognitive impairments and functional limitations, ICU survivors are an important target population for inter-disciplinary rehabilitation care. In order to improve the quality of survivorship, coordinated, stepped care, tailored to the patients' abilities and needs is highly warranted throughout the recovery continuum.

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SUMMARY

The advancements in critical care medicine result in a growing population of survivors of critical illness. However, many intensive care unit (ICU) survivors experience physical and cognitive impairments, and mental health problems after discharge from the ICU, known as post-intensive care syndrome (PICS). These impairments are associated with long-lasting restrictions in daily functioning and reduced health-related quality of life (QoL), and can also negatively affect family members (PICS-F). The nature of these restrictions require interdisciplinary rehabilitation care. However, there is no pathway or guideline for the prevention and treatment of the symptoms of PICS. PICS is not related to a specific medical diagnosis, and to date it is difficult to predict at an early stage, which patients are at highest risk for poor functional outcome. The investigation of potential prognostic and explanatory factors of functional recovery, and the use of appropriate screening instruments, may help to identify patients with need for interdisciplinary care. Moreover, a better understanding of the short- and long-term consequences of critical illness for functioning would support the development of targeted rehabilitation care for ICU survivors and their families, in order to improve functional recovery and quality of life. The aim of this thesis is to explore the course and prognosis of functioning in ICU survivors, and to investigate means for early identification of PICS in adult ICU-patients, who were mechanically ventilated for 48 hours or more. The knowledge assembled in this thesis contributes to the development of an optimal care pathway for ICU survivors and their families, in order to improve the quality of survivorship. In **Chapter 1**, the background and rationale underlying the aims of this thesis are introduced.

Chapter 2 describes the results of a cross-sectional study, evaluating the functional status and its potential determinants in 69 ICU survivors, immediately after discharge from the ICU. In this observational study, activities of daily living, muscle strength, sensitivity of the limbs, walking capacity, and cognitive functioning were assessed. In addition, the predictive value of functional status prior to ICU-admission, age, severity of illness, and duration of mechanical ventilation as potential determinants for functional status within the first week after ICU discharge was examined. Within the first week after ICU discharge, the overall functional status was poor (median Barthel Index 6 of 20), with 76% of the patients being severely dependent, 15% moderately dependent, and 9% slightly dependent on other people to perform activities of daily living (ADL). Median grip strength was 50% lower than normative data, and 73% of the patients were not able to walk independently (Functional Ambulation Categories ≤ 3). Besides the physical limitations, 30% of the patients had indications for cognitive impairments (Mini Mental State Examination < 24). The duration of mechanical ventilation was associated with poorer functional status immediately after discharge from the ICU, whereas age, QoL prior to ICU admission, and severity of illness at ICU admission were not. Reduced grip strength and walking ability were identified as explanatory factors for poorer functional status. With regard to the severe impairments and restrictions in performing ADL immediately after ICU discharge, we propose that all

patients ventilated for more than 48 hours in the ICU should be screened for physical, cognitive, or mental sequelae, in order to initiate interdisciplinary rehabilitation care, and goal setting. From the high prevalence of physical impairments after ICU discharge, and the results of previous studies, it is thought that ICU-acquired weakness (ICU-AW) is an important mediator for physical functioning in ICU survivors. The studies presented in **Chapter 3 and 4** investigate the impact of ICU-AW on the post-ICU functional outcome by comparing patients with and without ICU-AW.

Chapter 3 presents the results of a prospective observational study of 156 patients on the independent impact of ICU-AW on post-ICU mortality and physical functioning at 6 months after ICU discharge. ICU-AW was diagnosed as a Medical Research Council (MRC) sum score <48 in awake and attentive patients. Covariates were a priori defined as: age, gender, Charlson co-morbidity index, presence of septic shock, APACHE IV score and maximal SOFA score during admission. Twenty-three patients, of whom 20 with ICU-AW, died in the ICU, and another 25 patients (17 with ICU-AW) died during the 6 months follow-up after ICU discharge. Physical functioning was assessed in 96 survivors (39 patients with ICU-AW) using the Short-Form Health Survey (SF-36) physical functioning (PF) domain. ICU-AW was independently associated with higher post-ICU mortality and with clinically relevant poorer physical functioning at 6 months after ICU discharge. Also, patients with ICU-AW were less likely to be discharged home (33%) than patients without ICU-AW (75%). Based on these findings, patients with ICU-AW are to be considered a target population for rehabilitation care.

Chapter 4 describes the results of a longitudinal cohort study, comparing the functional health status with regard to physical, psychological and social functioning of 60 patients with and 73 patients without ICU-AW. Furthermore, predictors and explanatory factors of short- and long-term functional status were identified. Functional health status was assessed at 3, 6 and 12 months after ICU discharge, using the Sickness Impact Profile 68 (SIP68). ICU-AW was an independent predictor for impaired functional health status at 3 months after ICU discharge. Sixty-three percent of the patients with ICU-AW had severe restrictions in performing daily life activities, compared to 30% of the patients without ICU-AW. Also 1 year after ICU discharge, physical functioning was significantly more impaired in patients with ICU-AW compared to critically ill patients without ICU-AW. Patient-reported psychological and social functioning did not differ between patients with and without ICU-AW, during the first year after discharge. Social functioning remained severely restricted in the majority of ICU survivors, independent from ICU-AW. A structured interdisciplinary rehabilitation program may help ICU survivors to improve functional independence and participation in social life. Besides the wide range of long-lasting restrictions in daily functioning, surviving critical illness is also associated with reduced quality of life (QoL). In clinical practice, ICU survivors with similar degrees of functional disabilities showed considerable individual differences in QoL after discharge from the hospital.

We hypothesized that personal coping style might be associated with QoL, as found in various patient groups with chronic disease or traumatic injury.

Chapter 5 focuses on coping styles and quality of life (QoL) in ICU survivors. In a cross-sectional multicenter study, coping styles and its association with QoL were explored in 104 patients, 3 months after ICU discharge. Coping style (e.g., task-oriented coping, emotion-oriented coping, and avoidance coping) was assessed using the Coping Inventory for Stressful Situations (CISS-21), and QoL was assessed using the Physical Component Score (PCS) and Mental Component Score (MCS) derived from the 36-item Short Form Health Survey (SF-36). Emotion-oriented coping style was independently associated with reduced mental health (i.e., SF-36 MCS), but not with physical functioning (i.e., SF-36 PCS). ICU survivors with pre-ference for emotion-oriented coping style may be most in need of targeted psychoeducational interventions, such as coping skills training and problem solving therapy, in order to facilitate recovery. However, additional research is needed in order to determine the precise role that coping style plays in the long-term recovery of ICU survivors, and to consider how these may be adjusted. To reduce long-term physical, cognitive, and mental health problems among ICU survivors, post-Intensive Care Units (ICU) clinics have been advocated, but a format for optimal structure, timing, and care content has not yet been established.

Chapter 6 describes the implementation and evaluation of two post-ICU clinics in an academic and a general hospital. In a prospective multicentre study, 115 ICU-patients, who were mechanically ventilated ≥ 48 hours and discharged to their homes, were included. The feasibility of the post-ICU clinics was evaluated as 1) the number of eligible ICU survivors and the proportion that attended the clinic, 2) the prevalence of ICU-related abnormalities that required referral for further treatment, and 3) patient satisfaction. From the eligible patients, 49% (university hospital) and 67% (general hospital) visited the outpatient post-ICU clinic. The majority of all screened patients had functional restrictions, and 68% required referral for further diagnosis and treatment. The use of validated screening instruments with pre-defined cut-off points enables the identification of PICS in former ICU patients and their family members. In addition, providing information about PICS/PICS-F is very much appreciated by patients and family members. In conclusion, post-ICU clinics support the continuity of (rehabilitation) care after hospital discharge.

Chapter 7 comprises the general discussion. In this chapter, the main findings, methodological considerations, and clinical implications are reflected upon. Finally, recommendations for rehabilitation care as well as for future research are provided. This thesis shows that ICU-stay with mechanical ventilation ≥ 48 hours has an important impact on daily functioning in ICU survivors. During the first year after critical illness, impairments in body functions, limitations in activities and restrictions in participation are highly prevalent in a substantial proportion of ICU survivors, which in turn affects the quality of life in family members. Additionally, a majority of ICU survivors do not receive adequate

rehabilitation care after discharge from the hospital. These findings imply that ICU survivors and their next relatives should be closely monitored after discharge from the ICU and after hospital discharge, to early identify symptoms of PICS and to initiate appropriate interdisciplinary rehabilitation treatment. Therefore, we propose a structured, interdisciplinary stepped care rehabilitation pathway, consisting of clinical assessments with validated screening instruments, individualized interdisciplinary rehabilitation interventions, and adequate handover in the transition of care. For the development of such a stepped-care rehabilitation program, randomized clinical trials are needed to investigate the cost-effectiveness. Also, the effectiveness of specific interventions that focus on the various symptoms of PICS should be further investigated. In addition, early identification and triage of ICU survivors at low and high risk for poor functional recovery needs further investigations.

SAMENVATTING

De vooruitgang in de intensive care (IC) geneeskunde resulteert in een groeiende populatie van IC-patiënten die een ernstige ziekte overleeft. Echter, veel IC-overlevenden ervaren fysieke, cognitieve en psychische problemen na ontslag van de IC, ook wel het post-intensive care syndroom (PICS) genoemd. Deze IC-gerelateerde restverschijnselen leiden tot langdurige beperkingen in het dagelijks functioneren en verminderde kwaliteit van leven (KvL) en kunnen ook de KvL van familieleden negatief beïnvloeden (PICS-F). De aard van deze beperkingen vragen om interdisciplinaire revalidatiebehandeling. Echter, er bestaat geen zorgtraject of richtlijn voor de preventie en behandeling van de symptomen van PICS. PICS is niet gerelateerd aan een specifieke medische diagnose en tot op heden is het moeilijk om patiënten met een verhoogd risico op slecht functioneel herstel vroeg te identificeren. Om een geschikte triage te ontwikkelen, ter beoordeling of patiënten interdisciplinaire revalidatiebehandeling nodig hebben, is nader wetenschappelijk onderzoek nodig naar prognostische factoren voor functioneel herstel en naar screeningsinstrumenten. Bovendien is meer inzicht in de korte en lange termijn gevolgen van kritieke ziekte op het functioneren nodig om een gericht revalidatietraject voor IC-overlevenden en hun families te ontwikkelen. Het doel van dit proefschrift is om het verloop en de prognose van het functioneren van IC-overlevenden, die gedurende 48 uur of langer beademd zijn geweest, te verkennen en te onderzoeken op welke wijze symptomen van PICS vroegtijdig kunnen worden opgespoord. De kennis die in dit proefschrift is verzameld draagt bij aan de ontwikkeling van een optimaal revalidatietraject voor IC-overlevenden en hun familieleden, teneinde de kwaliteit van (over)leven te verbeteren. In **Hoofdstuk 1** worden de achtergrond en doestellingen die aan dit proefschrift ten grondslag liggen geïntroduceerd.

Hoofdstuk 2 beschrijft de resultaten van een dwarsdoorsnede-onderzoek, waarin de functionele status en de mogelijke determinanten voor functionele status direct na ontslag van de IC werden onderzocht. In deze observationele studie werden activiteiten van het dagelijks leven, spierkracht, sensibiliteit, loopcapaciteit en cognitief functioneren in 69 IC-patiënten geëvalueerd. Daarnaast werd de voorspellende waarde van de functionele status voorafgaand aan de IC-opname, leeftijd, ernst van de ziekte bij opname en beademingsduur als mogelijke determinanten voor functionele status binnen de eerste week na IC-ontslag onderzocht. In de eerste week na IC-ontslag was de algehele functionele status slecht (mediane Barthel Index score 6 van 20). Van de onderzochte patiënten was 76% in grote mate afhankelijk, 15% matig afhankelijk en 9% enigszins afhankelijk van de hulp van anderen voor het uitvoeren van activiteiten van het dagelijkse leven (ADL). De mediane knijpkracht was 50% lager ten opzichte van normgegevens en 73% van de patiënten was niet in staat om zelfstandig te lopen (Functional Ambulation Categories ≤ 3). Naast deze fysieke beperkingen had 30% van de patiënten aanwijzingen voor cognitieve stoornissen (Mini Mental State Examination <24). Een langere beademingsduur hing samen met een slechtere functionele status direct na ontslag van de IC, terwijl leeftijd, kwaliteit van leven vóór IC-

opname en ernst van de ziekte bij IC-opname niet geassocieerd waren. Verminderde knijpkracht en loopvermogen werden geïdentificeerd als verklarende factoren voor een slechtere functionele status. Gezien de ernstige functionele beperkingen in het uitvoeren van ADL onmiddellijk na IC-ontslag, adviseren wij om alle patiënten die langer dan 48 uur op de IC beademd zijn geweest te screenen op fysieke, cognitieve en mentale problemen, om zo vroeg mogelijk interdisciplinaire revalidatiebehandeling te starten. Op basis van de hoge prevalentie van lichamelijke beperkingen na IC-ontslag en de resultaten van eerdere studies, wordt aangenomen dat op de IC verworven spierzwakte (ICU-acquired weakness [ICU-AW]) een belangrijke bepalende factor is voor het fysiek functioneren op de lange termijn. In de studies in **Hoofdstuk 3 en 4** wordt de invloed van ICU-AW op de functionele status in IC-overlevenden onderzocht door patiënten met en zonder ICU-AW te vergelijken.

Hoofdstuk 3 beschrijft de resultaten van een prospectieve observationele studie van 156 patiënten naar de invloed van ICU-AW op post-IC sterfte en fysiek functioneren, 6 maanden na IC-ontslag. ICU-AW werd bij wakkere en instrueerbare patiënten vastgesteld aan de hand van manuele spierkrachtmeting volgens de Medical Research Council (MRC) som score van <48. Potentiele verstorende factoren werden a priori gedefinieerd als: leeftijd, geslacht, co-morbiditeit (Charlson co-morbiditeit index), het optreden van septische shock en ernst van de ziekte (APACHE IV score en SOFA score) bij IC-opname. Drieëntwintig patiënten (20 met ICU-AW) overleden op de IC en nog eens 25 patiënten (17 met ICU-AW) overleden binnen 6 maanden na IC-ontslag. Het fysiek functioneren werd in 96 IC-overlevenden gemeten (39 patiënten met ICU-AW) met de Short-Form Health Survey (SF-36), domein fysiek functioneren (PF). ICU-AW was onafhankelijk geassocieerd met een hogere post-IC sterfte en met een klinisch relevant slechter fysiek functioneren, 6 maanden na IC-ontslag. Ook werden er meer patiënten met ICU-AW naar een revalidatie-instelling ontslagen en konden patiënten zonder ICU-AW vaker direct naar huis worden ontslagen vanuit het ziekenhuis. Op basis van deze bevindingen dienen patiënten met ICU-AW te worden beschouwd als belangrijke doelgroep voor revalidatiebehandeling.

Hoofdstuk 4 beschrijft de resultaten van een longitudinale cohort studie, waarin de functionele status met betrekking tot het fysieke, psychische en sociale functioneren van 60 patiënten met en 73 patiënten zonder ICU-AW werd vergeleken. Daarnaast werden determinanten voor de functionele status op korte en lange termijn onderzocht. De functionele status werd op 3, 6 en 12 maanden na IC-ontslag gemeten met de Sickness Impact Profile 68 (SIP68). ICU-AW bleek een onafhankelijke voorspeller voor verminderde functionele status op 3 maanden na IC-ontslag. Drie maanden na IC-ontslag waren 63% van de patiënten met ICU-AW ernstig beperkt in het uitvoeren van dagelijkse activiteiten (ADL) in vergelijking tot 30% van de patiënten zonder ICU-AW. Ook 1 jaar na IC-ontslag waren patiënten met ICU-AW meer beperkt in hun fysiek functioneren dan patiënten zonder ICU-AW. Het psychisch en sociaal functioneren was vergelijkbaar bij patiënten met

en zonder ICU-AW op de verschillende meetmomenten. Onafhankelijk van ICU-AW was het sociaal functioneren in het merendeel van de IC-overlevenden ernstig beperkt gedurende het eerste jaar na IC-ontslag. Een gestructureerd interdisciplinair revalidatietraject zou IC-overlevenden kunnen helpen om hun functioneel herstel te verbeteren en de participatie in het sociale leven te optimaliseren. Naast het brede scala aan langdurige beperkingen in het dagelijks functioneren wordt het overleven van een ernstige ziekte ook in verband gebracht met een verminderde kwaliteit van leven (KvL). In de klinische praktijk zien we dat IC-patiënten met vergelijkbare functionele beperkingen na ontslag uit het ziekenhuis aanzienlijke individuele verschillen vertonen in KvL. Onze hypothese was dat de persoonlijke coping stijl mogelijk verband houdt met KvL, zoals dit ook in andere patiënten populaties met chronische ziekte of traumatisch letsel is aangetoond.

Hoofdstuk 5 richt zich op coping stijlen en kwaliteit van leven (KvL) in IC-overlevenden. In een cross-sectionele multicenter studie van 104 patiënten werden 3 maanden na IC-ontslag de coping stijlen en het verband met KvL onderzocht. Coping stijl (taakgerichte-, emotiegerichte- en vermijdingsgerichte coping) werd in kaart gebracht met de Coping Inventory for Stressful Situations (CISS-21) en kwaliteit van leven werd gemeten met de Physical Component Score (PCS) en Mental Component Score (MCS) van de 36-item Short Form Health Survey (SF-36). Een emotiegerichte coping stijl was onafhankelijk geassocieerd met een verminderde mentale gezondheid (SF-36 MCS), maar niet met fysiek functioneren (SF-36 PCS). Dit impliceert dat IC-overlevenden met een overwegend emotiegerichte coping stijl baat zouden kunnen hebben bij gerichte psycho-educatieve interventies, zoals probleemoplossende therapie of cognitieve gedragstherapie. Aanvullend onderzoek is nodig om de specifieke rol van coping stijl op het lange termijn herstel van IC-overlevenden te onderzoeken en na te gaan hoe deze kan worden beïnvloed. Om de langdurige fysieke, cognitieve en mentale gezondheidsproblemen bij IC-overlevenden te monitoren en te verminderen, worden IC-nazorg poli's aanbevolen. De optimale opzet, organisatievorm, timing en inhoud zijn nog niet vastgesteld.

Hoofdstuk 6 beschrijft de implementatie en evaluatie van twee IC-nazorg poli's in een academisch en een algemeen ziekenhuis. In een prospectieve multicenter studie werden 115 IC-patiënten geïncludeerd, die ≥ 48 uur op de IC waren beademd en na hun ziekenhuisverblijf met ontslag naar huis gingen. De haalbaarheid van de IC-nazorg poli werd onderzocht aan de hand van 1) het aantal geïncludeerde IC-patiënten die de nazorg poli bezochten, 2) de prevalentie van IC-gerelateerde problemen met noodzaak voor aanvullende behandeling, en 3) de patiënten tevredenheid. 49% (academisch ziekenhuis), respectievelijk 67% (algemeen ziekenhuis) van de patiënten die in aanmerking kwamen voor IC-nazorg bezochten de poli. Het merendeel van de patiënten had functionele beperkingen en voor 68% van de patiënten was verwijzing nodig voor aanvullende diagnostiek en behandeling. Het gebruik van gevalideerde screeningsinstrumenten met afkapwaardes maakt de identificatie van symptomen van PICS in ex IC-patiënten en hun

familieleden mogelijk. Daarnaast werd de verstrekte informatie over PICS/PICS-F zeer gewaardeerd door patiënten en familieleden. Op deze wijze ondersteunen IC-nazorg poli's de continuïteit van de (revalidatie) behandeling na ontslag uit het ziekenhuis.

Hoofdstuk 7 bevat de algemene discussie van het proefschrift. In dit hoofdstuk worden de belangrijkste bevindingen, methodologische tekortkomingen en klinische implicaties besproken. Tenslotte worden aanbevelingen voor een gestructureerd revalidatietraject en voor toekomstig onderzoek gegeven. Dit proefschrift toont aan dat een IC-opname met een beademingsduur van 48 uur of langer een grote invloed heeft op het dagelijks functioneren van IC-overlevenden. Gedurende het eerste jaar na kritieke ziekte worden in een aanzienlijk deel van de IC-overlevenden stoornissen in lichaamsfuncties, beperkingen in activiteiten en restricties in participatie gevonden, die ook de kwaliteit van leven van familieleden beïnvloeden. De meerderheid van de IC-overlevenden ontvangt onvoldoende revalidatiebehandeling na ontslag uit het ziekenhuis. Deze bevindingen impliceren dat IC-overlevenden en hun familieleden nauwlettend gevolgd moeten worden na ontslag van de IC en na ontslag uit het ziekenhuis om IC-gerelateerde symptomen vroeg te identificeren en passende interdisciplinaire revalidatiebehandeling te starten. Daarom adviseren wij een gestructureerd, interdisciplinair stepped-care revalidatietraject, bestaande uit een klinische screening met gevalideerde meetinstrumenten, geïndividualiseerde interdisciplinaire revalidatiebehandeling en adequate overdracht bij alle transities van zorg. Voor de verdere ontwikkeling van een dergelijk stepped-care revalidatietraject zijn gerandomiseerde klinische studies nodig om de (kosten-) effectiviteit te onderzoeken. Ook de effectiviteit van specifieke interventies, die gericht zijn op de verschillende symptomen van PICS, moeten verder worden onderzocht. Daarnaast is het nodig om de vroegtijdige identificatie en triage van IC-overlevenden met een hoog risico op verminderd functioneel herstel verder te onderzoeken.

CURRICULUM VITAE

PORTFOLIO

Daniela Dettling-Ihnenfeldt was born on March 17th 1970 in West-Berlin, Germany. In 1989 she graduated from secondary school at the Kant-Gymnasium in Berlin. Between 1989 and 1993 she studied classical and contemporary dance and dance pedagogy at the Frankfurt University of Music and Performing Arts in Frankfurt am Main. In 1993 she moved to Amsterdam, the Netherlands, to work as a dancer at the International Dance Theatre. Between 1995 and 1999 Daniela studied physiotherapy at the Amsterdam University of Applied Sciences. Since 1999 she works as a clinical physiotherapist at the department of Rehabilitation Medicine of the Academic Medical Center in Amsterdam. In the past 17 years she has specialized in the treatment of patients following major abdominal surgery and intensive care patients. Besides her work as a physiotherapist she also participated in several research projects of the department of Rehabilitation. In 2006 she received her Master degree of Evidence Based Practice (EBP) of the University of Amsterdam. From that time on, Daniela coordinated EBP projects for allied health professionals at the department of Rehabilitation. From March 2011 she carried out her PhD research 'The Post-Intensive Care Syndrome (PICS): impact of ICU-stay on functioning and implications for rehabilitation care', which was supervised by prof. dr. Frans Nollet and dr. Marike van der Schaaf and resulted in the current doctoral thesis. Daniela lives in Amersfoort with Dieter Dettling, their sons Dorian (2004) and David (2006) and daughter Dea (2009).

PhD student:	Daniela Susanne Dettling-Ihnenfeldt
PhD period:	March 2011 - February 2017
PhD supervisor:	Prof. dr. F. Nollet

1. PhD Training

	Year	Workload (Hours/ECTS)
Courses		
Clinical Data Management. AMC Graduate School	2011	7.5/0.3
Basic course in legislation and organization for clinical researchers (BROK). AMC Graduate School	2011	31/1.1
Reference Manager. AMC Graduate School	2012	2.5/0.1
Scientific Writing in English for Publication. AMC Graduate School	2012	42/1.5
Oral presentation in English. AMC Graduate School	2012	24/0.9
Re-registration BROK. VU University Medical Center, Amsterdam	2016	8/0.3
Presentations		
Research meetings, AMC		
ICU-aftercare. Research proposal (oral)	2010	14/0.5
ICU-aftercare. Progress report (oral)	2011	14/0.5
ICU-aftercare. Progress report, department of Intensive Care Medicine (Oral)	2012	14/0.5
ICU-aftercare. Results report (oral)	2012	14/0.5
Impact of ICU-AW on physical functioning and mortality. Research proposal (oral)	2011	14/0.5
Impact of ICU-AW on physical functioning and mortality. Progress report (oral)	2012	14/0.5
Impact of ICU-AW on functional recovery. Progress report (oral)	2014	14/0.5
Coping strategies and quality of life in patients after critical illness. Progress report (oral)	2014	14/0.5
Coping strategies and quality of life in patients after critical illness. Results report (oral)	2015	14/0.5
Impact of ICU-AW on functional recovery. Results report (oral)	2015	14/0.5

Other meetings

Physiotherapy and Intensive care. Work visit at the department of Physical Medicine and Rehabilitation, UZ Leuven, Belgium (oral)	2012	14/0.5
(Over)leven na Intensive care. Meeting department of Rehabilitation (oral)	2012	14/0.5
Evaluatie 1 jaar IC-nazorg. Team presentation (oral)	2011	14/0.5
Impact of ICU-AW on physical functioning. Team presentation (oral)	2011	14/0.5
Herstel na IC-opname: IC-nazorg op de afdeling revalidatie. Team presentation (oral)	2012	14/0.5
Rehabilitation after Intensive Care. Work visit of the chairman from the Dutch association for physiotherapy at the department of Rehabilitation (oral)	2013	14/0.5

(Inter)national conferences

Workshop ICU-aftercare / clinimetrics. Congress of the Dutch association of physiotherapists working at hospitals, Ede, The Netherlands (oral)	2011	14/0.5
ICU-after care: feasibility of post-ICU clinics and presentation of a rehabilitation manual. International meeting of physical therapists working on ICU's, World Confederation for Physical Therapy, Amsterdam, The Netherlands (oral)	2011	14/0.5
Specialized aftercare for Intensive Care patients. Annual congress of the Dutch association for physiotherapy, Amsterdam, The Netherlands (oral)	2012	14/0.5
Pre-operative inspiratory muscle training in patients undergoing esophagectomy. Annual congress of the Dutch association for physiotherapy, Amsterdam, The Netherlands (oral)	2012	14/0.5
IC-nazorg – de familie doet ertoe. Family centred care ICU – Erasmus MC, Rotterdam, The Netherlands (oral)	2013	14/0.5
Feasibility of post-intensive care clinics. AMC-conference 'IC in beweging', AMC, Amsterdam, The Netherlands (oral)	2013	14/0.5
I*mpact of ICU-acquired weakness on functional outcome*. 2nd European conference on weaning & rehabilitation in critical ill patients, Athens, Greece (poster and oral)	2014	14/0.5
Impact of ICU-acquired weakness on functional outcome. Congress of the association of rehabilitation specialists (VRA), Amsterdam, The Netherlands (poster)	2015	14/0.5

Feasibility of post-Intensive care unit clinics. 9th World Congress of the International Society of Physical and Rehabilitation Medicine, Berlin, Germany (poster)	2015	14/0.5
Coping and quality of life in ICU survivors. 3d European conference on weaning & rehabilitation in critical ill patients, Copenhagen, Denmark (poster and oral)	2015	14/0.5
Van Intensive care tot Afte care: continuïteit van zorg binnen de Fysiotherapie. Congress of the Dutch association of physiotherapists working at hospitals, Hilversum, The Netherlands (oral)	2016	14/0.5

Attended (Inter)national conferences

16th International congress of the World Confederation for Physical Therapy, June 21-22, Amsterdam, The Netherlands	2011	16/0.6
Round table conference ICU-aftercare, department of rehabilitation / NICE/ NVIC, September 12, AMC, Amsterdam, The Netherlands	2012	4/0.1
Annual congress of the Netherlands physiotherapy society, November 2, Amsterdam, The Netherlands	2012	8/0.3
Conference 'Family centred care ICU', April 11, Erasmus MC, Rotterdam, The Netherlands	2013	8/0.3
AMC-conference 'IC in beweging', September 5, AMC, Amsterdam, The Netherlands (organization & attendance)	2013	48/1.9
European conference on weaning & rehabilitation in critical ill patients, November 2-3, Vienna	2013	16/0.6
2nd European conference on weaning & rehabilitation in critical ill patients, November 6-8, Athens, Greece	2014	24/0.9
9th World Congress of the International Society of Physical and Rehabilitation Medicine, June 19-23, Berlin, Germany	2015	40/1.6
3d European conference on weaning & rehabilitation in critical ill patients, November 6-7, Copenhagen, Denmark	2015	16/0.6
4th European conference on weaning & rehabilitation in critical ill patients, November 12-13, Hamburg, Germany	2016	16/0.6

2. Teaching

	Year	Workload (Hours/ECTS)
Supervising students physiotherapy of the Amsterdam University of Applied Sciences. Project: data importation follow-up 'Inspiratory muscle training in patients undergoing oesophagectomy'	2013	8/0.3
Supervising students physiotherapy of the Amsterdam University of Applied Sciences. Project: data-analysis clinical measurements post-ICU clinic	2013	10/0.4

3. Publications

Peer reviewed

Dettling-Ihnenfeldt DS, Wieske L, Horn J, Nollet F, van der Schaaf M: Functional recovery in patients with and without intensive care unit acquired weakness. Am J Phys Med Rehabil 2016; Epub ahead of print.

Dettling-Ihnenfeldt DS, de Graaff AE, Beelen A, Nollet F, van der Schaaf M. Coping style and quality of life in Dutch intensive care unit survivors. Rehabil Psychol 2016;61:165-72.

van den Born-van Zanten SA, Dongelmans DA, **Dettling-Ihnenfeldt D**, Vink R, van der Schaaf M. Caregiver strain and posttraumatic stress symptoms of informal caregivers of intensive care unit survivors. Rehabil Psychol 2016;61:173-8

Wieske L, **Dettling-Ihnenfeldt DS**, Verhamme C, Nollet F, van Schaik IN, Schultz MJ, Horn J, van der Schaaf M. Impact of ICU-acquired weakness on post-ICU physical functioning: a follow-up study. Critical Care 2015;19:196.

Juultje Sommers, Raoul HH Engelbert, **Daniela Dettling-Ihnenfeldt**, Rik Gosselink, Peter E Spronk, Frans Nollet and Marike van der Schaaf. Physiotherapy in the intensive care unit: an evidence-based, expert driven, practical statement and rehabilitation recommendations. Clin Rehabil 2015;29:1051-63.

Wieske L, Verhamme C, Witteveen E, Bouwes A, **Dettling-Ihnenfeldt DS**, van der Schaaf M, Schultz MJ, van Schaik IN, Horn J. Feasibility and diagnostic accuracy of early electrophysiological recordings for ICU-acquired weakness: an observational cohort study. Neurocrit Care 2015;22:385-94.

Dettling-Ihnenfeldt DS, De Graaff AE, Nollet F, Van Der Schaaf M. Feasibility of Post-Intensive Care Unit Clinics: an observational cohort study of two different approaches. Minerva Anestesiol 2015;81:865-75.

Wieske L, Witteveen E, Verhamme C, **Dettling-Ihnenfeldt DS**, van der Schaaf M, Schultz MJ, van Schaik IN, Horn J. Early prediction of intensive care unit-acquired weakness using easily available parameters: a prospective observational study. PLoS One 2014;9:e111259.

Dettling DS, van der Schaaf M, Blom RL, Nollet F, Busch OR, van Berge Henegouwen MI. Feasibility and effectiveness of pre-operative inspiratory muscle training in patients undergoing oesophagectomy: a pilot study. Physiother Res Int 2013;18:16-26.

van der Schaaf M, **Dettling DS**, Beelen A, Lucas C, Dongelmans DA, Nollet F. Poor functional status immediately after discharge from an intensive care unit. Disabil Rehabil 2008;30:1812-8.

Meijer R, van Limbeek J, Kriek B, **Ihnenfeldt D**, Vermeulen M, de Haan R. Prognostic social factors in the subacute phase after a stroke for the discharge destination from the hospital stroke-unit. A systematic review of the literature. Disabil Rehabil 2004;26:191-7.

Meijer R, **Ihnenfeldt D**, Vermeulen M, De Haan R, Van Limbeek J. The use of a modified Delphi procedure for the determination of 26 prognostic factors in the sub-acute stage of stroke. Int J Rehabil Res 2003;26:265-70.

Meijer R, **Ihnenfeldt DS**, van Limbeek J, Vermeulen M, de Haan RJ. Prognostic factors in the subacute phase after stroke for the future residence after six months to one year. A systematic review of the literature. Clin Rehabil 2003;17:512-20.

Meijer R, **Ihnenfeldt DS**, de Groot IJ, van Limbeek J, Vermeulen M, de Haan RJ. Prognostic factors for ambulation and activities of daily living in the subacute phase after stroke. A systematic review of the literature. Clin Rehabil 2003;17:119-29.

Other

J. Sommers, **D. Dettling**, M. van der Schaaf, R. Tepaske en A.C.J.M. de Pont. Hoofdstuk 39: Mobiliseren van intensive care patiënten. In: A.C.J.M. de Pont, M.J. Schultz, F. Paulus, M.B. Vroom (red.) Protocollen voor de intensive care. Utrecht, Nederland: De Tijdstroom, 2015.

D. Dettling-Ihnenfeldt, M. van der Schaaf. Revalidatieboek voor Intensive Care patiënten. Amsterdam, Nederland: Afdeling Revalidatie, AMC, 2014. Available at: https://www.amc.nl/web/Research/Overview/Departments/Rehabilitation-Dutch/Rehabilitation-Dutch/Department.htm

CONTRIBUTION OF AUTHORS

Chapter 2: van der Schaaf M, Dettling DS, Beelen A, Lucas C, Dongelmans DA, Nollet F. Poor functional status immediately after discharge from an intensive care unit. Disabil Rehabil 2008;30:1812-8. MvS was responsible for the conceptualization and design of the study. MvS and DSD-I were responsible for the conduct of the study, the statistical analysis, interpretation of the data, drafting and revision of the manuscript. AB contributed to the interpretation of the data, and the revision of the manuscript. CL, DAD and FN contributed to the revision of the manuscript.

Chapter 3: Wieske L, Dettling-Ihnenfeldt DS, Verhamme C, Nollet F, van Schaik IN, Schultz MJ, Horn J, van der Schaaf M. Impact of ICU-acquired weakness on post-ICU physical functioning: a follow-up study. Critical Care 2015;19:196. LW, DSD-I, JH and MvdS were responsible for the conceptualization and design of the study. LW and DSD-I were responsible for the conduct of the study, the statistical analysis, interpretation of the data, drafting and revision of the manuscript. JH and MvdS contributed to the interpretation of the data, drafting and revision of the manuscript. CV, FN, INvS, and MJS contributed to the conceptualization of the study, and the revision of the manuscript.

Chapter 4: Dettling-Ihnenfeldt DS, Wieske L, Horn J, Nollet F, van der Schaaf M: Functional recovery in patients with and without intensive care unit acquired weakness. Am J Phys Med Rehabil 2016; epub ahead of print. DSD-I, LW, JH and MvdS were responsible for the conceptualization and design of the study. DSD-I and LW were responsible for the conduct of the study, the statistical analysis, and interpretation of the data. DSD-I was responsible for drafting and revision of the manuscript. LW, JH, FN and MvdS contributed to the revision of the manuscript.

Chapter 5: Dettling-Ihnenfeldt DS, de Graaff AE, Beelen A, Nollet F, van der Schaaf M. Coping style and quality of life in Dutch intensive care unit survivors. Rehabil Psychol 2016;61:165-72. DSD-I and MvdS were responsible for the conceptualization of the study. DSD-I was responsible for the conduct of the study, the statistical analysis, interpretation of the data, drafting and revision of the manuscript. AEdG contributed to the collection of the data, and revision of the manuscript. AB contributed to the interpretation of the data, and revision of the manuscript. FN contributed to the revision of the manuscript. MvdS contributed to the interpretation of the data, and the revision of the manuscript.

Chapter 6: Dettling-Ihnenfeldt DS, De Graaff AE, Nollet F, Van Der Schaaf M. Feasibility of Post-Intensive Care Unit Clinics: an observational cohort study of two different approaches. Minerva Anestesiol 2015;81:865-75. DSD-I, AEdG, FN and MvdS were responsible for the conceptualization and design of the study. DSD-I, AEdG and MvdS were responsible for the conduct of the study. DSD-I was responsible for the statistical analysis, interpretation of the data, drafting and revision of the manuscript. AEdG, FN and MvdS contributed to the revision of the manuscript.

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