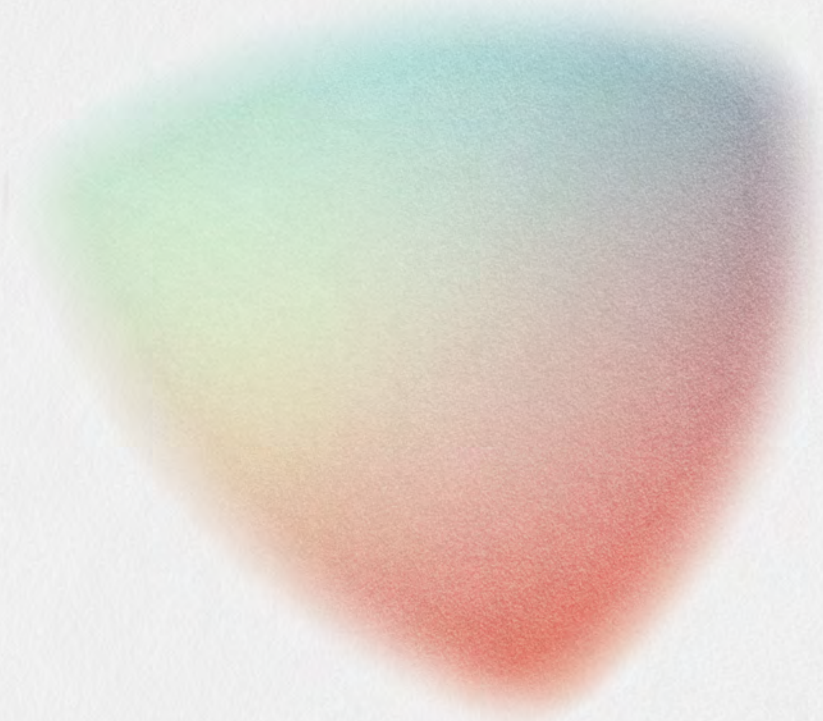
THE IMPACT OF CRITICAL ILLNESS

Long-term physical, mental and cognitive health problems in ICU survivors



Wytske Geense

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Long-term physical, mental and cognitive health problems in ICU survivors

Wytske Geense

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CHAPTER 1

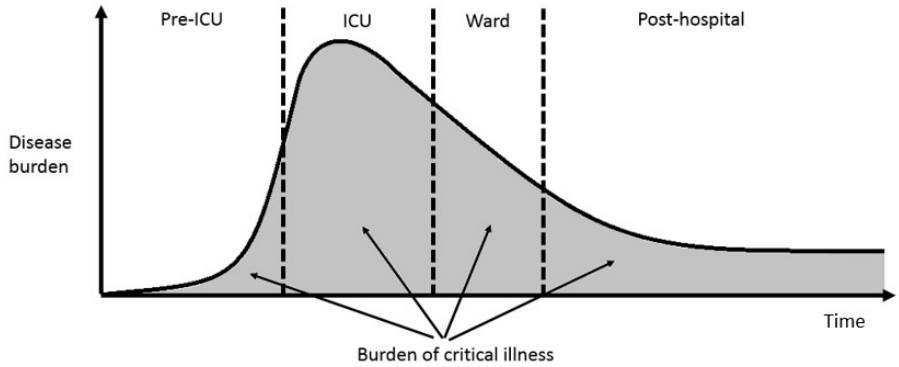
GENERAL INTRODUCTION AND THESIS OUTLINE

Shifting the paradigm from short-term mortality to long-term ICU outcomes
Patients are admitted to the intensive care unit (ICU) when they have, or are at risk of developing, acute life-threatening organ dysfunction including sepsis, respiratory insufficiency, heart failure, major trauma or high-risk surgery (1). The traditional goal of intensive care has been to decrease short-term mortality (2). Due to advances in science and practice, survival rates have substantially improved over the last decades (3, 4). In the Netherlands alone, 80.000-85.000 patients are annually admitted to an ICU and nowadays 85%-90% survive their admission (5). With this increasing number of ICU survivors, the personal and societal consequences of critical illness are of growing importance (6, 7). The first studies on long-term outcomes appeared two decades ago (8, 9), and although it became evident that many ICU patients did not fully recover, it remained unclear how critical illness and the intensive care treatment affects their long-term health and well-being (2, 6). This changing focus on outcomes, from short-term mortality towards the long-term consequences of critical illness and quality of survivorship, led to a paradigm shift in critical care medicine (10).

Post-intensive care syndrome (PICS)
In the following years, more studies revealed how remarkably common and devastating the long-term consequences of critical illness can be (4): from months to even years after their ICU discharge patients suffer from physical, mental and cognitive health problems (4, 11), and many will not return to their premorbid health status (Figure 1) (12). A common physical problem seen in ICU survivors is ICU acquired weakness, originating from critical illness polyneuropathy, myopathy and muscle atrophy. Patients can lose up to 15-20% of their total muscle mass by the end of the first week of ICU admission (13). Other frequently reported physical problems are pain, dyspnoea, and fatigue (13, 14).

In addition, many patients perceive their ICU admission as stressful, and mental problems can manifest as symptoms of anxiety (15), depression (16) and posttraumatic stress disorder (PTSD) (13, 17). Also nightmares, insomnia and hallucinations are reported (18). Furthermore, many patients suffer from cognitive impairments in memory, attention, executive function, and mental processing speed (3, 19).

Figure 1. The episode of critical illness.



The figure shows that an episode of critical illness is not just the period of time a patient spends in the ICU, but captures the period from the onset of the acute deterioration to the moment a patient's risk of late sequelae has returned to the baseline risk of a similar patients who has not incurred the acute critical illness (Adapted from Angus, et al, 2002 (2)).

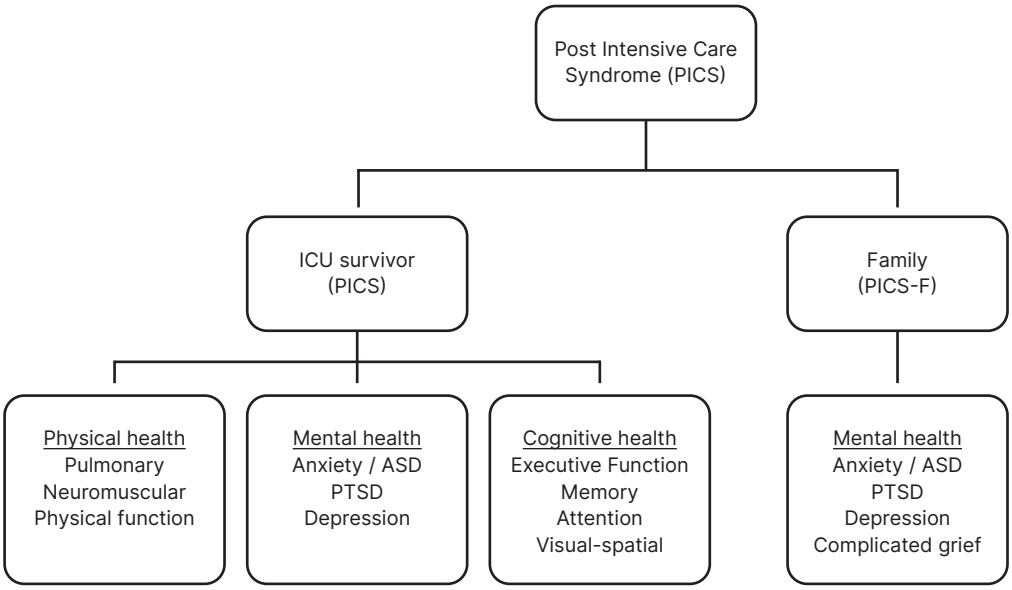
It is estimated that 25-50% of the ICU survivors will suffer from long-term problems in their physical, mental and/or cognitive health domain, but rates up to 80% (4) have also been reported. In 2012, the term 'post-intensive care syndrome' (PICS) was introduced to describe these *'new or worsening impairments in physical, mental, or cognitive health status arising after critical illness and persisting beyond acute care hospitalization*' (3) (Figure 2).

Impact of PICS on daily living

The adverse long-term outcomes have a major impact on ICU survivors daily living. The quality of life (QoL) in ICU survivors is significantly lower compared to the age and gender matched normal population in the years following ICU admission (20-22). Social roles and relationships with their partner, friends and family members change (14). Many are unable to participate in previous activities including hobbies and work; one year after discharge, a reduction in employment status is present in 70% of ICU survivors, with almost 50% being unemployed. Because of long-term sick leave or early retirement, one third does not return to their pre-existing level of income (23). In addition, the majority (80%) of the required care is provided by a family member, impacting family income as well (23). Over 20% of the patients still require help with activities in daily living one year after discharge (23). Although caregivers assistance can be beneficial for ICU survivors, caregivers suffer a substantial variety of burdens as well, including emotional distress, depression, anxiety

and symptoms of post-traumatic stress disorder (2, 24, 25). These problems are called post-intensive care syndrome-family (PICS-F) (Figure 2) (3).

Figure 2. Post-intensive care syndrome (PICS) conceptual diagram.



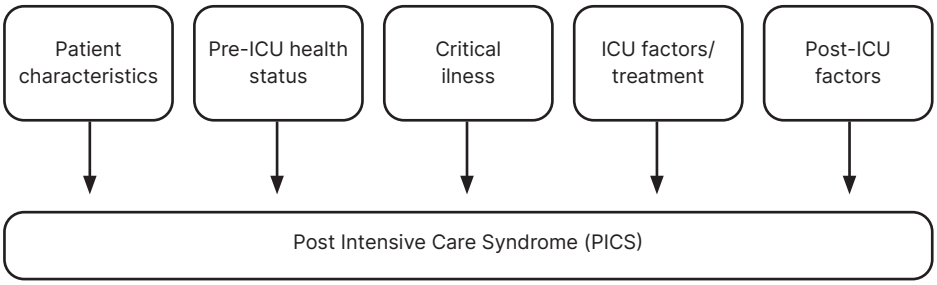
ASD: acute stress disorder; PTSD: post-traumatic stress disorder (Adapted from Needham et al., 2012 (3)).

Risk factors of PICS

Why some ICU survivors suffer from these long-term problems, while others don't, is not well understood (2). It is thought that the problems result from a complex mix of factors, such as patient characteristics (e.g. gender, coping skills), pre-ICU health status (e.g. frailty, comorbidities), reason for ICU admission (e.g. respiratory failure, trauma), patient course and adverse events (e.g. organ dysfunction, delirium), ICU treatment (e.g. mechanical ventilation, sedation) and post-ICU factors (e.g. social support, rehabilitation) (Figure 3) (26, 27). Especially the pre-ICU health status appears to be important, and possibly even more so than the critical illness itself (28-31). Premorbid psychiatric illness is, for example, strongly associated with prolonged post-ICU psychiatric morbidity (29), and frail patients are more likely to have worse functional outcomes after ICU discharge than non-frail patients (29, 32). Continued investigation of risk factors is essential to understand which

patient subgroups are prone to develop long-term problems, and for designing effective ICU and post-ICU interventions to mitigate these problems (33).

Figure 3. Risk factors post-intensive care syndrome



Interventions to mitigate or prevent PICS

To mitigate or even prevent long-term problems, numerous interventions have been developed in the last decade. In the ICU, interventions are tailored to known risk factors, including minimising sedation and immobility, and prevention of delirium (4). Also ICU diaries, electrical muscle stimulation, nutritional optimization and early psychological interventions are advocated (34). Beyond ICU discharge, rehabilitation programs, cognitive therapy, peer support, psychologic interventions and post-ICU clinics providing follow-up counselling and support for patients and their families are available (4, 34, 35). However, although a wide range of interventions have been implemented, research in this field in still in the early stages, and many interventions have not been shown to be effective yet (3).

MONITOR-IC study

To facilitate the development of preventative strategies, screening guidelines and treatment modalities, an improved understanding of the long-term outcomes is of the utmost importance (36). Up to now, rates of adverse long-term outcomes vary widely between studies, due to differences in study designs, patient populations, measurement tools and follow-up time frames (4). Studies have methodological flaws, such as small sample sizes, low response rates and use of non-validated instruments (37-41). In addition, many studies do not take the pre-ICU health status into account, overestimating thereby the attributable effects of critical illness (42, 43), and reporting prevalence rates

instead of incidence rates. Furthermore, outcomes in the physical, mental and cognitive health domains are interrelated (44), but studies often focus on one specific outcome only (45-47). Studies that do examine the physical, mental and cognitive health domains together are scarce; they are rather small (48), or include specific patients groups (49). For these reasons, the MONITOR-IC study was set up in 2016, the first Dutch multicentre prospective cohort study. The aim of the MONITOR-IC study is to assess the physical, mental and cognitive health outcomes, as well as the QoL, in thousands of ICU survivors during five years following their ICU admission. The pre-ICU health status is taken into account, and the outcomes are measured using validated and international recommended instruments (50).

Aims of this thesis

This is the first thesis using data of the MONITOR-IC study. This thesis focuses on the health outcomes and QoL before and in the first year following ICU admission, and interventions to prevent or mitigate the adverse outcomes. The aims of this thesis are to:

- study the health status of ICU survivors before ICU admission.
- determine ICU survivors' physical, mental, and cognitive health outcomes one year after ICU admission.
- study factors associated with one-year physical, mental and cognitive outcomes.
- assess QoL, and to gain insight into why ICU survivors experienced their QoL as reduced one year after ICU admission.
- assess the effectiveness of interventions to prevent or mitigate the long-term physical, mental and cognitive health problems in ICU survivors.

Outline of this thesis

This thesis starts with the study protocol of the MONITOR-IC study in **chapter 2**, the ongoing multicentre cohort study in which 5-years long-term outcomes of Dutch ICU survivors are assessed. Pre-ICU health status is important factor for the long-term outcomes. **Chapter 3** describes the health status and QoL before ICU admission in a large group of ICU survivors. The long-term outcomes are reported in chapter 4-6. **Chapter 4** describes the occurrence and cooccurrence of the physical, mental and cognitive health problems in

ICU survivors, associated risk factors, and the impact on daily functioning and QoL. **Chapter 5** zooms in on the changes in frailty in the year after ICU admission, and its associated factors. **Chapter 6** includes the results of a mixed method study in which ICU survivors, who reported a reduced QoL in the questionnaire, were interviewed to get insight into the specific problems they face in daily life. **Chapter 7** is a systematic review and meta-analysis in which the effectiveness is summarised of non-pharmacologic interventions to prevent or mitigate physical, mental and cognitive health problems in ICU survivors. The main findings and future implications described in this thesis are discussed in **chapter 8**, followed by an English and Dutch summary in **chapter 9** and **chapter 10**, respectively.

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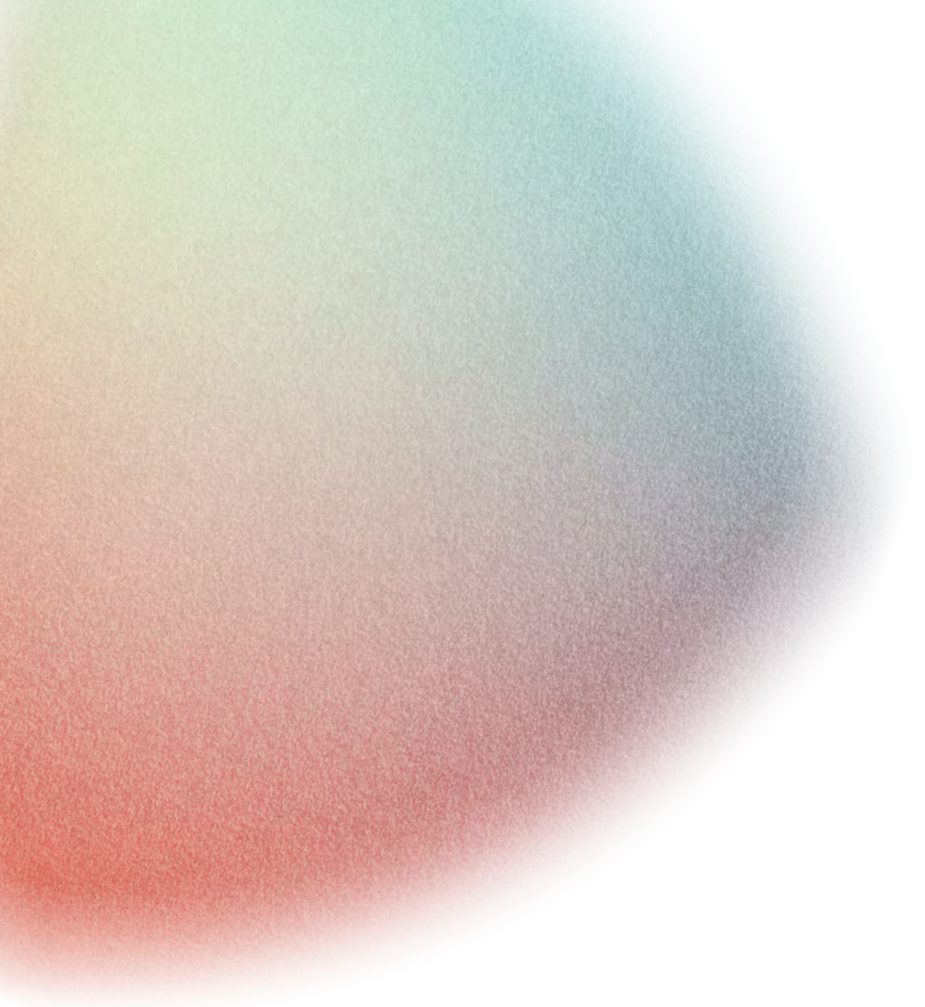

CHAPTER 2

MONITOR-IC STUDY, A MIXED METHODS PROSPECTIVE MULTICENTRE CONTROLLED COHORT STUDY ASSESSING 5-YEAR OUTCOMES OF ICU SURVIVORS AND RELATED HEALTHCARE COSTS: A STUDY PROTOCOL

Wytske Geense, Marieke Zegers, Hester Vermeulen, Mark van den Boogaard, Johannes van der Hoeven

BMJ Open, 2017

ABSTRACT

Introduction Due to advances in critical care medicine, more patients survive their critical illness. However, intensive care unit (ICU) survivors often experience long-term physical, cognitive and mental problems, summarized as post-intensive care syndrome (PICS), impacting their health-related quality of life (HRQoL). In what frequency PICS occurs, and to what extent this influences ICU survivors' HRQoL, is mostly unknown.
The aims of this study are therefore to study the: 1) 5-year patient outcomes, 2) predictors for PICS, 3) ratio between HRQoL of ICU-survivors and healthcare-related costs, and 4) care and support needs.

Methods The MONITOR-IC study is a multicentre prospective controlled cohort study, carried out in ICUs in four Dutch hospitals. Patients will be included between July 2016 and July 2021 and followed for five years. We estimated to include 12000 ICU-patients. Outcomes are the HRQoL, physical, cognitive and mental symptoms, ICU survivors' care and support needs, healthcare use and related costs. A control cohort of otherwise seriously ill patients will be assembled to compare long-term patient-reported outcomes.
We will use a mixed methods design, including questionnaires, medical data from patient records, cost data from health insurance companies and interviews with patients and family members.

Ethics and dissemination Insights from this study will be used to inform ICU patients and their family members about long-term consequences of ICU care, and to develop prediction and screening instruments to detect patients at risk for PICS. Subsequently, tailored interventions can be developed and implemented to prevent and mitigate long-term consequences. Additionally, insights into the ratio between HRQoL of ICU patients and related healthcare costs during 5years after ICU admission, can be used to discuss the added value of ICU care from a community perspective. The study has been approved by the research ethics committee of the Radboud University Medical Center (2016-2724).

Clinical trial registration NCT03246334

INTRODUCTION

The number of patients admitted to the Intensive Care Unit (ICU) is increasing every year (1). Meanwhile, advances in medical technologies allow more patients to survive their critical illness (2). With this growing number of ICU survivors, there is an urgent need to shift our focus from short-term mortality to long-term outcomes of ICU survivors (1, 3).

In 2002, the members of the international surviving intensive care Roundtable already discussed whether ICU survivors have optimal long-term outcomes, and whether decisions regarding ICU care would change with increasing knowledge of outcomes (4) and the associated costs (3). Costs of ICU care are high; 20% of the total hospital budget, with cost per day between threefold and fivefold greater in ICU departments than in general wards (5). These high costs are due to the need for highly trained staff, expensive modern equipment, and intensive use of diagnostic tests, pharmaceuticals and interventions (6). Although economic evaluation of care in the ICU is often ethically difficult (6), understanding of the costs and consequences associated with technologies, services and programmes aimed at reducing mortality and morbidity of patients with critical illness is important (6, 7).

Over the last two decades, it has become more and more clear how devastating and long-lasting the post-discharge consequences can be, and what the impact is on ICU survivors and their family (8). These long-term consequences are called post-intensive care syndrome (PICS), defined as 'new or worsening impairment in physical, cognitive, or mental health status arising and persisting after hospitalisation for critical illness (2). Examples of these physical impairments are pain, breathing difficulties, fatigue and loss of bodyweight resulting in physical weakness and problems in daily functioning and activities (1, 8-11). A total of 10%-75% of the ICU survivors are still suffering from these difficulties 1 year later (12). Cognitive problems, such as problems with memory, processing, planning and problem solving, are seen in 30%-80% of the ICU survivors (2, 8). Although these impairments can improve over several months, they can persist for many years as well (10). In addition, mental impairment, such as depression (13), anxiety (14), and sleep disturbances are common (1, 2). In 25% of the ICU survivors, post-traumatic stress disorder (PTSD) symptoms occur at 1-year follow-up (15). These PTSD symptoms can persist for 8 years (2). Moreover, ICU survivors experience a significant socioeconomic burden because of long-term sick leave, early retirement and need for assistance at home which is primarily given by informal caregivers,

impacting on family income (16, 17). Furthermore, ICU survivors experience a lower quality of life (18), leading to high utilization of healthcare services and related costs (16, 19).
Although some risk factors for PICS are known (such as immobility, pre-existing impairments, age, sedation, duration of mechanical ventilation, delirium and sepsis) (3, 10, 20), continued investigation of risk factors and underlying mechanisms is essential to understand which subgroups of patients are prone to develop PICS (3, 10). Interventions and strategies to prevent or mitigate PICS, such as ICU diaries, early mobilisation, post-discharge rehabilitations and follow-up consultations with specialised nurses for ICU survivors, were recently described (1, 21-25). However, conclusive evidence for these interventions is lacking or limited (24, 26-29). Moreover, the majority of the healthcare professionals are still not aware of PICS, and interventions available for ICU survivors are therefore often not provided (1, 3).
More insight is necessary to better define the scope of long-term ICU symptoms and associated healthcare costs (3). Incidence rates of PICS differ largely in studies, which is due to differences in study patient populations, comorbidities, measurement tools and time frames (2). Additionally, previous studies addressing PICS often have limited focus or methodological limitations such as small sample sizes, low response rates, short follow-up, use of non-validated or unreliable instruments, no control group and absence of a pre-admission (baseline) measurement (30-35).
For this reason, we set up a controlled cohort study called the MONITOR-IC. In this study, with a 5-year follow-up, we aim to study the ICU survivors' long-term outcomes, their health-related quality of life (HRQoL) and their needs, in order to identify specific types of patients who are at risk for specific impairments, factors affecting their recovery and to target effective interventions both in the ICU and later during the fragile recovery period (3, 8, 36). Additionally, we aim to get more insight into the ratio between the HRQoL and related healthcare costs to discuss the added value of ICU care from a community perspective.

OBJECTIVES

Overarching objective

To quantify and describe the extent of the physical, mental and cognitive long-term outcomes and HRQoL of ICU survivors during 5 years following ICU admission, in order to ultimately improve care for ICU patients.

Specific research questions

1. What are the post-intensive care symptoms that patients experience during 5 years after ICU admissions and what is their HRQoL?
2. What are important predictors for the various physical, cognitive and mental long-term outcomes?
3. What is the ratio between HRQoL and healthcare-related costs?
4. What are the care and support needs of ICU survivors during five years after ICU admission?

METHODS/DESIGN

Study design and setting

The MONITOR-IC study is a multicentre prospective controlled cohort study in which long-term outcomes of ICU patients are studied for a period of 5 year.

The study will be carried out in ICUs of four hospitals in the Netherlands; one academic hospital, one teaching and two non-teaching hospitals. ICU patients will be recruited between July 2016 and July 2021 with a subsequent follow-up for 5 years. Mixed methods will be used to collect data, including questionnaires, medical data from patient records, cost data from health insurance companies and interviews with ICU survivors and their family members.
To compare the outcomes, such as the quality of life and experienced symptoms of ICU patients with non-ICU patients, we will set up a control group as well.

Study population and eligible criteria

ICU patients are eligible to participate when they are 16 years or older; admitted at least 12 hours to a trauma, medical, neurosurgery or cardiac surgery ICU; and gave written informed consent (or by their legal representative).
Patients are eligible for the control cohort when they are 16 years or older and admitted either to the ICU for less than 12 hours, or to the post anaesthesia care unit, the medium care or high dependency unit, for instance, for monitoring during short interventions, such as bronchoalveolar lavage or insertion of a central venous catheter.
Patients are not eligible for the study when they have a life expectance of <48 hours; receive palliative care; are admitted for a donor procedure; cannot read and speak the Dutch language; or are not able to fill in the questionnaire and do not have family members/ legal representatives either.
For the MONITOR-IC study, we estimated to include 12000 patients. This

estimation is based on: 1) the initial ICU admissions in the academic hospital and the three other participating hospitals together (2500 and 2200 respectively per year), and 2) an estimated response rate of 60%, which is based on previous conducted ICU studies (37, 38). In the control cohort, we will include approximately 3000 patients during the next 4 years.

Patient recruitment

Patients scheduled for ICU admission after elective surgery will be recruited at the outpatient clinic (anaesthesiology or cardiac surgery) (Figure 1). Patients with a non-scheduled admission will be recruited at the ICU. Patients will receive information by ICU nurses and intensivists regarding the aim, content and relevance of the study, and will be asked for participation.

Informed consent is asked for the questionnaires, data from the patients' individual medical record (MR) and data from their health insurance company. In case patients are unable to give consent, their legal representative will be asked.

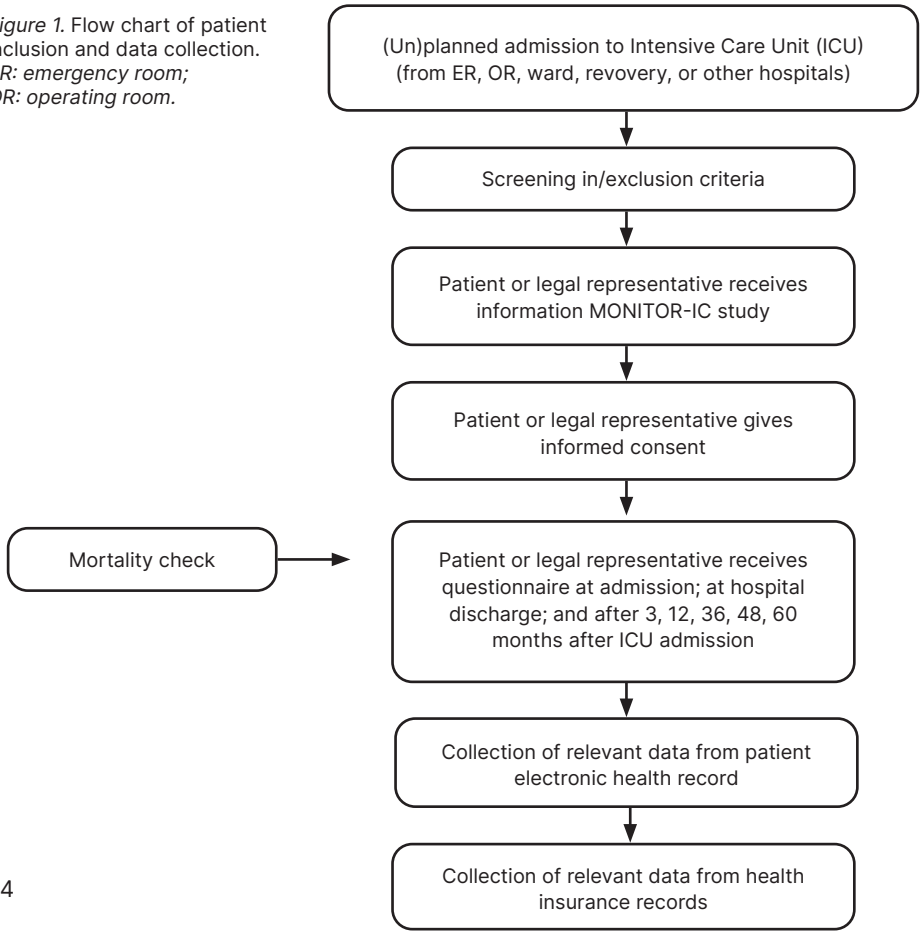

Figure 1. Flow chart of patient inclusion and data collection.
ER: emergency room;
OR: operating room.

Outcomes measures

The outcomes of the MONITOR-IC study are the HRQoL among ICU survivors and their physical (fatigue, vulnerability and frailty), cognitive and mental (anxiety, depression and stress) impairments. Additional outcomes are the patients' care and support needs, their healthcare use and related costs.

Data collection

Different methods will be used to collect data among ICU patients, including questionnaires, patients' MR, database of healthcare cost data of Dutch health insurance companies and interviews with patients and their family members (Table 1).

Table 1. Research questions and methods

Research question	Methods
1. What are the post-intensive care symptoms that patients experience during 5 years after ICU admission and what is their HRQoL?	Questionnaires MR
2.What are important predictors for the various physical, cognitive and mental long-term outcomes?	Questionnaires MR
3.What is the ratio between HRQoL and healthcare related costs?	Questionnaires Health insurance database
4.What are the care and support needs of ICU survivors during 5 years after ICU admission?	Questionnaires Interviews with ICU survivors and their family members

Questionnaires

All patients, or their relatives in case patients are not able to fill in the questionnaire themselves, will be approached to fill in the self-administered paper-based or online questionnaire (depending on their preferences) eight times: at ICU admission (T0), at hospital discharge (T1), after 3 months (T2), 12 months (T3), 24 months (T4), 36 months (T5), 48 months (T6) and 60 months after ICU admission (T7). To get insight into the situation before the ICU admission, the baseline questionnaire (T0) is provided when the patients is asked for informed consent. This could be preoperatively for the planned admissions or after admission at the ICU. Then, patients are asked to rate their situation before the ICU admission.

The investigators keep track on when patients should receive the next

questionnaire or the postal or telephone reminders after 4 and 6 weeks.
The questionnaire is established in close collaboration with worldwide experts in the fields of ICU long-term outcomes and the FCIC (Family and Patient-Centered Intensive Care); the Dutch foundation for ICU survivors and their family members.

The components in the questionnaire vary at different measurement points (see Table 2, and for more information regarding the domains and items see supplementary file 1) but contain the following:

- *Patients' health status and HRQoL* will be assessed using the 36-Item Short Form Survey (SF-36)(39) and the 5-level EQ-5D version (EQ-5D-5L) (40). Both questionnaires are validated instruments and applicable in different countries and languages. The SF-36 is a comprehensive instrument, measuring the general health status and quality of life, consisting of eight different health domains. The EQ-5D-5L is a simple instrument to measure the HRQoL (4). Although the SF-36 is the most often used questionnaires measuring quality of life in intensive care patients (41), the EQ-5D-5L is added since this questionnaire can be best used for the calculation of quality adjusted survival, a key measure of health effects for cost effectiveness assessments (4).
- *Patients' level of frailty and vulnerability* will be assessed using the Clinical Frailty Score (CFS) (42). Frailty is common in patients with critical illness and is associated with poorer outcomes in terms of ICU and hospital mortality, impairment in HRQoL and functional dependence (43). The CFS is simple, short and reliably measures frailty. Using the CFS it is possible to predict outcomes more effectively (44).
  The level of fatigue, which is not well covered by the other included questionnaires, will be measured using the CIS-8, a subscale of the Checklist Individual Strength (CIS-20) (45), and is used by ICU patients before (37).
- Critical illness and ICU treatment are associated with long-term *cognitive impairment* (46) which will be measured using the validated abbreviated 14-item Cognitive Failure Questionnaire (CFQ-14) (47). The original CFQ-25 (48) is often used to screen ICU survivors for cognitive problems; however, the number of questions and missing values is a limitation (47). Therefore, we have chosen the shorter version which is highly correlated with the original questionnaire (48).

- The *mental impairments* will be assessed using the Hospital Anxiety and Depression Scale (HADS) to determine the levels of anxiety and depression (49). The HADS is the most often used questionnaire to measure symptoms of anxiety and depression in ICU survivors (41).
  Subjective distress, caused by traumatic events, will be measured using the Impact of Event Scale Revised (IES-R) (50), a standardized measure of PTSD symptoms.
- *Care needs and support from professionals and informal caregivers* will be measured using questions created by our research team, former ICU patients and members of the FCIC, and by previous studies among chronic patients (51).
- *Social consequences* will be measured using the novel question set designed by Griffiths et al (16), to determine changes in family circumstances, socioeconomic stability and care requirements.

Although we are aware of the overlap between the used questionnaires, it will allows us to check the reliability. For more information regarding the questionnaires, domains and scores, see supplementary file 1.

Medical data
Patients' demographics and information regarding their diagnosis and treatment, such as primary conditions, pre-existing comorbidity, disease severity, sepsis, (re)admission, length of mechanical ventilation, length of ICU stay, delirium, pain, expected mortality, will be extracted from their MR and the NICE (Dutch National Intensive Care Evaluation) registry (52).

Health insurance data
Healthcare use and related costs, covered by the Dutch healthcare insurance, will be retrieved from Vektis, a Dutch organization which collects and manage health insurance claimed data of all health insurance companies in the Netherlands (53). These data are collected based on the diagnosis treatment combination; a total set of activities carried out by the hospital and medical specialists. Additionally, data is collected regarding nursing days, visits at the outpatient clinic and emergency department, nursing homes, ambulance transport, consultation with general practitioner, paramedical care (including physiotherapist, occupational therapist, dietitian and speech therapist), prescribed medication, mental healthcare and revalidation. The Vektis

database contains data from all healthcare insured citizens and covers 99% of the total Dutch population. Using patient's unique insurance number, we are able to merge patient's insurance data with the questionnaire data and medical data from the MR at patient level.
Care delivered by community nurses and informal caregivers is not included in the Vektis database and will be studied via the questionnaire.

Interviews
To get insight into the experiences of ICU survivors during 5 years after ICU admission and their need for support, face-to-face semi-structured interviews will be conducted with ICU survivors and their family members. Interviews will take place at the participants' preferred location (home or clinic). Interviews will be conducted until data saturation is reached.
Patients will be purposively sampled based on various experienced outcomes, such as the quality of life, daily functioning, anxiety, depression, and their experienced needs for more information or emotional support. Experienced and trained researchers will conduct the interviews using a topic guide. This guide will be developed using the current literature and experience of the research team and will cover the following subjects: experiences with the ICU admission and follow-up, experienced problems and needs for support. All interviews will be audio recorded and transcribed verbatim.

Table 2. Overview of used scales in the questionnaire and time frame

Methods	**Outcome**	**Used scales**	**T0**	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**
			(ICU) admission	Discharge hospital	3 months	12 months	24 months	36 months	48 months	60 months
Questionnaire	Demographic data		X							
	Health status and HRQoL	SF-36	X		X	X	X	X	X	X
		EQ-5D	X		X	X	X	X	X	X
	Physical impairments	CFS	X	X	X	X	X	X	X	X
		CIS-8	X		X	X	X			
	Cognitive impairments	CFQ-14	X		X	X	X			X
	Mental impairments	HADS	X		X	X	X			X
		IES-R			X	X	X			X
	New symptoms after ICU admission				X	X	X	X	X	X
	Care needs and professionals support/ informal caregivers				X	X	X			X
	Social consequences					X	X			X

Analysis

Questionnaires, MR and health insurance data

During the data collection, data are checked on a regular basis to identify out-of-range answers, inconsistent responses and missing data. Data from the questionnaires, MR and healthcare insurance data will be merged at patient level. Descriptive statistics will be used to describe baseline characteristics and the incidence of long-term outcomes. Regression analysis will be used to determine associations between patient characteristics, treatment and long-term outcomes. Subgroups will be identified based on their illness and condition (eg, sepsis, delirium, comorbidities, acute respiratory distress syndrome (ARDS)), treatment (eg, length of ICU stay, duration of mechanical ventilation, dialysis) and social demographics (age, gender, education, family setting, and so on).

In order to predict the various physical, cognitive and mental long-term outcomes, multiple prediction models will be developed. Multivariable linear (for continuous outcome variables) and logistic (for dichotomous outcome variables) regression analysis will be performed. Linear and logistic multilevel models will be used to compare long-term outcomes between the study population (cohort) and control cohort group.

To determine the ratio between HRQoL and patient outcomes and the health-related costs, quality-adjusted life years (QALYs) will be calculated. QALYs are a measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. QALYs are calculated by estimating the years of life remaining for particular treatment and weighting each year with a quality of life score (54). SPSS 22 (Software Package for the Social Sciences) will be used for data analysis.

Interviews

For the analysis of the interview data, the constant comparative method (55) will be used. Relevant data will be identified and structured by open, axial and selective coding.

Two researchers will independently code the transcripts to minimize subjectivity in findings. The differences and similarities between the codes will be discussed together, and in case of disagreement, a third researcher will be involved. In the meetings with the team, the codebook will be refined and emerging categories and themes will be discussed.

Data analysis will be supported with the use of Atlas.ti, a qualitative data analysis program.

Ethics

The MONITOR-IC study will be conducted complying with the Dutch Personal Data Protection Act. The study has been approved by the research ethics committee of the Radboud University Medical Center, CMO region Arnhem-Nijmegen (2016-2724). The study is registered in the ClinicalTrials.gov database (NCT03246334).

Relevance of findings

The results of the MONITOR-IC study will be disseminated through international and national publications and presentations. We will quantify and describe the extent of the physical, cognitive and mental long-term outcomes of ICU survivors, their healthcare use and their needs (Box 1).

This knowledge is of importance for patients, healthcare professionals, managers and health insurers to develop and evaluate the (after)care for ICU patients taking their health status and needs into account. Patients and their family members could be better informed about the possible long-term physical, cognitive, mental and social consequences after ICU discharge. Moreover, the inclusion of thousands of ICU patients in this study allows us to study several patient subgroups; for example, the quality of life and specific care needs of patients after sepsis, ARDS or delirium. Using these disease-specific insights, prediction and screening instruments can be developed to determine patients at risk for long-term consequences. Subsequently, interventions, such as diaries, early mobilisation and follow-up consultations for patients and their family members, could be adjusted, established and implemented to prevent or mitigate long-term consequences. Furthermore, long-term effects of important changes in health policy will be visible, whereby evaluation of effectiveness and efficacy of (changes in) policy on micro, meso and macro level is possible. Healthcare professionals will be better able to weigh up the options in the decision-making process concerning ICU admission, treatment options and the added value for individual patients, which will improve shared decision-making with patients and their families as well.

Finally, this study gives more perspectives into the ratio between the patients' HRQoL and healthcare costs. Over the last decades, the ICU care is overwhelmed with new and also costly technologies and therapies, resulting in increasing costs, but without actually insight in the added value for patient and their health outcomes. Consequently, an open ethical dialogue, based on this ratio and what this ratio might be, is then possible.

Box 1. Relevance of study

1. Information about long-term outcomes for patients and their family members
2. Support for treatment choices for multiple medical specialties, in particular intensive care
3. Coordination of care by personalised follow-up care for post-ICU patients
4. Adjustments in healthcare policy for post-ICU patients
5. Screenings instrument for early signs and symptoms
6. Establishing and implementing interventions to prevent or mitigate long-term consequences
7. Information for health insurance companies for purchasing care and professional associations for guideline development
8. Detecting unnecessary ICU care
9. Evaluation of changes in ICU healthcare policy on long-term effects

The strengths of the MONITOR-IC study are the thorough and comprehensive methodological approach, inclusion of thousands of ICU patients, 5-year follow-up, use of mixed methods and the combination of data regarding patients' HRQoL, healthcare use and patients' needs. Moreover, the baseline questionnaire includes questions relating to the patient's situation before the ICU admission. Therefore, we are able to compare the experienced post-ICU symptoms and related HRQoL with the situation before the admission.
There are also some limitations that need to be addressed. We aimed to included more than 12000 patients. However, patients have to fill in eight questionnaires during 5 years. High loss to follow-up rates are likely due to high mortality rates (56). Furthermore, the post-ICU symptoms and consequences are based on the reported outcomes by patients themselves. This could lead to bias due to overestimation or underestimation of their own symptoms, for example, their cognitive functioning. Using the data of the health insurances companies regarding, for example, patients' visits to the general practitioner or medical specialist, we try to overcome this. Moreover, PICS occurs among ICU survivors and their family members and relatives, also called PICS-Family (PICS-F) (57). These long-term consequences in families of survivors and non-survivors consist of psychological, physical and social consequences as well

(58-60). Although it is important to increase awareness of these possible long-term consequences on family members (2), we decided to focus only on the ICU survivors. In the future extension of this study, family members might be included as well.

Acknowledgements
We gratefully acknowledge the Family and Patient Centered Intensive Care (FCIC), the national foundation for ICU survivors and their family members, for their close cooperation. We are also grateful to Cees Zimmerman and Grietje Marten-van Stijn, respectively intensivists and ICU nurse of the ICU follow-up outpatient clinic in the Radboud university medical center, as co-designers of this study.

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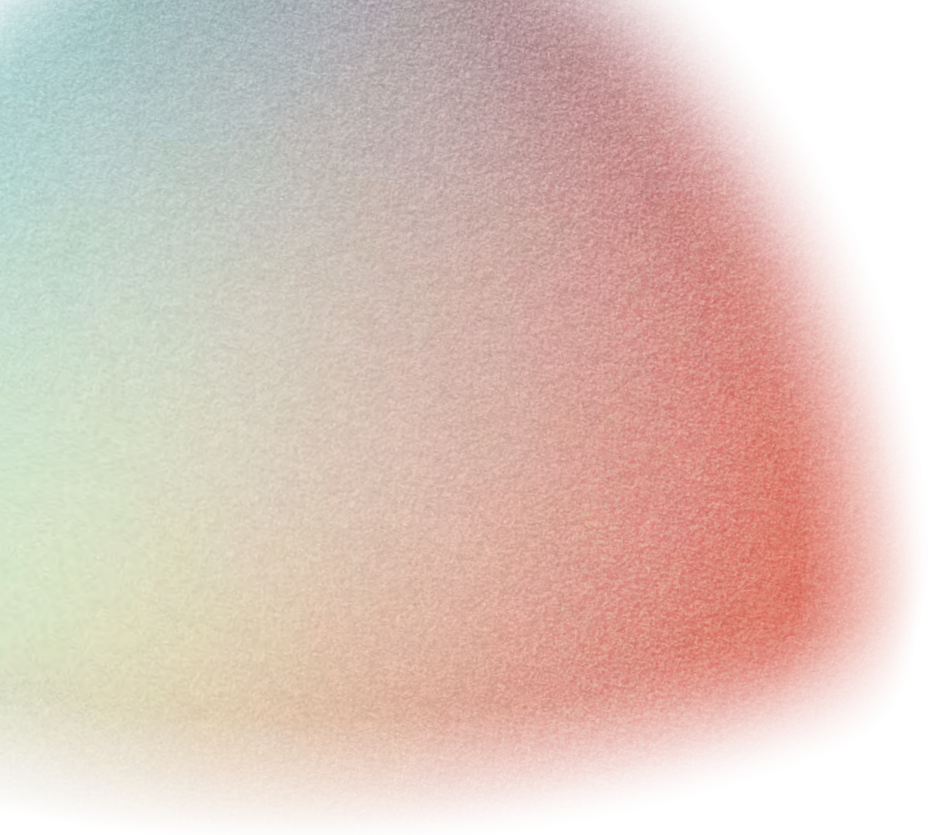
Supplementary file 1. Overview of validated instruments

Item	Questionnaire	Questions	Domains	Score
Health status and related quality of life	SF-36 (Short Form Health Survey) (39)	36	1. Physical functioning (10 items) 2.Role limitations because of physical health problems (4 items) 3. Bodily pain (2 items) 4. Social functioning (2 items) 5. General mental health (5 items) 6. Role limitations because of emotional problems (3 items) 7. Vitality (4 items) 8. General health perceptions (5 items) Change in general health (1 item)	35 of the 36 items are used for the calculation of the eight domain scores and two summary scores: the physical component summary (PCS) and mental component summary (MCS) scores. Each domain is scored from 0 (worst score) to 100 (best score). The lower the score, the more disability.
	EQ-5D-5L (40)	5	1. Mobility (1 item) 2. Self-care (1 item) 3. Usual activities (1 item) 4. Pain and discomfort (1 item) 5. Anxiety and depression (1 item) The EQ-5D-5L also comprises a visual analogue scale (VAS) to record perceptions of the participants own current overall health.	Each domain is scored on a five point scale. The range of the VAS scale is from 0 to 100.
Physical impairments	CFS (Clinical Frailty Score) (42)	1	Frailty (1 item)	One 9-point scale ranging from 1 'Very fit' to 9 'Terminally ill'.
	CIS-8 (Subscale of the Checklist Individual Strength, CIS-20) (45)	8	Fatigue (8 items)	A 7 point scale, ranging from 'No that is not right' (1) to 'Yes that is right'(7). A total sum score of 35 or more indicates sever fatigue.

Supplementary file 1. Continued

Item	Questionnaire	Questions	Domains	Score
Cognitive impairments	CFQ-14 (Abbreviated versions of the Cognitive Failure Questionnaire) (47, 48)	14	1.Memory (4 items) 2.Distractibility (5 items) 3.Social blunders (4 items) 4.Names (1 item)	Each item is scored on a 5 point sale, ranging from 0 (never) to 4 (very often). A total sum is calculated and a higher score indicates more cognitive failure.
Mental impairments	HADS (Hospital Anxiety and Depression Scale) (49)	14	1. Anxiety (HADS-A) (7 items) 2. Depression (HADS-D) (7 items)	Each item on the questionnaire is scored on a 4-point scale, ranging from 0-3. Scores range between 0 and 21 for depression and for anxiety. Higher scores indicate higher symptom frequencies: 0-7 is normal, 8-10 is mild, 11-14 is moderate and 15-21 is severe.
	IES-R (Impact of Event Scale Revised) (50)	22	Subjective stress, caused by traumatic events	This lists consists of 22 questions, with a 5-point scale ranging from 0 (not at all) to 4 (extremely). Total scores range from 0 to 88, with score of 33 or above as best cut off for a probable diagnosis of PTSD.



CHAPTER 3

PHYSICAL, MENTAL AND COGNITIVE HEALTH STATUS OF ICU SURVIVORS BEFORE ICU ADMISSION: A COHORT STUDY

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Critical Care Medicine, 2020

ABSTRACT

Objective Although patient's health status before ICU admission is the most important predictor for long-term outcomes, it is often not taken into account, potentially overestimating the attributable effects of critical illness. Studies that did assess the pre-ICU health status often included specific patient groups or assessed one specific health domain. Our aim was to explore patient's physical, mental and cognitive functioning, as well as their quality of life before ICU admission.

Design Baseline data were used from the longitudinal prospective MONITOR-IC cohort study.

Setting ICUs of four Dutch hospitals.

Patients Adult ICU survivors (n=2467) admitted between July 2016 and December 2018.

Interventions None.

Measurements and main results Patients, or their proxy, rated their level of frailty (Clinical Frailty Scale), fatigue (Checklist Individual Strength-8), anxiety and depression (Hospital Anxiety and Depression Scale), cognitive functioning (Cognitive Failure Questionnaire-14), and quality of life (Short Form-36) before ICU admission. Unplanned patients rated their pre-ICU health status retrospectively after ICU admission. Before ICU admission, 13% of all patients was frail, 65% suffered from fatigue, 28% and 26% from symptoms of anxiety and depression, respectively, and 6% from cognitive problems. Unplanned patients were significantly more frail and depressed. Patients with a poor pre-ICU health status were more often likely to be female, older, lower educated, divorced or widowed, living in a healthcare facility, and suffering from a chronic condition.

Conclusion In an era with increasing attention for health problems after ICU admission, the results of this study indicate that a part of the ICU survivors already experience serious impairments in their physical, mental and cognitive functioning before ICU admission. Substantial differences were seen between patient subgroups. These findings underline the importance of accounting for pre-ICU health status when studying long-term outcomes.

INTRODUCTION

With increasing survival rates of ICU patients (1, 2), leading to millions of ICU survivors worldwide every year (3), the focus of outcomes in critical care medicine is shifting from short-term mortality towards long-term consequences of critical illness (3, 4). Subsequently, it has become clear that many ICU survivors suffer, for months to even years, from physical, mental and cognitive health problems (3, 5, 6), also known as 'post-intensive care syndrome' (PICS) (3). It impacts their daily functioning and quality of life (1, 3), and is associated with higher healthcare utilization due to readmissions, institutionalization, and required rehabilitation (7).

It is still largely unknown why some ICU patients successfully recover, whereas others do not (8). Although it is generally thought that long-term problems result from a complex relationship among patient characteristics, pre-ICU health status, critical illness, ICU treatments, and post-ICU factors (5, 9-11), recent studies have shown that the strongest predictors of long-term outcomes are not factors related to ICU admission or critical illness, but factors related to the health status before ICU admission (12-19). Pre-ICU psychological morbidity is, for example, strongly associated with symptoms of depression after critical illness (20), and pre-ICU frailty with a lower quality of life and functional dependency after ICU discharge (21).

It is, therefore, remarkable that many studies on long-term outcomes of ICU patients do not take the pre-existing health status into account (12, 22), potentially inducing bias by overestimating the attributable effects of critical illness (14, 23-25). Besides, a full understanding of the pre-ICU health status would help us to better characterize patients before their ICU admission (15) and to identify patients who are at greatest risk for specific impairments, and who may benefit from preventive interventions (3). Additionally, because the ideal outcome for our patients is to return to their preexisting state or a state expected for a person of the same age and medical condition (4), insight in the pre-ICU health status may guide the treatment decision-making [14, 18]. Previous studies that did assess the pre-ICU health status focused often on one specific patient group, such as patients of 80 years old or older (26), or on one specific pre-ICU health domain, for example, cognitive functioning (13, 27), frailty (21) or quality of life (28, 29).

Because PICS comprises impairments in physical, mental and cognitive health (3), the aims of this study were to get insight into the pre-ICU physical, mental and cognitive health status and quality of life of ICU patients, and to assess differences between patient subgroups.

MATERIALS AND METHODS

Study design

Data were obtained from a large ongoing longitudinal prospective multicenter cohort study (MONITOR-IC study) (ClinicalTrials.gov: NCT03246334). The MONITOR-IC study started in 2016, aiming to study 5-year physical, mental, and cognitive health outcomes of ICU survivors. Detailed information regarding this study is described in the study protocol (30). The study has been approved by the research ethics committee of the Radboud university medical center, CMO region Arnhem-Nijmegen (2016-2724). Each included participant or legal representative provided written informed consent.

Study population

Patients were included when they were 16 years old or older and admitted for at least 12 hours to the ICU of one of the participating hospitals (one academic and three teaching hospitals) between July 2016 and December 2018. Patients with a life expectancy of less than 48 hours, receiving palliative care, or who could not read or speak the Dutch language were excluded.

Data collection

Patients with a planned ICU admission received an information letter and informed consent form at the preoperative outpatient clinic. After informed consent, they were asked to complete the questionnaire a few days before their ICU admission. Patients with an unplanned ICU admission received the information letter and informed consent form while being in the ICU, or it was provided to their proxy. After informed consent, patients were asked to complete the questionnaire by rating their health retrospectively, recalling their health status before ICU admission.

Depending on patients' or their proxies' preferences, a self-administrated paper-based or online questionnaire was provided. Reminders were sent after 4 weeks, and 2 weeks later, a phone call was made. If patients did not respond in 90 days, they were excluded from the study.

Outcomes

The questionnaire consisted of the following validated instruments (more information about the instruments can be found in the study protocol) (30):

Frailty was measured using the Dutch version (31) of the Clinical Frailty Scale (CFS) (32), consisting of one item comprising nine pictographs with a

description of vulnerability and functional status. The score ranges from 1 'very fit' to 9 'terminally ill', with higher scores indicating more frailty. Patients were classified as 'non-frail' (CFS score, 1-4) or as 'frail' (CFS score, 5-9).

Fatigue was measured using the eight-item subscale of the Checklist Individual Strength (CIS)-20 (33), consisting of a seven-point rating scale, with a total score ranging from 8 to 56. Higher scores indicate higher levels of fatigue. A score of greater than or equal to 27 indicated 'mild fatigue', and a score of greater than or equal to 37 indicated 'severe fatigue'.

Symptoms of *anxiety* and *depression* were measured using the Hospital Anxiety and Depression Scale (HADS) (34), consisting of a seven-item anxiety subscale (HADS-Anxiety) and seven-item depression subscale (HADS-Depression). The four-point Likert scale ranged from 0 to 3, with total scores per subscale ranging from 0-21, with higher scores indicating higher levels of anxiety or depression. Scores were categorized as 'normal' (0-7), 'mild' (8-10), 'moderate' (11-14) and 'severe' (15-21).

Cognitive functioning was assessed using the abbreviated 14-item Cognitive Failure Questionnaire (CFQ)-14 (35). The five-point Likert scale ranged from 0 ('never') to 4 ('very often'). The scores were transformed to a 0-100 total score, with higher scores indicating more cognitive failure. A cut-off of greater than 43 was used to distinguish normal from abnormal score (36). This instrument has been added to the questionnaire in February 2017. Data regarding the cognitive health status of patients who were included between July 2016 and February 2017 are, therefore, missing.

Quality of life was assessed with the 36-Item Short Form Survey (SF-36) (37), consisting of eight domains, scoring from 0-100, with higher scores indicating better quality of life. Scores were aggregated into two summary measures: Physical Component Summary (PCS) and Mental Component Summary (MCS) scores.

Patient demographics, such as age, sex, education level and marital status, were retrieved from the questionnaire. Other variables, such as admission type (classified as elective surgical, medical or urgent surgical), Acute Physiology and Chronic Health Evaluation (APACHE) IV score, ICU and hospital length of stay (LOS) were retrieved from the electronic health record.

Statistical analysis

The focus of the MONITOR-IC study is the health outcomes of ICU survivors; therefore, only ICU survivors were included in the analysis. Continuous data

were, depending on their distribution, presented as means with standard deviations (SD) or medians with interquartile range (IQR), and categorical data with numbers and percentages. Because the majority of the included patients had a planned ICU admission, we analyzed patients with a planned and unplanned ICU admission separately.

Differences in characteristics and outcomes between planned and unplanned ICU patients were analyzed using the independent-samples t-test, Mann-Whitney U test, or chi-square test. Differences between patients and proxies were analyzed in the same way. Missing values in the CIS-8, HADS, CFQ-14 and SF-36 were imputed using the half-rule (38), in which missing items were replaced with the mean of the answered items, if at least half of the items in the (sub)scale had been answered or half plus one in case of scales with an odd number of items.

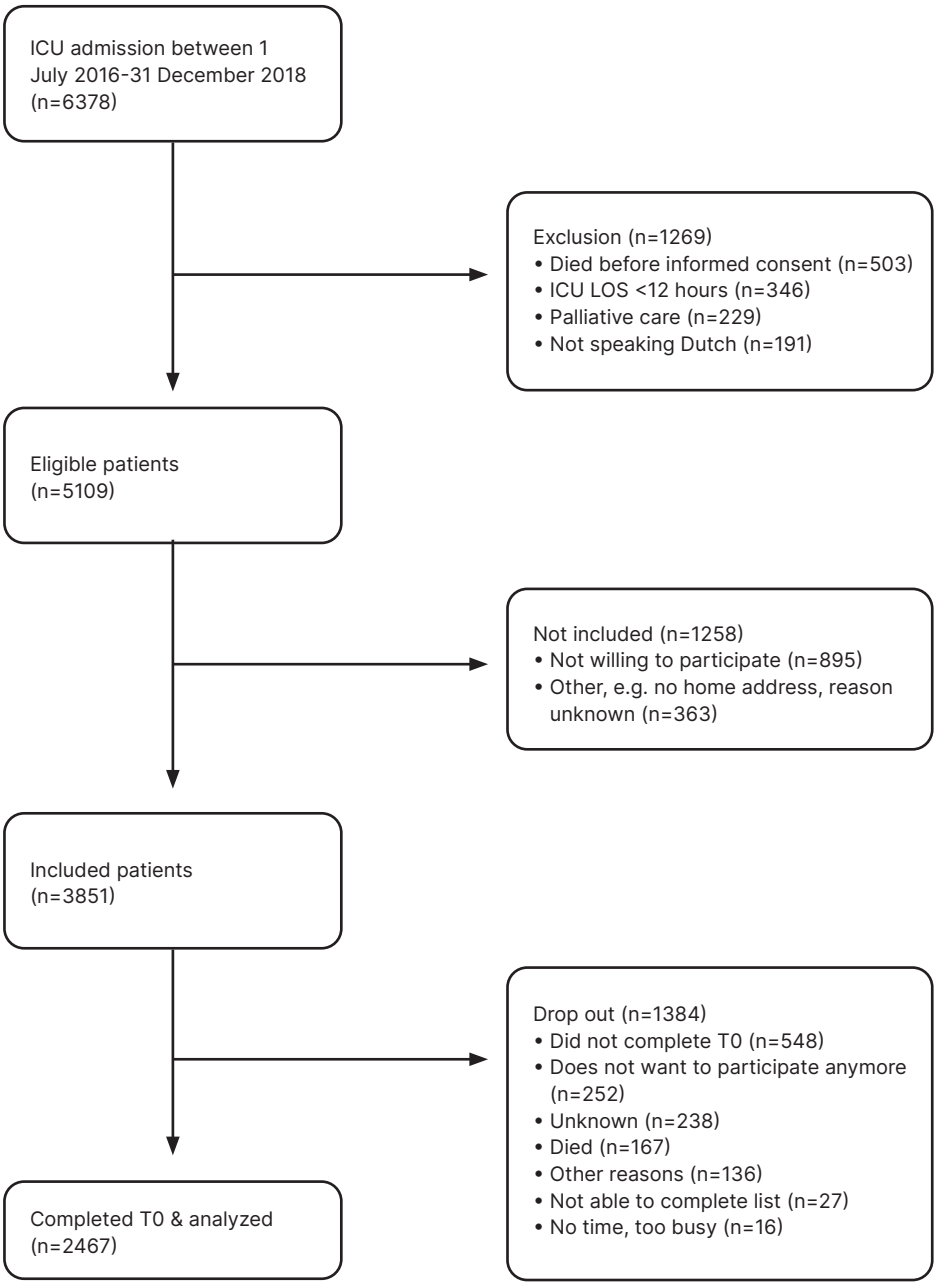
To assess the generalizability of the findings, characteristics of study participants were compared with ICU survivors of all Dutch hospitals (n=82) being admitted between July 2016 and December 2018 as well. Data from these patients were retrieved from the Dutch National Intensive Care Evaluation registry (39), a national quality registry for ICU care, in which patient demographic, clinical, and ICU characteristics are registered.

Statistical analyses were conducted using IBM SPSS Statistics for Windows (version 25.0; IBM Corp., Armonk, NY). Values of p less than 0.05 were considered statistically significant.

RESULTS

Of the 5109 patients who were eligible for this study, 3851 patients were included, of which 2467 (64%) completed the questionnaire (Figure 1). The main reasons for dropout were no return of the questionnaire or withdrawal.

Figure 1. Flow diagram multicenter cohort study



LOS: length of stay

Patient characteristics

The mean age of the 2467 patients was 62.2 years (±14.3) and 64% was male (Table 1). A quarter suffered from a chronic condition, with chronic obstructive pulmonary disease (32%) being most prevalent. The median ICU and hospital LOS were 1 days [1-3 d] and 9 days [6-14 d], respectively.

Compared to all ICU survivors (n=183,362) in the Netherlands, our study participants were slightly younger, had less chronic conditions, and their hospital mortality rate was lower. However, the APACHE-IV scores, ICU LOS, and post-ICU LOS were higher (Supplementary file 1).

Unplanned versus planned ICU admission

The majority of the patients (60%) had a planned ICU admission. Patients with an unplanned admission (n=985) were significantly more often female (42% vs 32%), younger (mean age, 60 vs 64 yr), had higher mean APACHE-IV scores (60 vs 50), and a longer median ICU (2 vs 1 d) and hospital (12 vs 8 d) LOS compared to patients with a planned admission (n=1482) (Table 1).

Patient versus proxy

Nineteen percent of the questionnaires were completed by a proxy (n=476). Patients who were not able to complete the questionnaire by themselves were more often female (43% vs 34%), living in a healthcare facility (4.5% vs 0.6%), having a medical (49% vs 24%) or urgent surgical (22% vs 9%) ICU admission, higher mean APACHE-IV scores (65 vs 51), and a longer median ICU (3 vs 1 d) and hospital (15 vs 8 d) LOS compared with patients who completed the questionnaire themselves (n=1906) (Supplementary file 2).

Pre-ICU physical, mental and cognitive functioning, and quality of life

Thirteen percent of the patients (n=310) was frail before ICU admission (Table 2). Severe levels of fatigue were experienced by 43% of the patients (n=1051), mild levels by 22% (n=520) and normal levels of fatigue by 35% (n=852). Mild, moderate, and severe symptoms of anxiety were experienced by 15%, 10% and 3% of the patients, and symptoms of depression by 15%, 9% and 3% of the patients, respectively. Six percent (n=116) of the patients rated their cognitive functioning as abnormal. The mean quality of life SF-36 PCS and MCS scores were 41.6 (±11.6) and 47.5 (±11.4), respectively. Compared with 1 year before ICU admission, 49% of the patients (n=1186) rated their health status as declined, 41% (n=986) as the same, and 10% (n=235) as improved.

Table 1. Patient, clinical and ICU characteristics: differences between patients with an unplanned and planned ICU admission

Characteristics	Total group of patients (n=2467)	Unplanned ICU admissions (n=985)	Planned ICU admissions (n=1482)	P value
Male sex, n (%)	1577 (63.9)	570 (57.9)	1007 (67.9)	<.001*
Age, mean (SD)	62.2 (14.3)	60.0 (15.8)	63.6 (13.0)	<.001*
Categories, n (%)				
• 16-39	194 (7.9)	120 (12.2)	74 (5.0)	<.001*
• 40-64	1016 (41.2)	397 (40.3)	619 (41.8)	
• 65-79	1108 (44.9)	418 (42.4)	690 (46.6)	
• ≥80	149 (6.0)	50 (5.1)	99 (6.7)	
Education, n (%)				
• Low	786 (32.6)	326 (34.0)	460 (31.7)	.381
• Middle	1047 (43.4)	414 (43.2)	633 (43.6)	
• High	577 (23.9)	218 (22.8)	359 (24.7)	
Marital status, n (%)				
• Unmarried/ single	418 (17.2)	196 (20.2)	222 (15.2)	<.001*
• Married	1682 (69.0)	617 (63.5)	1065 (72.7)	
• Divorced	140 (5.7)	70 (7.2)	70 (4.8)	
• Widowed	196 (8.0)	89 (9.2)	107 (7.3)	
Household composition, n (%)				
• Alone	412 (17.1)	192 (20.0)	220 (15.2)	<.001*
• With someone else[1]	1964 (81.4)	746 (77.7)	1218 (83.9)	
• Healthcare facility	36 (1.5)	22 (2.3)	14 (1.0)	
One or more chronic conditions[2], n (%)	629 (25.5)	286 (29.0)	343 (23.1)	<.001*
Admission type, n (%)				
• Medical	702 (28.5)	649 (65.9)	53 (3.6)	<.001*
• Urgent surgical	288 (11.7)	269 (27.3)	19 (1.3)	
• Elective surgical	1477 (59.9)	67 (6.8)	1410 (95.1)	
APACHE IV score, mean (SD)	54.1 (21.6)	60.9 (26.6)	49.6 (16.0)	<.001*
ICU LOS, median [IQR]	1 [1-3]	2 [1-5]	1 [1-1]	<.001*
Hospital LOS, median [IQR]	9 [6-14]	12 [6-22]	8 6-12]	<.001*
Hospital mortality, n (%)	7 (0.3)	6 (0.6)	1 (0.1)	.019*

IQR: interquartile range; LOS: length of stay

** Statistical significant difference (p<0.05) between the unplanned and planned admitted patients.*

[1] For example, partner, children, parents

[2] Immunological insufficiency, AIDS, hematological malignancy, metastatic neoplasm, cirrhosis, cardiovascular insufficiency, respiratory insufficiency, COPD, chronic dialysis or renal insufficiency

Table 2. Health status and quality of life before ICU admission: differences between patients with an unplanned and planned ICU admission

Physical, mental, and cognitive functioning	Total group of patients (n=2467)	Unplanned ICU admissions (n=985)	Planned ICU admissions (n=1482)	P value
Frailty, median [IQR]a	3 [2-4]	3 [2-4]	3 [2-4]	
Categories[1], n (%)				
• Non frail	2125 (87.3)	801 (82.6)	1324 (90.4)	<.001*
• Frail	310 (12.7)	169 (17.4)	141 (9.6)	
Fatigue, median [IQR]a	34 [20-45]	34 [18-46]	34 [22-43.5]	
Categories[2], n (%)				
• Normal fatigue	852 (35.2)	360 (37.3)	492 (33.7)	.014*
• Mild fatigue	520 (21.5)	180 (18.7)	342 (23.4)	
• Severe fatigue	1051 (43.4)	425 (44.0)	627 (42.9)	
Anxiety, median [IQR]a	5 [2-8]	4 [2-8]	5 [2-8]	
Categories[3], n (%)				
• Normal	1769 (72.4)	719 (74.0)	1050 (71.3)	.014*
• Mild symptoms	361 (14.8)	136 (14.0)	225 (15.3)	
• Moderate symptoms	234 (9.6)	84 (8.7)	150 (10.2)	
• Severe symptoms	80 (3.3)	32 (3.3)	48 (3.3)	
Depression, median [IQR]a	4 [2-8]	4 [1-8]	4 [2-7.75]	
Categories[3], n (%)				
• Normal	1801 (73.7)	697 (71.6)	1104 (75.0)	.028*
• Mild symptoms	372 (15.2)	145 (14.9)	227 (15.4)	
• Moderate symptoms	212 (8.7)	101 (10.4)	111 (7.5)	
• Severe symptoms	60 (2.5)	30 (3.1)	30 (2.0)	
Cognitive functioning, median [IQR]a	20.6 [11.4-29.8]	20.4 [10.7-30.0]	21.0 [11.9-29.7]	
Categories[4], n (%)				
• Normal	1832 (94.0)	693 (92.8)	1139 (94.8)	.062
• Abnormal	116 (6.0)	54 (7.2)	62 (5.2)	
Quality of life				
Short Form-36, mean (SD)b				
• Physical function	61.7 (30.9)	59.5 (33.9)	63.1 (28.6)	.006*
• Role physical	44.3 (45.1)	48.7 (46.0)	41.4 (44.4)	<.001*
• Bodily pain	70.4 (28.2)	68.8 (30.6)	71.4 (26.5)	.033*
• General health	54.0 (22.9)	53.2 (25.6)	54.6 (20.9)	.143
• Vitality	56.3 (23.0)	55.8 (24.6)	56.5 (21.8)	.475
• Social function	68.0 (28.0)	66.9 (30.4)	68.7 (26.1)	.136
• Role emotional	68.5 (42.9)	69.5 (43.5)	67.8 (42.5)	.378
• Mental health	73.4 (19.1)	73.2 (20.5)	73.6 (18.2)	.582
• Physical component score	41.6 (11.6)	41.4 (12.3)	41.8 (11.1)	.423
• Mental component score	47.5 (11.4)	47.5 (12.2)	47.6 (10.9)	.868

IQR: interquartile range

*a Lower scores indicate better health outcomes; b Higher scores indicate better health outcomes; *Statistical significant difference between the unplanned and planned admitted ICU patients (p value <.05)*

[1] Frailty was defined by a score of ≥5 on the Clinical Frailty Scale (CFS)

[2] Mild fatigue was defined by a score of 27-36, severe fatigue by a score ≥37 on the Checklist individual Strength (CIS)

[3] Mild anxiety and depression symptoms were defined by a score of 8-10, moderate symptoms by a score of 11-14 and severe symptoms by a score of ≥15 on the Hospital Anxiety and Depression Scale (HADS)

[4] Abnormal cognitive function was defined by a score of >43 on the Cognitive Failure Questionnaire (CFQ)

Unplanned versus planned admitted ICU patients

Unplanned and planned ICU patients differed in their pre-ICU health status (Table 2, and supplementary file 3). Patients with an *unplanned* ICU admission were more often frail (17% vs 10%) and experiencing symptoms of moderate (10% vs 7.5%) or severe depression (3% vs 2%) than patients with a planned ICU admission. Patient with a *planned* ICU admission were more often suffering from mild fatigue (23% vs 19%). No significant differences between the two groups were seen in anxiety and quality of life PCS and MCS scores.

Patient versus proxy

Differences in pre-ICU health status were also seen in questionnaires completed by patients or proxies: in the proxy-completed questionnaires, patients experienced significantly more problems in frailty (23% vs 10%), severe fatigue (51% vs 41%), and symptoms of anxiety (36% vs 25%) or depression (36% vs 24%). Furthermore, proxies reported lower quality of life scores on most of the subdomains and PCS of the SF-36. No differences were found in cognitive functioning and SF-36 MCS (Supplementary file 4).

Other subgroups

Significant differences in pre-ICU health status and quality of life were also seen between subgroups of patients (Table 3). In general, patients with a poor health status and lower quality of life before ICU admission were more often female, older, lower educated, divorced or widowed, living in a healthcare facility, and suffering from a chronic condition.

Table 3. Differences between subgroups in pre-ICU physical, mental, and cognitive health status, and quality of life

	Frailty CFS (1-9)[a] Median [IQR]	**Fatique CIS-8 (8-56)**[a] Median [IQR]	**Anxiety HADS-A (0-21)**[a] Median [IQR]	**Depression HADS-D (0-21)**[a] Median [IQR]	**Cognitive function CFQ-14 (0-100)**[a] Median [IQR]	**Quality of life SF-36 PCS (0-100)**[b] Mean (SD)	**Quality of life SF-36 MCS (0-100)**[b] Mean (SD)
Gender							
• Female	3 [2-4]***	37 [25-47]***	6 [3-9]***	5 [2-8]***	21.4 [12-31]*	39.5 (11.9)***	45.9 (11.8)***
• Male	2 [2-3]	32 [18-43]	4 [2-7]	4 [1-7]	20.4 [10.8-29.2]	42.8 (11.3)	48.4 (11.1)
Age							
• 16-39	2 [1-4]***	32 [14-44]*	4 [2-8]*	3 [1-6.8]***	18 [7.7-28.8]*	44.6 (12.4)***	47.3 (12.1)
• 40-64	2 [2-3]	35 [21-46]	5 [2-8]	4 [1-8]	19.7 [10.4-28.9]	42.3 (11.8)	47.4 (11.3)
• 65-79	3 [2-4]	33 [20-43.3]	5 [2-8]	5 [2-8]	21.3 [12.1-30.4]	40.9 (11.2)	47.5 (11.5)
• 80 and older	3 [2-4]	33.5 [24-44.3]	4 [1-6]	4 [2-8]	23.1 [12-32.2]	37.8 (10.5)	49.7 (10.4)
Education							
• Low	3 [2-4]***	36 [24-46.3]***	5 [2-9]***	5 [2-9]***	20.4 [10.8-30.1]	39.4 (11.2)***	46.0 (12.2)***
• Middle	3 [2-4]	34 [21-44.8]	5 [2-8]	4 [2-8]	20.8 [11.7-30.4]	41.6 (11.8)	47.6 (11.2)
• High	2 [2-3]	28 [16-41]	4 [1-7]	3 [1-6]	20.9 [11.6-29]	44.8 (11.1)	49.2 (10.4)
Marital status							
• Single	3 [2-4]***	34 [18-43]**	4 [2-7]	4 [1-7]***	20.5 [11-29.1]***	42.5 (12.0)***	47.2 (11.4)*
• Married	3 [2-3.8]	33 [20-44]	5 [2-8]	4 [2-8]	20.6 [11.4-29.8]	42.0 (11.5)	47.9 (11.3)
• Divorced	3 [2-4]	38 [25-46]	5 [3-8]	5 [3-9]	20.7 [12.2-33.9]	40.2 (11.8)	45.2 (12.1)
• Widowed	3 [2-5]	37 [25.5-46.8]	5 [2-9]	5 [2-8]	21.6 [12.5-30.5]	37.7 (11.3)	46.4 (11.7)
Household composition							
• Alone	3 [2-4]***	36 [25-46]**	5 [2-8]	4 [2-9]**	21.8 [12.9-31.6]*	39.1 (11.0)***	46.1 (11.6)*
• With someone else	3 [2-3]	33 [19-44]	5 [2-8]	4 [1-8]	20.4 [11-29.5]	42.3 (11.6)	47.8 (11.4)
• Healthcare facility	5 [2.3-6.8]	38 [26.5-49]	6 [2-12]	5 [2-8]	22.2 [12.2-35.5]	32.5 (12.1)	45.5 (11.3)
Chronic condition							
• No	2 [2-3]***	32 [18-43]***	4 [2-8]***	4 [1-7]***	20.8 [11.4-29.8]	43.3 (11.3)***	47.9 (11.5)**
• Yes	3 [2-4]	38.9 [29-48]	5 [3-8]	5 [3-9]	20.3 [11.5-30.4]	36.5 (11.1)	46.3 (11.0)

[a] *Lower scores indicate better health outcomes;* [b] *Higher scores indicate better health outcomes;*
*Statistical significant difference between the subgroups: * p-value= 0.01-0.05; ** p-value 0.001-0.01; *** p-value <0.001*
CFS: Clinical Frailty Scale; CIS-8: Checklist Individual Strength; HADS: Hospital Anxiety and Depression Scale; CFQ-14: Cognitive Failure Questionnaire; SF-36: Short Form

DISCUSSION

In this large cohort study of ICU survivors, we showed that before ICU admission, 13% of the patients was already frail, 65% suffered from fatigue, and 28% and 26% from respectively symptoms of anxiety and depression. Six percent experienced problems in their cognitive functioning. Patients with a poor pre-ICU health status were more likely to be female, older, lower educated, divorced or widowed, living in a healthcare facility, and suffering from a chronic condition. Substantial differences were seen between patients with a planned and unplanned ICU admission.

Whereas previous studies often assessed one specific pre-ICU health outcome, for example, cognitive functioning (13, 27) or quality of life (28, 29), we assessed patient's physical, mental, and cognitive functioning, as well as the quality of life, thereby providing a more complete picture of the pre-ICU health status. However, rates of pre-ICU frailty, anxiety, depression, and cognitive impairment are lower compared with other studies (13, 17, 27, 40, 41). This may be explained by differences in inclusion criteria: in other studies, only elderly patients (13, 27) or medical patients with an ICU LOS of more than 48 hours (41) were included. Nevertheless, quality of life is in line with previous studies (28, 29, 42, 43), and significantly lower than the quality of life experienced by the general Dutch population (44). The patient subgroups that experience a worse pre-ICU health status are consistent with those reported in other studies as well (21, 27, 28).

Implication for clinical practice

In recent decades, the key question in intensive care medicine has changed from "Will my patient survive or die" into "How will my patient survive" (45). However, the use of accurate ICU prognostic models, such as the APACHE-IV or Simplified Acute Physiology Scores (SAPS), is not sufficient to answer this question: they predict short-term survival (46), but are unable to predict important outcomes for ICU survivors, namely physical, mental, and cognitive functioning, return to work, and quality of life in the months and years following ICU discharge (47, 48).

"Study the past if you would define the future" proclaimed Confucius. Insight in patients' pre-ICU health status is paramount. First of all because it could support clinical decision-making and set shared treatment goals (46, 49-51). Besides, patients and their relatives can be better informed about possible

long-term outcomes based on their functional status before admission (16, 52). Second, it helps to identify specific types of patients who are at risk for specific long-term problems and could benefit from preventive interventions (13, 15). For example, long-term mental health problems following ICU admission could be modifiable if distressed patients are identified and receive treatment early (53), including psychologic support, education, and coping strategies (54). And third, accounting for the pre-ICU health status is important for assessing the impact of critical illness and ICU exposure on long-term outcomes. Failing to account for pre-existing diseases and comorbidities before ICU admission may overestimate the attributable effect of critical illness and ICU stay (19, 25, 55). Besides, it could improve the evaluation of interventions (14, 56), because it is plausible that subgroups of patients respond differently to interventions (14).

Limitations

This study has several limitations. First, half of the patients completed the questionnaire after ICU admission, recalling their health status before admission. Although this was the only way we could assess the pre-ICU health status in patients with an unplanned admission, it could have led to recall bias, potentially leading to an overestimation of baseline function (24, 55). Second, 20% of the questionnaires were completed by proxies, showing significantly worse outcomes in frailty, fatigue, anxiety, and depression, compared with questionnaires completed by patients themselves. The usefulness and reliability of proxies assessments could be criticized because their perception of baseline status could differ from the patient (28, 55). On the other hand, studies have demonstrated that proxies are able to reliably assess patient's pre-ICU quality of life (42, 57). The alternative, excluding patients who are unable to complete the questionnaire by themselves, also introduced bias (28). And third, the question is whether commonly used standardized outcome measures, such as the SF-36 and HADS, adequately reflect patients experiences. A previous study, in which standardized outcomes measures were compared with findings from qualitative interviews, concluded that it is reliable to use standardized outcome measures for physical and mental health impairment (58). However, they emphasized that caution is needed in interpreting self-reported cognitive function. Additionally, a recent published study found no clinically relevant correlation between subjective and objective cognitive function, highlighting thereby the complexity of cognitive function

testing. In our study, cognitive impairment rates were lower than expected and it is likely that these rates were an underestimation (59).

Conclusions

In an era with increasing attention for health problems after ICU admission, the results of this study indicate that a part of the ICU survivors already experience impairments in their physical, mental, and cognitive functioning before their ICU admission. More than half of the patients suffered from fatigue and a quarter from symptoms of anxiety and depression. A lower proportion was frail or cognitive impaired. Substantial differences in impairment rates were seen between patient subgroups. These findings underline the importance of accounting for the health status before ICU admission when studying long-term outcomes in ICU patients.

Acknowledgements

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Supplementary file 1. Differences between study participants and Dutch ICU survivors: unplanned versus planned ICU admissions

	Study population (n=2467)				Dutch ICU survivors (n=183,362) [23][a]			
	Unplanned (n=985)		Planned (n=1482)		Unplanned (n=62701)		Planned (n=120661)	
Age categories, n (%)								
• 16-20	32	(3.2)	17	(1.1)	1912	(1.6)	360	(0.6)
• 20-30	38	(3.9)	25	(1.7)	6561	(5.4)	867	(1.4)
• 30-40	50	(5.1)	32	(2.2)	7273	(6.0)	1416	(2.3)
• 40-50	76	(7.7)	95	(6.4)	10672	(8.8)	4097	(6.5)
• 50-60	197	(20.0)	284	(19.2)	19250	(16.0)	10424	(16.6)
• 60-70	292	(29.6)	508	(34.3)	28534	(23.6)	18869	(30.1)
• 70-80	250	(25.4)	422	(28.4)	30516	(25.3)	20613	(32.9)
• 80-90	49	(5.0)	98	(6.6)	14545	(12.1)	5751	(9.2)
• 90+	1	(0.1)	1	(0.1)	1398	(1.2)	304	(0.5)
Male, n (%)	570	(57.9)	1007	(67.9)	69277	(57.4)	41705	(66.5)
Chronic condition[1], n (%)	286	(29.0)	343	(23.1)	40183	(33.3)	18019	(28.7)
Admission type, n (%)								
• Medical	649	(65.9)	53	(3.6)	88360	(73.2)	2189	(3.5)
• Acute surgical	269	(27.3)	19	(1.3)	20063	(16.6)	1107	(1.8)
• Elective surgical	67	(6.8)	1410	(95.1)	11288	(9.4)	59350	(94.1)
• Unknown (donor procedure)	0	(0.0)	0	(0.0)	950	(0.8)	55	(0.1)
APACHE III*** score, median (IQR)	58	[41-76]	48	[39-49]	54	[38-73]	44	[34-55]
ICU LOS, median [IQR]	2	[1-5]	1	[1-1]	1.5	[0.8-3.4]	0.9	[0.8-1.2]
Post ICU days, median [IQR]	8	[4-15]	6	[4-8]	6.4	[3.2-12.8]	4.5	[2.6-7.4]
Hospital mortality, n (%)	6	(0.6)	1	(0.1)	6898	(5.7)	833	(1.3)

APACHE: Acute Physiology and Chronic Health Evaluation; ICU: intensive care unit; IQR: interquartile range; LOS: length of stay [a] ICU survivors admitted to a Dutch ICU between 1 July 2016 and 31 December 2018; [1]Chronic diagnosis are immunological insufficiency, AIDS, hematological malignancy, metastatic neoplasm, cirrhosis, cardiovascular insufficiency, respiratory insufficiency, COPD, chronic dialysis, renal insufficiency [23] van de Klundert N, Holman R, Dongelmans DA, de Keizer NF, (2015) Data Resource Profile: the Dutch National Intensive Care Evaluation (NICE) Registry of Admissions to Adult Intensive Care Units. Int J Epidemiol 44: 1850-1850h

Supplementary file 2. Differences in characteristics of patient who completed the questionnaires themselves (n=1906) or whose proxy completed the questionnaire (n=476)

	Completed by patient (n=1906)		**Completed by proxy (n=476)**		**P value**
Male sex, n (%)	1253	(65.7)	273	(57.4)	.001*
Age, mean (SD)	62.1	(13.4)	61.4	(17.7)	.401
Categories, n (%)					
• 16-39	129	(6.8)	64	(13.4)	<.001*
• 40-64	843	(44.2)	150	(31.5)	
• 65-79	832	(43.7)	223	(46.8)	
• ≥80	102	(5.4)	39	(8.2)	
Education, n (%)					
• Low	514	(27.5)	228	(49.1)	<.001*
• Middle	851	(45.6)	171	(36.9)	
• High	502	(26.9)	65	(14.0)	
Marital status, n (%)					
• Unmarried/ single	321	(17.1)	90	(19.0)	<.001*
• Married	1327	(70.5)	300	(63.4)	
• Divorced	114	(6.1)	22	(4.7)	
• Widowed	119	(6.3)	61	(12.9)	
Household composition, n (%)					
• Alone	313	(16.8)	79	(17.0)	<.001*
• With someone else1	1543	(82.6)	365	(78.5)	
• Healthcare facility	12	(0.6)	21	(4.5)	
One or more chronic conditions[2], n (%)	465	(24.4)	134	(28.2)	.091
Admission type, n (%)					
• Medical	456	(23.9)	231	(48.5)	<.001*
• Urgent surgical	179	(9.4)	104	(21.8)	
• Elective surgical	1271	(66.7)	141	(29.6)	
APACHE IV score3, mean (SD)	51.2	(19.0)	65.4	(27.6)	<.001*
ICU LOS, median [IQR]	1	[1-2]	3	[1-11]	<.001*
Hospital LOS, median [IQR]	8	[5-12]	15	[8-31]	<.001*
Hospital mortality, n (%)	1	(0.1)	6	(1.3)	<.001*

APACHE: Acute Physiology and Chronic Health Evaluation; IQR: interquartile range; LOS: length of stay; SD: standard deviation

** Statistical significant difference (p<.05) between patient and proxy completed questionnaires*

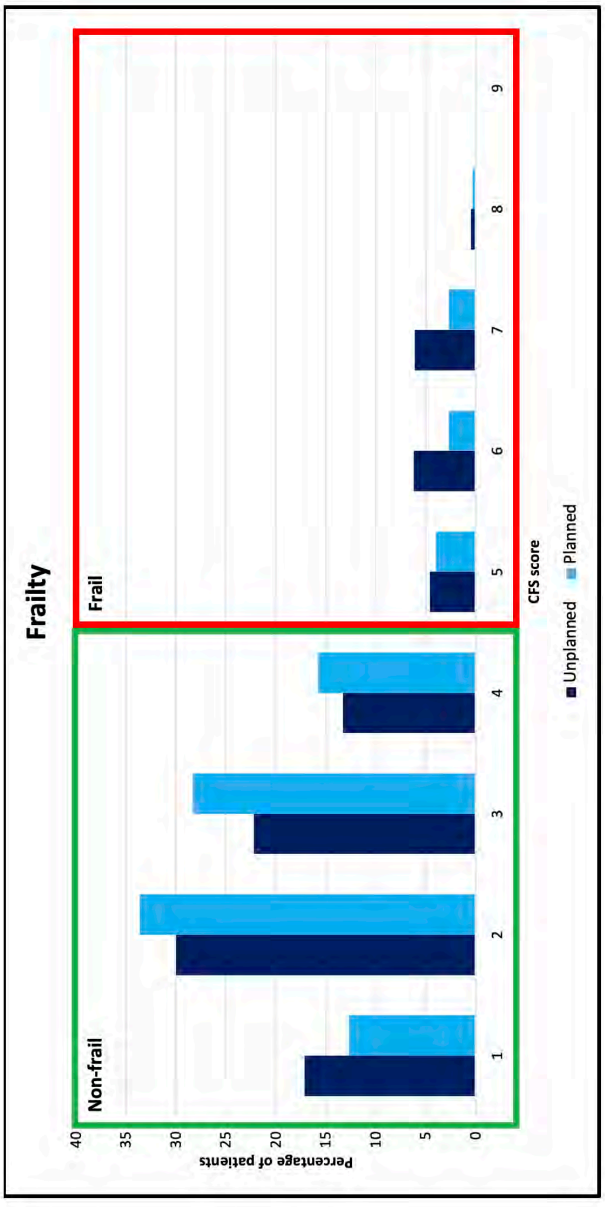
[1] E.g. partner, children, parents

[2] Immunological insufficiency, AIDS, hematological malignancy, metastatic neoplasm, cirrhosis, cardiovascular insufficiency, respiratory insufficiency, COPD, chronic dialysis or renal insufficiency

[3] Acute Physiology and Chronic Health Evaluation

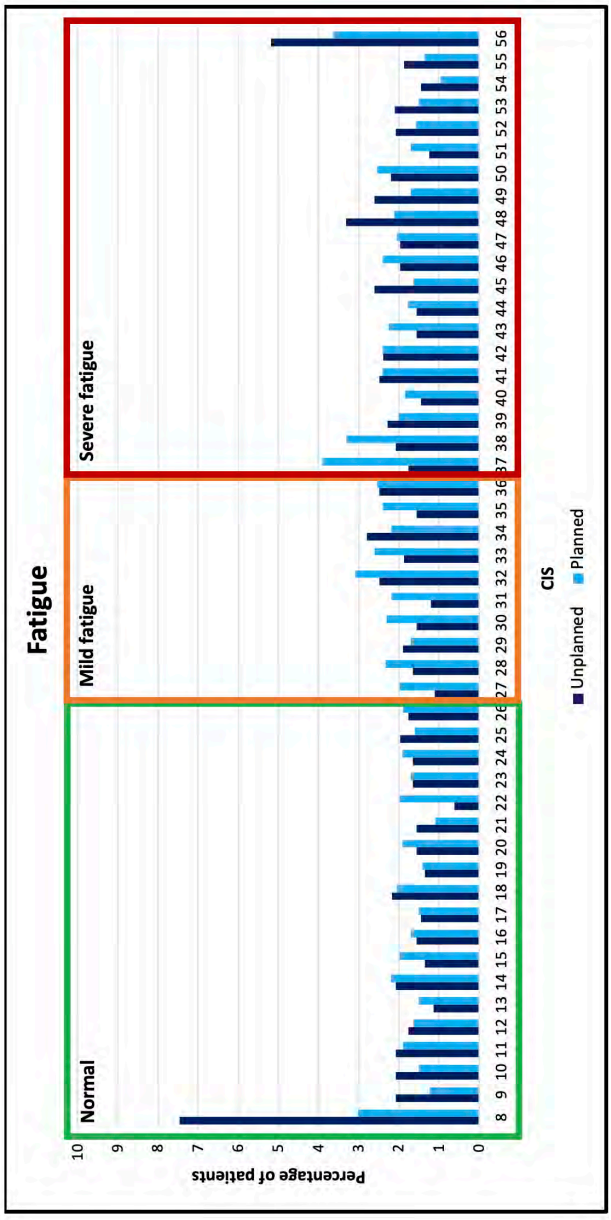
In 85 questionnaires it was unknown whether the patient or the proxy completed the questionnaire. The questionnaires were therefore not included in the analysis.

Supplementary file 3. Charts of physical, mental and cognitive health outcomes for unplanned and planned ICU patients



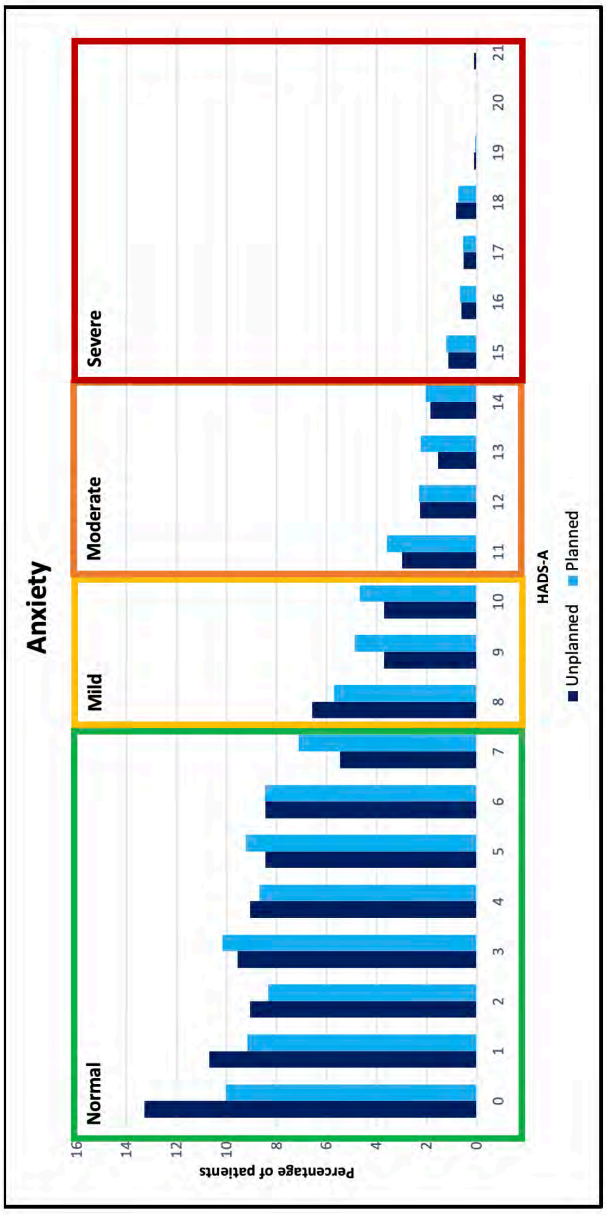
Non-frail: CFS score 1-4; Frail: CFS score 5-9

Supplementary file 3. Charts of physical, mental and cognitive health outcomes for unplanned and planned ICU patients



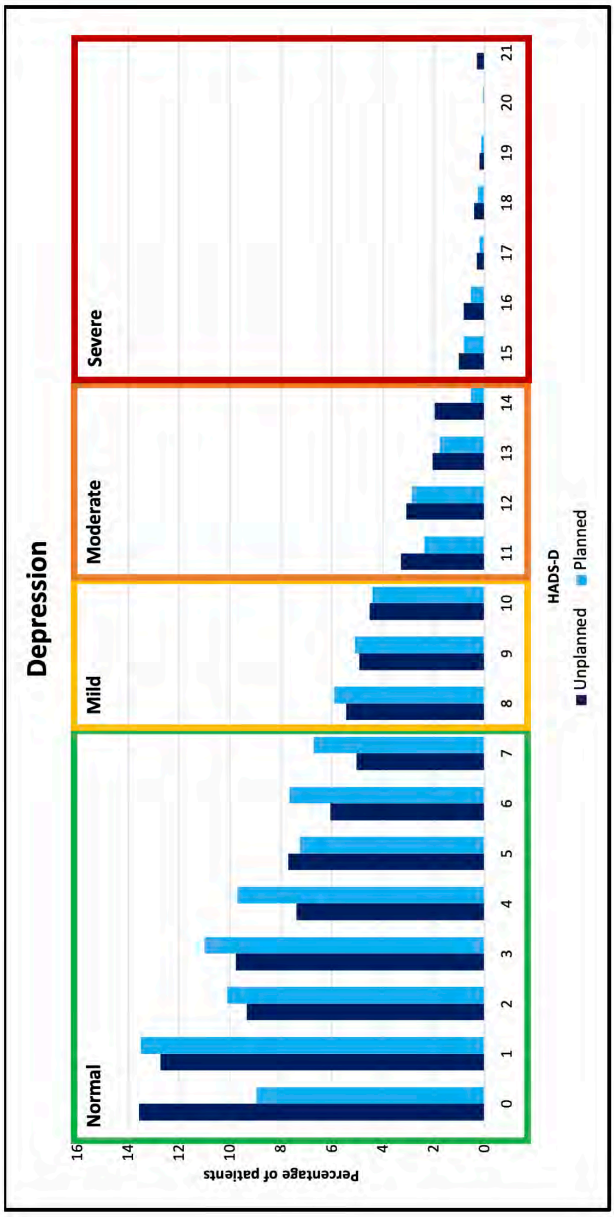
Normal levels of fatigue: CIS-8 score 8-26; Mild fatigue: CIS-8 core 27-36; Severe fatigue: CIS-8 score 36-56

Supplementary file 3. Charts of physical, mental and cognitive health outcomes for unplanned and planned ICU patients



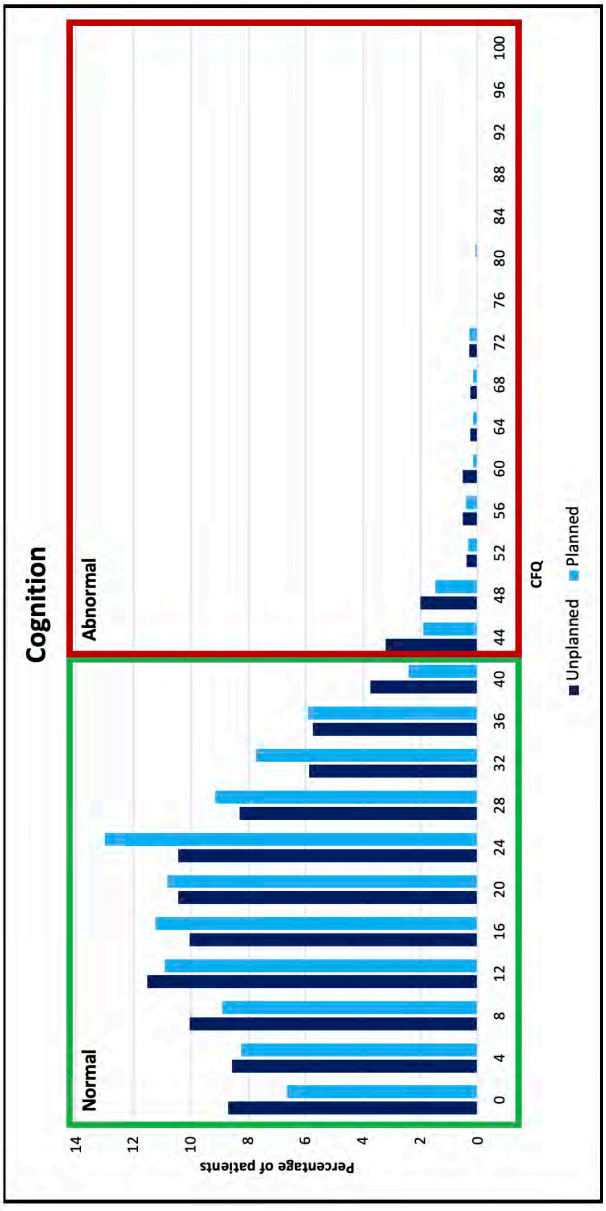
Normal symptoms of anxiety: HADS-A score 0-7; Mild symptoms of anxiety: HADS-A score 8-10; Moderate symptoms of anxiety: HADS-A score 11-14; Severe symptoms of anxiety: HADS-A score 15-21

Supplementary file 3. Charts of physical, mental and cognitive health outcomes for unplanned and planned ICU patients



Normal symptoms of depression: HADS-D score 0-7; Mild symptoms of depression: HADS-D score 8-10; Moderate symptoms of depression: HADS-D score 11-14; Severe symptoms of depression: HADS-D score 15-21

Supplementary file 3. Charts of physical, mental and cognitive health outcomes for unplanned and planned ICU patients



Normal cognitive function: CFQ score 0-43; Abnormal cognitive function: CFQ score 44-100

Supplementary file 4. Difference in patient's pre-ICU health status between patient and proxy completed questionnaires

Physical, mental and cognitive functioning	Patients (n=1906)		Proxies# (n=476)		P value
Frailty, median [IQR]a	3	[2-4]	3	[2-4]	
Categories[1], n (%)					
• Non frail	1691	(89.9)	364	(77.4)	<.001*
• Frail	191	(10.1)	106	(22.6)	
Fatigue, median [IQR]a	33	[20-43]	37	[21-48]	
Categories[2], n (%)					
• Normal fatigue	678	(36.0)	154	(33.3)	<.001*
• Mild fatigue	433	(23.0)	71	(15.3)	
• Severe fatigue	774	(41.1)	238	(51.4)	
Anxiety, median [IQR]a	4	[2-8]	6	[2-10]	
Categories[3], n (%)					
• Normal	1420	(75.0)	299	(64.0)	<.001*
• Mild symptoms	271	(14.3)	72	(15.4)	
• Moderate symptoms	156	(8.2)	67	(14.3)	
• Severe symptoms	47	(2.5)	29	(6.2)	
Depression, median [IQR]a	4	[2-7]	5	[2-10]	
Categories[3], n (%)					
• Normal	1446	(76.3)	299	(63.9)	<.001
• Mild symptoms	283	(14.9)	74	(15.8)	
• Moderate symptoms	131	(6.9)	71	(15.2)	
• Severe symptoms	35	(1.8)	24	(5.1)	
Cognitive functioning, median[4] [IQR]	20.8	[11.7-30.2]	19.0	[9.5-29.0]	
Categories, n (%)					
• Normal	1457	(94.4)	315	(92.4)	.147
• Abnormal	86	(5.6)	26	(7.6)	
Quality of life					
SF-36, mean (SD)[b]					
• Physical function	63.9	(29.2)	54.5	(35.6)	<.001*
• Role physical	43.6	(44.8)	48.4	(46.6)	.048*
• Bodily pain	71.6	(27.2)	66.7	(31.7)	.003*
• General health	55.1	(22.2)	49.7	(25.5)	<.001*
• Vitality	57.7	(22.1)	51.0	(25.8)	<.001*
• Social function	69.3	(26.8)	63.4	(31.9)	<.001*
• Role emotional	69.9	(42.1)	65.0	(45.0)	.037*
• Mental health	74.6	(18.4)	68.4	(21.5)	<.001*
• PCS	42.0	(11.3)	40.6	(12.5)	.029*
• MCS	47.4	(11.5	47.7	(11.3)	.550

IQR: Interquartile range; SD: standard deviation
 # In 85 questionnaires it was unknown whether the patient or the proxy completed the questionnaire.
[a]Lower scores indicate better health outcomes; [b]Higher scores indicate better health outcomes.
** Statistical significant difference between patient outcomes between questionnaires completed by patients or their proxy (p value <.05) [1] Frailty was defined by a score of ≥5 on the Clinical Frailty Scale (CFS) [2] Mild fatigue was defined by a score of 27-36, severe fatigue by a score ≥37 on the Checklist individual Strength (CIS) [3] Mild anxiety and depression symptoms were defined by a score of 8-10, moderate symptoms by a score of 11-14 and severe symptoms by a score of ≥15 on the Hospital Anxiety and Depression Scale (HADS) [4] Abnormal cognitive function was defined by a score of >43 on the Cognitive Failure Questionnaire (CFQ)*

CHAPTER 4

NEW PHYSICAL, MENTAL, AND COGNITIVE PROBLEMS 1 YEAR AFTER ICU ADMISSION: A PROSPECTIVE MULTICENTER STUDY

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ABSTRACT

Rationale Comprehensive studies addressing the incidence of physical, mental, and cognitive problems after ICU admission are lacking. With an increasing number of ICU survivors, an improved understanding of post-ICU problems is necessary.

Objectives To determine the occurrence and cooccurrence of new physical, mental, and cognitive problems among ICU survivors 1 year after ICU admission, their impact on daily functioning, and risk factors associated with 1-year outcomes.

Methods Prospective multicenter cohort study, including ICU patients ≥16 years of age, admitted for ≥12 hours between July 2016 and June 2019. Patients, or proxies, rated their health status before and 1 year after ICU admission using questionnaires.

Measurements and mean results Validated questionnaires were used to measure frailty, fatigue, new physical symptoms, anxiety and depression, post-traumatic stress disorder, cognitive impairment, and quality of life. Of the 4793 patients included, 2345 completed the questionnaires both before and 1 year after ICU admission. New physical, mental, and/or cognitive problems 1 year after ICU admission were experienced by 58% of the medical patients, 64% of the urgent surgical patients, and 43% of the elective surgical patients. Urgent surgical patients experienced a significant deterioration in their physical and mental functioning, whereas elective surgical patients experienced a significant improvement. Medical patients experienced an increase in symptoms of depression. A significant decline in cognitive functioning was experienced by all types of patients. Pre-ICU health status was strongly associated with post-ICU health problems.

Conclusions Overall, 50% of ICU survivors suffer from new physical, mental, and/or cognitive problems. An improved insight into the specific health problems of ICU survivors would enable more personalized post-ICU care.

Trial registration NCT03246334 (clinical trials.gov)

INTRODUCTION

Many ICU survivors experience an array of long-lasting health problems, collectively labelled as post-intensive care syndrome (PICS) and defined as new or worsening physical, mental, and cognitive impairments that arise after critical illness and persist beyond acute care hospitalization (1). Symptoms such as pain, muscle weakness, dyspnea, depression, anxiety, post-traumatic stress symptoms, and problems with attention and memory are common (1). These problems can be profound, last for months or even years, and significantly impact survivors' daily functioning, ability to return to work, quality of life (QoL), and associated healthcare costs (2). Precise occurrence rates are unclear because the rates vary widely among post-ICU physical (25-80%), mental (8-57%), and cognitive (30-80%) impairments (3, 4). Although the critical care community is increasingly aware of these long-term problems, there is still a general lack of awareness among patients, families, and the posthospital care community (4). Furthermore, post-ICU care is still fragmented and, with the increasing number of ICU patients and survivors every year (5), the need for coordinated and structured post-ICU care is urgent. To achieve this, an improved understanding of these long-term problems is deemed necessary. Although PICS is multidimensional, comprehensive studies including all three areas of PICS are lacking (6-8). In addition, although previous studies report prevalence rates of post-ICU problems, preexisting health status is not taken into account, thereby creating a biased picture of post-ICU problems in ICU survivors (9). That is, the incidence rates of new, post-ICU, problems are rarely assessed.

Given this gap, the aims of this study were to determine the occurrence and cooccurrence of new physical, mental, and cognitive problems among ICU survivors 1 year after ICU admission, their impact on daily functioning, and risk factors associated with problems at 1 year.

METHODS

Study design

Data from the MONITOR-IC study, a large, ongoing, longitudinal, prospective multicenter cohort study (ClinicalTrials.gov: NCT03246334), are used. Detailed information is included in the study protocol (10). The study has been approved by the research ethics committee of the Radboud university medical center (Arnhem-Nijmegen, the Netherlands) (2016-2724). Each participant, or

their legal representative, provided written informed consent. This study has been reported in line with the Strengthening the Reporting of Observational studies in Epidemiology guidelines (11).

Study population

Between July 1, 2016, and June 30, 2019, adults ICU patients (≥ 16 yr of age) of four hospitals were potentially included in the sample, provided they had been admitted to an ICU for at least 12 hours. This limitation was imposed to exclude ICU patients being monitored during a short intervention such as a bronchoalveolar lavage. Patients were also excluded if they had a short life expectancy (≤48 hours), were receiving palliative care, or could not read and speak Dutch. Patients were grouped by type of ICU admission: medical admission (nonsurgical admission, e.g. pneumonia, cardiac arrest), urgent surgical admission (acute surgical problem, e.g. spinal cord decompression, aneurysm), or elective surgical admission (planned surgery with ICU monitoring and/or treatment after surgery, e.g. coronary artery bypass grafting, esophageal resection).

Data collection

Patients, or their proxies, completed a baseline questionnaire addressing their health status before ICU admission. Elective surgical patients received the baseline questionnaire at the preoperative outpatient clinic and completed the questionnaire a few days before their ICU admission. Medical and urgent surgical patients received the baseline questionnaire while in the ICU. These patients, or their proxy, were then asked to rate their health status retrospectively, recalling their health status before ICU admission. One year after ICU admission, the follow-up questionnaire was sent out. Depending on their preferences, patients received the questionnaires online or on paper. For the baseline measurement, a reminder was sent after 4 weeks, and a telephoned reminder was provided 2 weeks later if necessary. For the 1-year questionnaire, reminders were sent after 2 and 4 weeks.

Outcomes

The following outcomes were assessed:

1. Frailty was measured using the Clinical Frailty Scale (CFS) (12), consisting of one item with a score ranging from 1 (very fit) to 9 (terminally ill). Patients were classified as ‘nonfrail’ (score 1-4) or ‘frail’ (5-9) (13).

2. Fatigue was assessed using the 8-item subscale of the 20-Item Checklist Individual Strength (14), which uses a 7-point rating scale, with the total score in the range of 8-56. A score of ≥ 27 is considered to indicate fatigue.
3. New or worsened physical problems, subsequent to ICU admission, were measured using the questionnaire 1 year after ICU admission, which included a list of 30 items (see Supplementary file 1). The 4-point Likert-scale options were dichotomized into 'no problems' (no or mild symptoms) or 'problems' (moderate or severe symptoms).
4. Symptoms of anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS) (15), which includes a 7-item anxiety subscale (HADS-A) and a 7-item depression subscale (HADS-D). Answers were given on a 4-point Likert scale ranging from 0 to 3, with the total possible score thus ranging from 0-21 for each. A score of ≥8 on a subscale indicates symptoms of anxiety or depression.
5. Symptoms of post-traumatic stress disorder (PTSD) 1 year after ICU admission were assessed using the Impact of Event Scale-Revised (IES-R) (16). The 22 items on this scale were rated from 0 (not at all) to 4 (extremely). A threshold of ≥1.6 (for the mean score of all the items) was used to define clinically significant PTSD symptoms (17).
6. Cognitive health was measured using the abbreviated 14-Item Cognitive Failure Questionnaire, which covers domains of daily life failures, such as perception, memory, and motor function (18). Answers to the 14 questions were given on a 5-point Likert scale ranging from 0 (never) to 4 (very often). Overall scores were factored to give a 0-100 range. A cut-off of >43 was used to distinguish abnormal from normal functioning (19).
7. QoL was assessed using the 36-item Short Form Survey (SF-36) (20), which covers eight domains, with scores ranging from 0-100 and higher scores indicating a better QoL. Scores were aggregated into two summary measures: a Physical Component Summary (PCS) and a Mental Component Summary (MCS).

Patient demographics, such as age, sex, and education level, were addressed in the baseline questionnaire. Clinical variables, including, for example, admission type, severity-of-illness score (Acute Physiology and Chronic Health Evaluation IV [APACHE]-IV), and ICU and hospital lengths of stay (LOS) were retrieved from the electronic health record.

Statistical analysis

Only patients who completed both the baseline and 1-year questionnaires (constituting complete cases) were included in the analyses. To assess the direction and magnitude of possible participation bias, various characteristics were compared between complete cases and nonresponders (i.e. completed only the baseline questionnaire) and between complete cases and nonsurvivors (completed baseline questionnaire but died within the first year after ICU admission) using the independent sample t test, Mann-Whitney *U* test, or chi-square test.

Differences in the characteristics of medical, urgent surgical, and elective surgical patients were assessed using an ANOVA, Kruskal-Wallis test, or chi-square test as appropriate. Where there were missing values in the CIS-8, HADS, CFQ-14, and SF-36 scales, these were imputed using the half-rule (21). Missing values in the IES-R were replaced with the individual mean, provided that 75% of the items were completed. Statistical differences between pre-ICU results and outcomes 1 year after ICU admission in the various categories were assessed using the McNemar's Test, and the SF-36 mean difference scores with the paired *t* test.

To assess the cooccurrence of health problems 1 year after ICU admission, outcomes were first dichotomized using the cutoffs specified above and were then categorized into three health domains: physical health (including frailty, fatigue, and new or worsened physical problems), mental health (including anxiety, depression, and PTSD), and cognitive health (cognitive impairment). Cooccurrence was defined as the presence of problems in two or all three health domains.

To report newly experienced post-ICU health problems, *incidence* rates were calculated, thereby excluding patients with related pre-ICU impairments. So, for example, patients who were frail in the baseline survey were excluded when measuring 1-year frailty. *Prevalence* rates (when patients with the health problems before ICU admittance are included) are provided in Supplementary file 3, 4 and 5.

To explore risk factors associated with new symptoms of frailty, fatigue, anxiety, depression, PTSD, and cognitive impairment 1 year after ICU admission, multivariable logistic regression analyses were conducted, with patient characteristics, pre-ICU health status, and ICU characteristics included as covariates. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. The variables were simultaneously entered into multivariable

logistic regression models. All statistical analyses were performed using the SPSS statistical package (version 25; IBM). Values of $p<.05$ were considered to indicate statistical significance.

RESULTS

Study population

Of the 6466 eligible patients, 4793 patients were included, of whom 3320 completed the baseline questionnaire, and 2345 (71%) of these also the 1-year questionnaire (Figure 1). Of the 2345 complete cases, 649 patients (28%) had a medical reason for admission, 284 (12%) an urgent surgical reason for admission, and 1412 (60%) an elective surgical reason for admission. Medical patients were more often suffering from a chronic condition, had a higher APACHE IV score, and had a longer stay in ICU. Elective surgical patients were significantly more likely to be male, older, and suffering from fatigue and anxiety before ICU admission, whereas the urgent surgical patients were least likely to be suffering from pre-ICU health problems. The majority of the medical (75%), urgent surgical (71%), and elective surgical patients (92%) completed the baseline questionnaire themselves (Table 1).

The nonresponders to the second survey (n=766) and nonsurvivors (n=209) differed significantly from the patients with complete cases: before ICU admission, they more often had a chronic condition, physical or mental health problems, and a lower QoL (Supplementary file 2).

Figure 1. Flow diagram multicenter cohort study

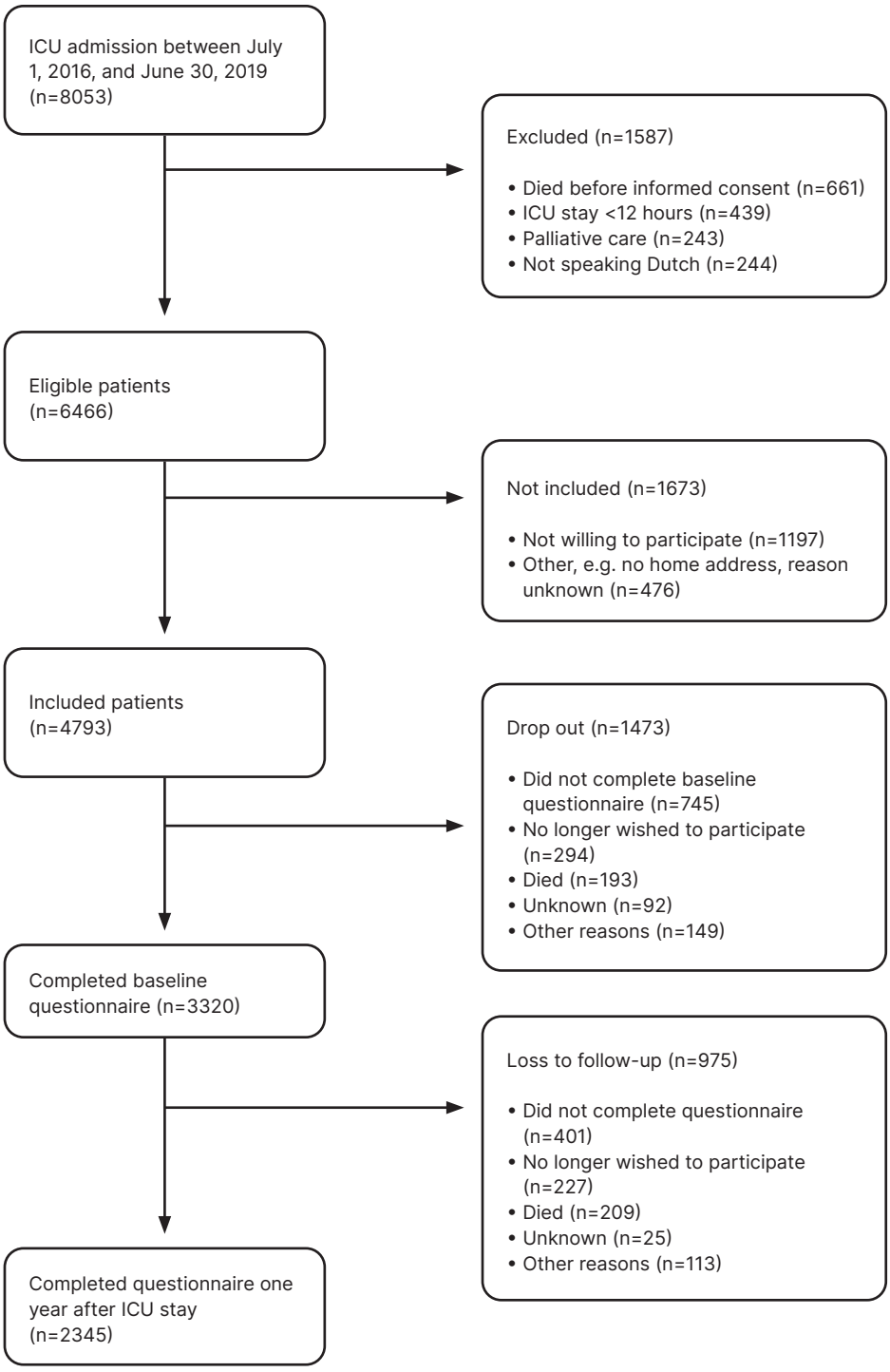

Table 1. Characteristics of medical, urgent surgical, and elective surgical ICU-admitted patients

Patient characteristics	Medical (n=649)		Urgent surgical (n=284)		Elective surgical (n=1412)		P-value
Sex, n (%)							
• Female	253	(39.0)	114	(40.1)	420	(29.7)	<.001*
• Male	396	(61.0)	170	(59.9)	992	(70.3)	
Age, yr, mean (SD)	60.7	(14.4)	59.8	(16.0)	64.5	(11.9)	<.001*
Education, n (%)							
• Low	208	(33.0)	82	(29.1)	411	(29.7)	.323
• Middle	254	(40.3)	132	(46.8)	596	(43.1)	
• High	169	(26.8)	68	(24.1)	378	(27.3)	
Marital status, n (%)							
• Unmarried/single	115	(17.9)	51	(18.3)	181	(12.9)	<.001*
• Married	432	(67.1)	194	(69.5)	1052	(75.3)	
• Divorced	52	(8.1)	17	(6.1)	63	(4.5)	
• Widowed	45	(7.0)	17	(6.1)	102	(7.3)	
Household composition, n (%)							
• Living alone	114	(18.0)	40	(14.2)	204	(14.6)	.018*
• With someone else[a]	506	(80.1)	239	(85.1)	1180	(84.7)	
• Healthcare facilit	12	(1.9)	2	(0.7)	9	(0.6)	
Chronic conditionb, n (%)							
• No	427	(65.8)	243	(85.6)	1108	(78.5)	<.001*
• Yes	222	(34.2)	41	(14.4)	304	(21.5)	
Pre-ICU healt status							
Frailty categories1, n (%)							
• Non-frail	523	(81.5)	260	(91.9)	1279	(91.4)	<.001*
• Frail	119	(18.5)	23	(8.1)	120	(8.6)	
Fatigue categories2, n (%)							
• No fatigue	246	(38.3)	132	(47.0)	494	(35.3)	<.001*
• Fatigue	396	(61.7)	149	(53.0)	905	(64.7)	
Anxiety categories3, n (%)							
• No anxiety	502	(78.0)	228	(80.9)	1025	(73.0)	<.004*
• Anxiety	142	(22.0)	54	(19.1)	380	(27.0)	
Depression categories3, n (%)							
• No depression	495	(76.9)	225	(79.5)	1082	(77.0)	.624
• Depression	149	(23.1)	58	(20.5)	324	(23.0)	
Cognitive functioning categories4, n (%)							
• Normal	509	(93.4)	214	(93.0)	1156	(94.4)	.561
• Abnormal	36	(6.6)	16	(7.0)	68	(5.6)	
Quality of life, mean (SD)							
• PCS	41.9	(12.4)	44.8	(11.6)	42.5	(10.8)	.003*
• MCS	49.4	(11.2)	49.4	(11.0)	47.6	(11.0)	.002*

Table 1. Continued

Patient characteristics	Medical (n=649)		Urgent surgical (n=284)		Elective surgical (n=1412)		P-value
ICU characteristics							
APACHE IV score, mean (SD)	62.1	(26.5)	57.6	(22.9)	49.8	(15.0)	<.001*
ICU LOS, median [IQR]	3	[1-6]	2	[1-6]	1	[1-1]	<.001*
Hospital LOS, median [IQR]	11	[6-21]	14	[9-24]	8	[5-11]	<.001*

[a] Such as a partner, children, parents; [b]Immunological insufficiency, AIDS, hematological malignancy, metastatic neoplasm, cirrhosis, cardiovascular insufficiency, respiratory insufficiency, COPD, chronic dialysis or renal insufficiency. [1]Frailty was defined as a score of ≥5 on the CFS; [2] Fatigue was defined as a score of ≥27 CIS; [3]Anxiety and depression symptoms were defined as a score of ≥8 on the HADS; 4Substantial PTSD symptoms were defined as a score of ≥1.6 (total score divided by 22) on the IES-R; 5 Abnormal cognitive function was defined as a score of >43 on the Cognitive Failure Questionnaire (CFQ).
*Definition of abbreviations: APACHE IV: Acute Physiology and Chronic Health Evaluation IV; IQR: interquartile range; LOS: length of stay; MCS: mental component score; PCS: physical component score; SD: Standard deviation *Statistically significant difference (p<.05) among patients with a medical ICU admission, patients with an urgent surgical ICU admission, and patients with an elective surgical ICU admission .*

Cooccurrence and occurrence of new post-ICU problems

One year after ICU admission, 58% of the medical ICU patients, 64% of the urgent surgical IC patients, and 43% of the elective surgical ICU patients were suffering from new physical, mental, and/or cognitive health problems (Figure 2). Most patients were only experiencing problems in a single health domain, with physical problems being the most common (Figure 2). Only 12% of the medical patients, 30% of the urgent surgical patients, and 9% of the elective surgical patients were experiencing problems in two domains, and only 4%, 5%, and 1%, respectively, were experiencing problems in all three domains (Figure 2).

Major differences were found in the occurrence of new post-ICU problems among medical, urgent surgical, and elective surgical patients. Urgent surgical patients suffered the most, and substantial differences were seen compared with elective surgical patients in, for example, frailty (12% vs 4%), fatigue (45% vs 24%), weakened condition (38% vs 25%), muscle weakness (22% vs 10%), anxiety (20% vs 9%), depression (20% vs 10%), and cognitive impairment (13% vs 6%) (Figure 3 and Supplementary file 1). The percentages in medical patients were similar but slightly lower than those of the urgent surgical patients.

Before ICU admission, many medical and elective surgical patients were already suffering from health problems such as fatigue (>60%) and anxiety (>20%). One year after admission, elective surgical patients overall experienced a significant improvement, whereas urgent surgical patients experienced a significant deterioration in their physical and mental health. A significant deterioration in cognitive functioning was seen in all three groups (Supplementary file 4).

Figure 2. Co-occurrence of newly experienced physical, mental, and cognitive health problems one year after ICU admission

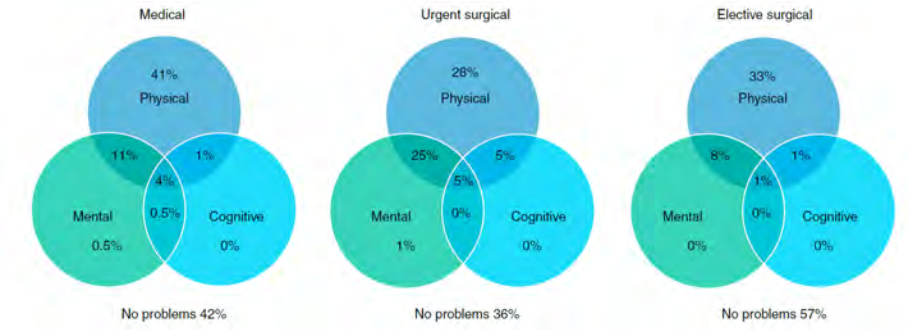

Figure 3. Occurrence of newly experienced physical, mental, and cognitive health problems 1 year after ICU admission

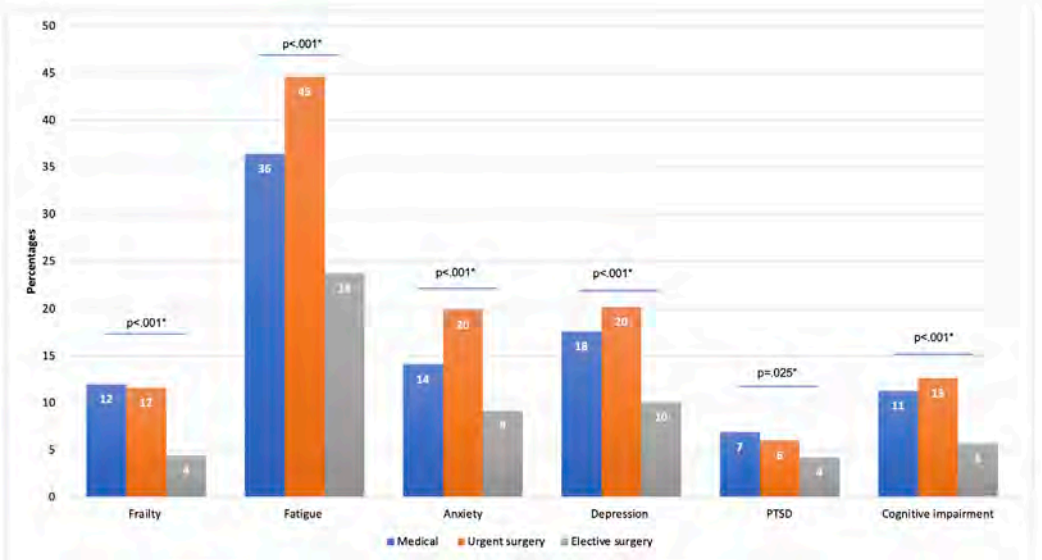

Table 2. Associations between patient characteristics, pre-ICU health status, and ICU-related characteristics and new physical, mental, and cognitive outcomes 1 year after ICU admission

	Frailty [1]		Fatigue [2]		Anxiety [3]		Depression [3]		PTSD [4]		Cognitive impairment [5]	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Patient characteristics												
Sex, male	0.51 (0.33-0.78)	.002*	0.49 (0.33-0.72)	<.001*	0.75 (0.53-1.07)	.114	1.07 (0.76-1.53)	.687	0.76 (0.49-1.20)	.242	0.73 (0.50-1.06)	.103
Age												
• 16-39 yr												
• 40-64 yr	0.70 (0.27-1.80)	.458	1.14 (0.56-2.31)	.724	0.59 (0.30-1.15)	.121	0.97 (0.48-1.98)	.939	0.36 (0.16-0.81)	.014*	0.69 (0.35-1.40)	.306
• 65-79 yr	1.01 (0.39-2.60)	.990	1.19 (0.57-2.47)	.642	0.53 (0.26-1.04)	.066	1.19 (0.57-2.45)	.644	0.39 (0.17-0.91)	.030*	0.44 (0.21-0.92)	.030*
• ≥80 yr	3.78 (1.22-11.70)	.021*	0.69 (0.23-2.11)	.520	0.35 (0.12-1.03)	.057	0.91 (0.33-2.56)	.865	0.37 (0.11-1.29)	.120	0.36 (0.10-1.23)	.104
Education												
• Low (ref)												
• Middle	0.58 (0.37-0.93)	.023*	0.69 (0.45-1.06)	.092	0.73 (0.49-1.08)	.115	0.67 (0.46-0.96)	.029*	0.67 (0.42-1.07)	.096	1.03 (0.68-1.56)	.886
• High	0.69 (0.39-1.22)	.202	0.69 (0.44-1.09)	.112	0.72 (0.46-1.13)	.150	0.52 (0.34-0.81)	.004*	0.32 (0.15-0.68)	.003*	0.74 (0.44-1.26)	.266
Household												
• Alone(ref)												
• Multiple	0.81 (0.48-1.35)	.419	0.78 (0.47-1.29)	.338	0.95 (0.61-1.50)	.840	0.69 (0.46-1.05)	.082	0.60 (0.35-1.02)	.058	0.78 (0.48-1.26)	.313
• Nursing home	1.65 (0.25-10.64)	.601	0.82 (0.08-8.17)	.865	0.00 (0.00-∞)	.999	0.45 (0.09-2.29)	.336	1.29 (0.24-6.98)	.766	2.19 (0.39-12.24)	.371
Pre-ICU health												
Chronic condition	1.40 (0.88-2.22)	.153	1.37 (0.84-2.24)	.204	0.85 (0.56-1.30)	.463	1.00 (0.68-1.48)	.996	0.95 (0.57-1.59)	.836	0.80 (0.51-1.25)	.322
Frailty			0.88 (0.30-2.62)	.822	1.19 (0.70-2.03)	.516	1.59 (0.92-2.72)	.094	1.00 (0.54-1.85)	.993	0.68 (0.37-1.25)	.210
Fatigue	2.01 (1.19-3.41)	.009*			1.57 (1.07-2.31)	.020*	1.60 (1.12-2.27)	.009*	1.21 (0.69-2.15)	.505	1.47 (0.94-2.30)	.089

[1] Frailty was defined by a score of ≥5 on the Clinical Frailty Scale (CFS); [2] Fatigue was defined by a score of ≥27on the Checklist individual Strength (CIS); [3] Anxiety and depression symptoms were defined by a score of ≥ 8 on the Hospital Anxiety and Depression Scale (HADS); [4] Substantial PTSD symptoms were defined by a score of ≥1.6 (total score dived by 22) on the Impact of Event Scale Revised (IES-R); [5] Abnormal cognitive function was defined by a score of >43 on the Cognitive Failure Questionnaire (CFQ)

Table 2. Continued

	Frailty [1]		Fatigue [2]		Anxiety [3]		Depression [3]		PTSD [4]		Cognitive impairment [5]	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Anxiety	0.91 (0.53-1.57)	.738	1.41 (0.47-2.55)	.262			2.56 (1.72-3.82)	<.001	2.72 (1.62-4.59)	<.001*	2.30 (1.49-3.55)	<.001*
Depression	1.90 (1.12-3.23)	.017*	2.50 (1.15-5.43)	.021*	1.85 (1.16-2.94)	.009*			1.48 (0.86-2.53)	.157	1.49 (0.94-2.34)	.087
Cognitive failure	1.88 (0.92-3.81)	.082	1.18 (0.32-4.38)	.809	1.88 (0.90-3.95)	.094	0.95 (0.42-2.16)	.905	1.60 (0.83-3.08)	.162		
ICU characteristics												
Admission												
• Medical (ref)												
• Urgent surgical	0.83 (0.45-1.52)	.543	0.88 (0.52-1.49)	.646	1.72 (1.05-2.84)	.032*	1.32 (0.81-2.16)	.264	1.11 (0.55-2.21)	.775	1.16 (0.67-2.00)	.594
• Elective surgical	0.42 (0.25-0.69)	.001*	0.51 (0.34-0.78)	.002*	0.85 (0.55-1.30)	.449	0.59 (0.39-0.88)	.010*	0.65 (0.38-1.10)	.110	0.51 (0.33-0.78)	.002*
APACHE IV	1.00 (0.99-1.01)	.352	0.99 (0.98-1.00)	.129	1.00 (0.99-1.01)	.594	0.99 (0.98-1.00)	.147	1.00 (0.99-1.02)	.542	1.01 (1.00-1.02)	.088
ICU LOS	1.00 (0.97-1.04)	.963	0.99 (0.95-1.04)	.791	1.02 (0.99-1.06)	.194	1.02 (0.99-1.05)	.190	1.03 (0.98-1.07)	.223	1.00 (0.96-1.04)	.959
Hospital LOS	1.03 (1.02-1.05)	<.001*	1.04 (1.02-1.06)	<.001*	1.01 (0.99-1.02)	.545	1.01 (1.00-1.03)	.061	0.98 (0.96-1.01)	.208	0.99 (0.97-1.01)	.548

[1] Frailty was defined by a score of ≥5 on the Clinical Frailty Scale (CFS); [2] Fatigue was defined by a score of ≥27on the Checklist individual Strength (CIS); [3] Anxiety and depression symptoms were defined by a score of ≥ 8 on the Hospital Anxiety and Depression Scale (HADS); [4] Substantial PTSD symptoms were defined by a score of ≥1.6 (total score dived by 22) on the Impact of Event Scale Revised (IES-R); [5] Abnormal cognitive function was defined by a score of >43 on the Cognitive Failure Questionnaire (CFQ)

Factors associated with post-ICU health problems

Patients' pre-ICU physical, mental, and/or cognitive health status was strongly associated with new post-ICU problems (Table 2). For example, patients who were anxious before admission were more likely to be suffering 1 year later from symptoms of depression (adjusted odds ratio [aOR], 2.56; 95% CI, 1.72-3.82) and PTSD (aOR, 2.72; 95% CI, 1.62-4.59), whereas patients who were fatigued before admission were more likely to report post-ICU frailty (aOR, 2.01; 95% C,I 1.19-3.41), anxiety (aOR, 1.57; 95% CI, 1.07-2.31), and depression (aOR, 1.60; 95% CI, 1.12-2.27). Furthermore, a lengthy hospital stay was significantly associated with frailty (aOR, 1.03; 95% CI, 1.02-1.05) and fatigue (aOR, 1.04; 95% CI, 1.02-1.06). Being older (age ≥80 yr) was also associated with frailty (aOR, 3.78; 95% CI, 1.22-11.70).

Factors that were significantly associated with a lower likelihood of physical, mental, or cognitive health problems 1 year after ICU admission were a higher education level and having been admitted for elective surgery (Table 2). Male patients were less likely to report frailty (aOR, 0.51; 95% CI, 0.33-0.78) and fatigue (aOR, 0.49; 95% CI, 0.33-0.72) than female patients.

Impact on daily functioning

In terms of their QoL 1 year after a period in the ICU, those admitted as urgent surgical patients were experiencing a significant *decline* (in seven of the eight SF-36 subdomains and in their PCS and MCS scores) whereas elective surgical patients perceived a significant *improvement*, with significantly higher mean scores on all eight SF-36 domains and in the PCS and MCS scores (Supplementary file 6). Those admitted as medical patients did not experience a significant change in their QoL. Furthermore, of the patients who were in employment when admitted, 43% of the medical patients, 54% of the urgent surgical patients, and 34% of the elective surgical patients experienced work-related problems because of their critical illness: they were still on sick leave, working fewer hours, had opted for early retirement, or had given up their job.

DISCUSSION

In this longitudinal prospective multicenter study, 58% of the medical patients, 64% of the urgent surgical patients, and 43% of the elective surgical patients were suffering from new physical, mental, and/or cognitive health problems 1 year after ICU admission. Physical problems were most frequently reported. Relative to their pre-ICU health status, urgent surgical patients experienced

a significant deterioration in their physical and mental health and their QoL, whereas elective surgical patients experienced a significant improvement. A significant deterioration in cognitive functioning was seen in all categories of patients. Pre-ICU health status was strongly associated with long-term health problems, whereas having a higher education level and being male were associated with fewer problems.

Physical problems are known to be common after ICU admission (22, 23). In the present study, almost 40% of the medical and urgent surgical patients were suffering 1 year after ICU admission from a weakened condition, and 20% were suffering from muscle weakness. Patients can lose 15-20% of their muscle mass within the first week of ICU admission, and many patients, despite therapy, will never return to their preadmission state (24). Other reported problems we identified, such as dyspnea, fatigue, and pain, are also consistent with findings of other studies (5, 24).

Given that the vast majority of previous studies have focused on *prevalence* rates of post-ICU problems, the reported rates are logically higher than the *incidence* rates found in our study. For example, meta-analyses of mental health problems have reported pooled rates of anxiety (34%), depression (29%), and PTSD (22%) (25-27), and, in a systematic review on cognitive impairment, rates between 4% and 62% were found, with most of the included studies reporting rates higher than those found in our study (28). Note, however, that these differences in rates could also be due to heterogeneity in included patients, instruments used, duration of follow-up, or definitions used (29).

The cooccurrence of new PICS problems 1 year after ICU admission has recently been described elsewhere (7). In that study, disabilities related to activities of daily living, depression, and cognitive impairment were used as outcomes. They concluded that cooccurring PICS problems were present in 20% of the medical and surgical ICU patients. This rate is higher than the cooccurring PICS problems in our study for elective surgical patients (10%) and medical patients (16%) but lower than those for urgent surgical patients (35%). Differences in the outcomes measured and the instruments used might explain these differences.

Although numerous factors, including critical illness and ICU treatment, are associated with the long-term problems that ICU survivors experience (30-32), the strongest association has repeatedly been found to be with pre-ICU health status (1, 26, 27, 33), a finding that our data support. Given this

relationship, it is surprising that more cohort studies on long-term outcomes do not take preexisting health into account (9), thereby likely overestimating the effects attributable to critical illness and ICU admission. The incidence rates of post-ICU problems found in our study were substantially lower than the prevalence rates: for example, the incidence of fatigue was almost 30% lower than the prevalence in our sample of medical ICU patients.

Urgent surgical patients and, to a lesser extent, medical patients experienced a *deterioration* in their physical and mental health status, and their QoL, 1 year after ICU admission, whereas elective surgical patients experienced an *improvement*. There are several plausible explanations for this. Patients with an unplanned admission (i.e. medical and urgent surgical patients) tend to have either an acute, potentially reversible, life-threatening organ disfunction or a high risk of developing one (34), whereas elective surgery patients are often admitted after a medical procedure to alleviate their symptoms and improve their survival likelihood (35). After surgery, elective patients requiring short-term monitoring of vital organ functions are often placed in an ICU, and they tend to spend less time in the ICU and in the hospital than medical and urgent surgical patients and require a shorter period of mechanical ventilation (36), longer durations of all these interventions are known as risk factors for adverse long-term outcomes (4). Another possible explanation is that elective surgical patients are better prepared and informed about their ICU admission, treatment, and recovery trajectory, aspects which can reduce stress and increase comfort levels (37). Furthermore, post-ICU care might be better organized for elective surgical patients than for medical patients, with, for example, clinical pathways and rehabilitation programs for CABG patients (38).

Strengths and limitations of the study

This study has several strengths. First, a very large number of ICU patients with medical, urgent surgical, or elective surgical reasons for admission were included, making reliable comparisons between groups possible and differences in post-ICU recovery visible. Physical, mental, and cognitive health outcomes, as well as QoL, were assessed, thereby providing a complete picture of the health status of ICU survivors. According to relevant stakeholders, including patients, family members, and researchers, these outcomes (including return to work) are the most important outcomes to measure (39). Moreover, because it was possible to adjust for pre-ICU health status, a valid picture of the impact

of critical illness and an ICU stay on the post-ICU problems could emerge. Furthermore, because instruments recommended in the core outcomes set, including the SF-36, HADS, and IES-R (8), were used, comparison with other studies is possible.

However, this study also has several limitations. First, the study's outcomes were measured using patient-reported outcome measures (PROMs). Although PROMS can be used as screening instruments to aid the detection of health problems and to monitor the impact of illness and treatment on patients' functioning and health status, PROMs should not be used as diagnostic tools (29, 40-42). Second, nonresponse bias is likely because the individuals included in the analysis had a significantly better pre-ICU health status than nonsurvivors and nonresponders, which is associated with better long-term health outcomes. Consequently, the health problems reported after 1 year are likely to be an underestimation. Third, some relevant risk factors could not be included in the logistic regression analysis because data were not available. These include delirium duration, multisystem organ dysfunction, sedation, and duration of mechanical ventilation, which are known risk factors for physical, mental, and cognitive health problems (43). Fourth, the majority of the medical (75%) and urgent surgical (71%) ICU patients completed their baseline questionnaire after ICU admission, and the retrospective estimation of their pre-ICU health status might involve recall bias (44). In addition, cognitive deterioration, as a result of the ICU stay and critical illness, might have led to an inaccurate assessment of pre-ICU health status (45). Fifth, and finally, it is likely that physical problems are over-represented in this study because more instruments addressing physical health than regarding mental and cognitive health were included.

Implications for clinical practice

During ICU admission, patients who are at risk of developing physical, mental, and/or cognitive health problems should be identified (46). Patients at risk include, for example, those with preexisting functional disability, mental health problems and cognitive dysfunction, or significant physical or neurological injuries or those suffering from delirium, acute stress reactions, and intrusive memories of traumatic events during ICU stay (46, 47). A comprehensive needs assessment is necessary to establish patients' rehabilitation goals and needs (47) and to start early interventions to prevent and mitigate long-term adverse outcomes (1, 26) with, for example, physical therapy and early mobilization

(47, 48), ICU diaries (49), or cognitive interventions (48). In patients with preexisting mental health problems, psychological interventions, including support, education, and coping strategies, could start in advance during ICU admission (50, 51).
Rehabilitation continuity is important on being discharged from the ICU and hospital and can be achieved by having a plan for ongoing treatment, including medication, nutrition, and therapy, in place (47). Informing patients about their recovery, symptoms that could frequently occur, and how they can manage activities in their daily lives is necessary (47). Furthermore, outpatient physical therapy and in-home cognitive therapy (48) should be considered, together with follow-up monitoring after discharge, for example, in post-ICU follow-up clinics (52) to review patients' recovery and reassess their health and social needs (46, 47). The appropriateness of a one-size-fits-all approach is doubtful (53) because major differences are seen in post-ICU problems and in the post-ICU recovery trajectories of the patients in the present study. Tailored interventions are needed to individualize therapy. Furthermore, it is important to raise awareness, not only among patients but also in their families, policymakers, and healthcare providers, including rehabilitation specialists and general practitioners, of the long-term problems that ICU survivors can experience and their ongoing care needs (1, 4, 48).

Conclusions

One year after ICU admission, around 60% of the medical and urgent surgical ICU survivors and 40% of the elective surgical ICU survivors were suffering from new physical, mental, and/or cognitive health problems that were impacting on their QoL and ability to return to work. Urgent surgical patients were especially likely to experience a significant decline in their health status and QoL, whereas elective surgical patients were experiencing an improvement 1 year after ICU admission. A decline in cognitive functioning was seen in all groups: the medical, urgent surgical, and elective surgical patients. The study provides further evidence that pre-ICU health status is an important determinant of long-term post-ICU problems.

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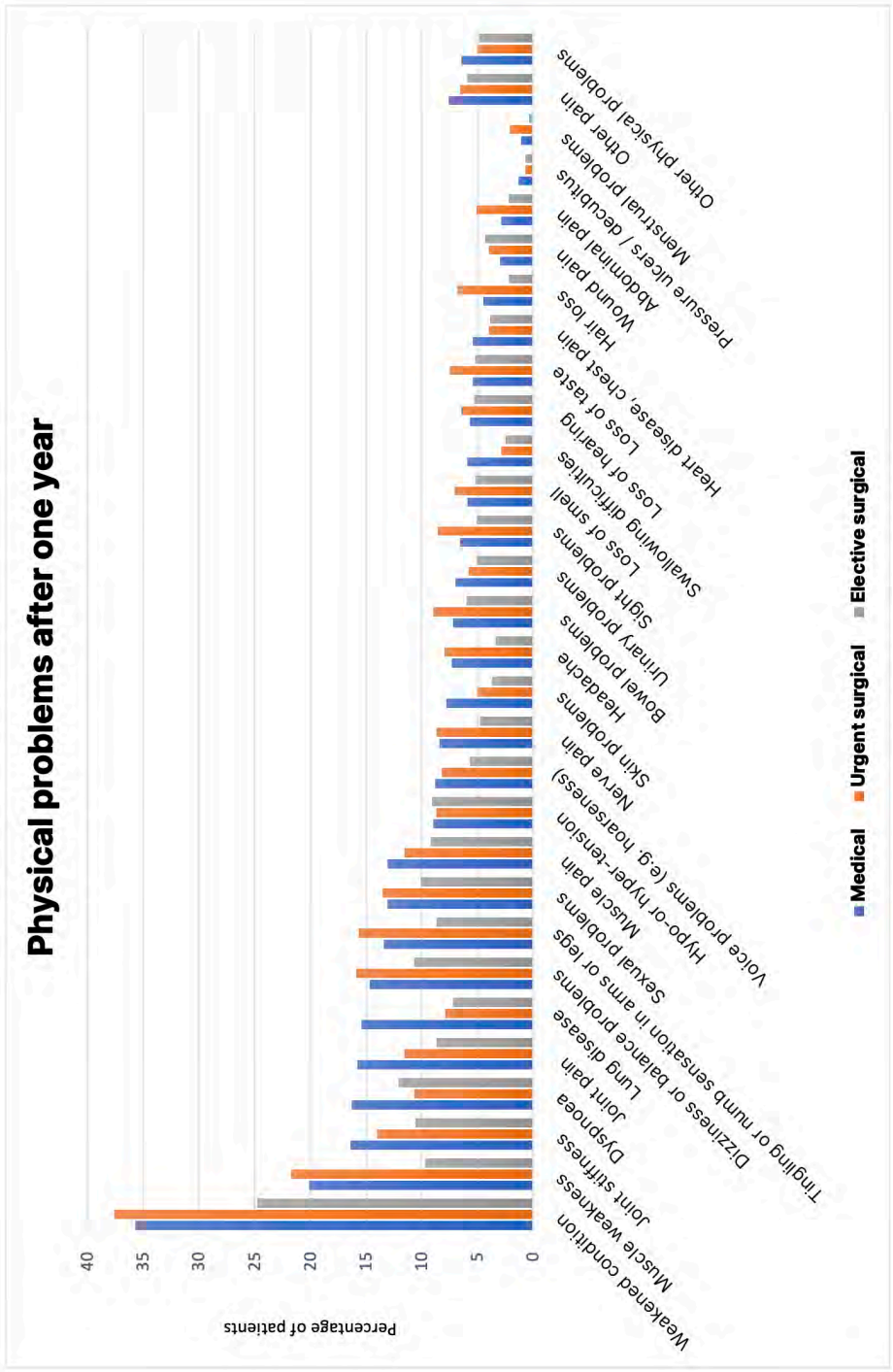
Supplementary file 1. New or worsened physical problems one year after ICU admission



Supplementary file 1.

Physical problem	Medical	Urgent surgical	Elective surgical
Weakened condition	35.7	37.6	24.8
Muscle weakness	20.1	21.7	9.7
Joint stiffness	16.4	14.0	10.6
Dyspnoea	16.3	10.7	12.1
Joint pain	15.8	11.6	8.7
Lung disease	15.4	7.9	7.2
Dizziness or balance problems	14.7	15.9	10.7
Tingling or numb sensation in arms or legs	13.4	15.7	8.7
Sexual problems	13.1	13.5	10.1
Muscle pain	13.1	11.6	9.2
Hypo-or hyper-tension	9.0	8.7	9.1
Voice problems (e.g. hoarseness)	8.8	8.2	5.7
Nerve pain	8.4	8.7	4.8
Skin problems	7.8	5.0	3.7
Headache	7.3	8.0	3.4
Bowel problems	7.2	9.0	6.0
Urinary problems	7.0	5.8	5.1
Sight problems	6.6	8.6	5.1
Loss of smell	5.9	7.1	5.2
Swallowing difficulties	5.9	2.9	2.5
Loss of hearing	5.7	6.5	5.3
Loss of taste	5.4	7.5	5.2
Heart disease, chest pain	5.4	4.0	3.9
Hair loss	4.5	6.8	2.2
Wound pain	3.0	4.0	4.3
Abdominal pain	2.9	5.1	2.2
Pressure ulcers / decubitus	1.3	0.7	0.7
Menstrual problems	1.1	2.1	0.4
Other pain	7.6	6.6	5.9
Other physical problems	6.5	5.0	4.9

Supplementary file 2. Characteristics of complete cases, non-responders and non-survivors

Patient characteristics	Complete cases (n=2345)		Non-responders (n=766)		P-value	Non-survivors (n=209)		P-value
Gender, n (%)								
• Female	787	(33.6)	316	(41.3)	<.001*	70	(33.5)	.984
• Male	1558	(66.4)	450	(58.7)		139	(66.5)	
Age, mean (SD)	62.9	(13.3)	60.1	(16.2)	<.001*	66.9	(11.4)	<.001*
Education, n (%)								
• Low	701	(30.5)	305	(40.5)	<.001*	86	(42.4)	<.001*
• Middle	982	(42.7)	320	(42.4)		85	(41.9)	
• High	615	(26.8)	129	(17.1)		32	(15.8)	
Marital status, n (%)								
• Unmarried / single	347	(15.0)	173	(22.8)	<.001*	21	(10.2)	.064
• Married	1678	(72.3)	468	(61.6)		150	(72.8)	
• Divorced	132	(5.7)	45	(5.9)		12	(5.8)	
• Widowed	164	(7.1)	74	(2.0)		23	(11.2)	
Household composition, n (%)								
• Living alone	358	(15.5)	150	(20.1)	.003*	38	(18.8)	.001*
• With someone else[a]	1925	(83.5)	582	(78.1)		156	(77.2)	
• Healthcare facility	23	(1.0)	13	(1.7)		8	(4.0)	
One or more chronic condition[b], n (%)								
• No	1778	(75.8)	527	(68.8)	<.001*	114	(54.5)	<.001*
• Yes	567	(24.2)	239	(31.2)		95	(45.5)	
Pre-ICU health status								
Frailty (CFS), median [IQR]	3	[2-4]	3	[2-4]	<.001*	3	[2-4]	<.001*
Fatigue (CIS-8), median [IQR]	33	[19-44]	36	[23-46]	<.001*	37	[24-49]	<.001*
Anxiety (HADS-A), median [IQR]	4	[2-7]	5	[3-9]	<.001*	5	[2-8]	.027*

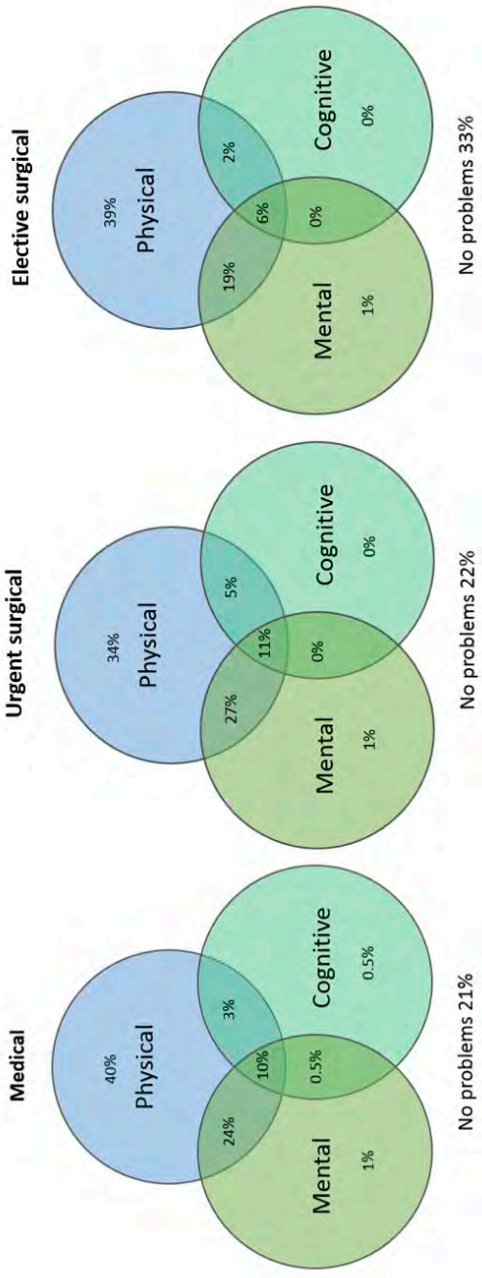
[a] *Such as partner, children, parents;* [b] *Immunological insufficiency, AIDS, hematological malignancy, metastatic neoplasm, cirrhosis, cardiovascular insufficiency, respiratory insufficiency, COPD, chronic dialysis or renal insufficiency.*
**Statistically significant difference (p<.05) between complete cases and non-responders or between complete cases and non-survivors*

Supplementary file 2. Continued

Patient characteristics	Complete cases (n=2345)		Non-responders (n=766)		P-value	Non-survivors (n=209)		P-value
Depression (HADS-D), median [IQR]	4	[2-7]	5	[2-9]	<.001*	6	[2-10]	<.001*
Cognitive function (CFQ-14), median [IQR]	20.6	[11.7-29.6]	21.1	[11.6-30.9]	.288	18.5	[9.8-30.4]	.358
Quality of life, mean (SD)								
• PCS	42.6	(11.4)	41.0	(11.5)	.002*	36.8	(11.4)	<.001*
• MCS	48.3	(11.1)	46.1	(11.8)	<.001*	45.4	(11.6)	.001*
ICU and clinical characteristics								
Admission type, n (%)								
• Medical	649	(27.7)	276	(36.0)	<.001*	81	(38.8)	.002*
• Acute surgical	284	(12.1)	100	(13.1)		16	(7.7)	
• Elective surgical	1412	(60.2)	390	(50.9)		112	(53.6)	
APACHE IV score, mean (SD)	54.2	(20.6)	53.9	(23.8)	.730	63.2	(26.5)	<.001*
ICU LOS, median [IQR]	1	[1-3]	1	[1-3]	.106	2	[1-4]	<.001*
Hospital LOS, median [IQR]	9	[6-14]	9	[5-16]	.618	13	[7-23]	<.001*

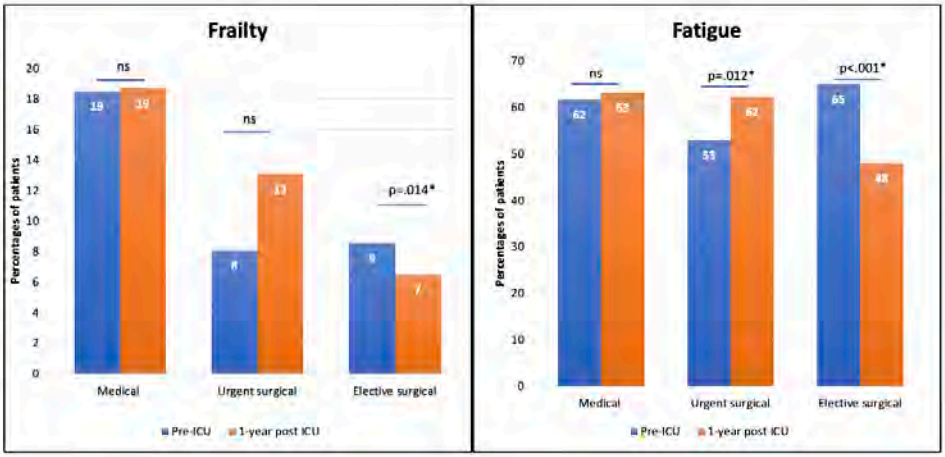
[a] *Such as partner, children, parents;* [b] *Immunological insufficiency, AIDS, hematological malignancy, metastatic neoplasm, cirrhosis, cardiovascular insufficiency, respiratory insufficiency, COPD, chronic dialysis or renal insufficiency.*
**Statistically significant difference (p<.05) between complete cases and non-responders or between complete cases and non-survivors*

Supplementary file 3. Cooccurrence of physical, mental, and cognitive health problems one year after ICU admission (prevalence)

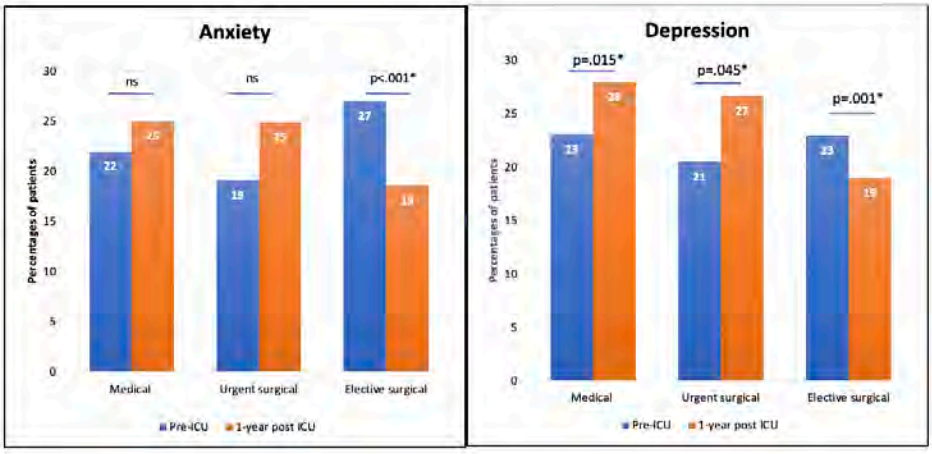


Supplementary file 4. Occurrence of physical, mental, and cognitive problems before and one year after ICU admission

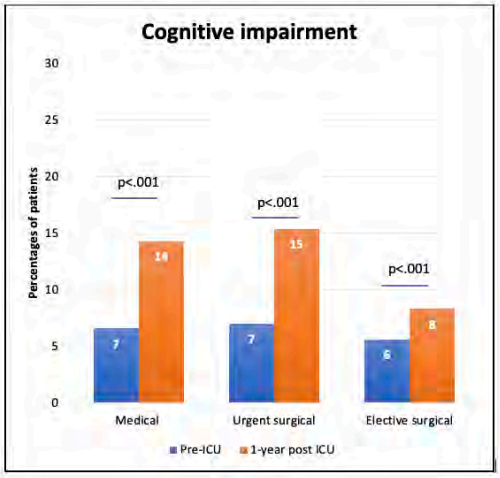
Physical problems



Mental problems



Coginitive problems



Supplementary file 5. Associations between patient characteristics, pre-ICU health status and ICU-related characteristics and physical, mental, and cognitive outcomes one year after ICU admission

	Frailty [1]		Fatigue [2]		Anxiety [3]		Depression [3]		Cognitive impairment [5]	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Patient characteristics										
Male sex	0.48 (0.34-0.68)	<.001*	0.61 (0.49-0.77)	<.001*	0.80 (0.61-1.04)	.090	1.17 (0.89-1.53)	.257	0.82 (0.58-1.15)	.244
Age										
• 16-39 yr										
• 40-64 yr	0.96 (0.42-2.21)	.930	1.38 (0.85-2.26)	.193	0.84 (0.47-1.49)	.546	1.40 (0.73-2.70)	.310	0.80 (0.41-1.59)	.527
• 65-79 yr	1.34 (0.58-3.11)	.496	1.48 (0.90-2.44)	.127	0.72 (0.40-1.29)	.266	1.56 (0.80-3.03)	.192	0.45 (0.22-0.92)	.029*
• ≥80 yr	4.00 (1.48-10.79)	.006*	1.39 (0.71-2.73)	.337	0.68 (0.30-1.55)	.358	1.78 (0.77-4.13)	.181	0.52 (0.18-1.50)	.230
Education										
• Low (ref)										
• Middle	0.54 (0.37-0.79)	.002*	0.77 (0.60-0.98)	.036*	0.66 (0.49-0.88)	.004*	0.67 (0.51-0.89)	.005*	0.93 (0.64-1.35)	.709
• High	0.57 (0.35-0.91)	.020*	0.69 (0.52-0.91)	.008*	0.69 (0.49-0.98)	.037*	0.51 (0.39-0.72)	<.001	0.62 (0.38-1.01)	.055
Household										
• Alone(ref)										
• Multiple	0.71 (0.47-1.09)	.118	0.70 (0.52-0.94)	.018*	0.75 (0.54-1.05)	.093	0.62 (0.45-0.85)	.003*	0.75 (0.48-1.15)	.188
• Nursing home	2.82 (0.83-9.61)	.097	1.26 (0.31-5.13)	.744	0.11 (0.01-0.94)	.044*	0.55 (0.13-2.34)	.422	1.55 (0.33-7.40)	.581
Pre-ICU health										
Chronic condition	1.57 (1.09-2.27)	0.16*	1.60 (1.23-2.06)	<.001*	0.98 (0.72-1.32)	.890	1.20 (0.90-1.60)	.219	0.92 (0.61-1.37)	.676
Frailty	4.11 (2.77-6.07)	<.001*	1.00 (0.69-1.45)	.985	1.14 (0.78-1.66)	.512	0.76 (0.52-1.12)	.165	0.67 (0.39-1.15)	.145
Fatigue	1.65 (1.03-2.63)	.036*	3.59 (2.86-4.51)	<.001*	1.35 (0.99-1.84)	.058	1.59 (1.17-2.17)	.003*	1.28 (0.84-1.93)	.248
Anxiety	1.02 (0.66-1.56)	.944	1.21 (0.91-1.60)	.188	5.09 (3.80-6.82)	<.001*	1.88 (1.40-2.53)	<.001*	2.25 (1.51-3.35)	<.001*
Depression	1.78 (1.16-2.72)	.008*	1.94 (1.44-2.62)	<.001*	1.45 (1.06-1.97)	.020*	4.65 (3.45-6.27)	<.001*	1.29 (0.85-1.96)	.235
Cognitive failure	1.29 (0.72-2.33)	.388	1.50 (0.92-2.44)	.105	2.18 (1.40-3.39)	.001*	1.23 (0.78-1.95)	.376	8.57 (5.39-13.62)	<.001*

[1] Frailty was defined by a score of ≥5 on the Clinical Frailty Scale (CFS); [2] Fatigue was defined by a score of ≥27on the Checklist individual Strength (CIS); [3] Anxiety and depression symptoms were defined by a score of ≥ 8 on the Hospital Anxiety and Depression Scale (HADS); [4] Abnormal cognitive function was defined by a score of >43 on the Cognitive Failure Questionnaire (CFQ)

Supplementary file 5. Continued

	Frailty [1]		Fatigue [2]		Anxiety [3]		Depression [3]		Cognitive impairment [5]	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
ICU characteristics										
Admission										
• Medical (ref)										
• Urgent surgical	0.76 (0.45-1.30)	.322	1.01 (0.70-1.46)	.950	1.09 (0.71-1.66)	.697	1.13 (0.75-1.70)	.564	1.23 (0.74-2.03)	.430
• Elective surgical	0.41 (0.27-0.62)	<.001*	0.52 (0.40-0.68)	<.001*	0.68 (0.49-0.93)	.016*	0.59 (0.43-0.81)	.001*	0.56 (0.37-0.84)	.005*
APACHE IV	1.00 (0.99-1.01)	.536	0.99 (0.99-1.00)	.013*	1.00 (0.99-1.01)	.944	1.00 (0.99-1.01)	.780	1.01 (1.00-1.02)	.103
ICU LOS	0.99 (0.96-1.02)	.546	1.02 (0.99-1.06)	.119	1.01 (0.98-1.04)	.445	1.00 (0.98-1.03)	.746	0.99 (0.96-1.03)	.572
Hospital LOS	1.03 (1.01-1.04)	<.001*	1.02 (1.00-1.03)	.015*	1.01 (0.99-1.02)	.437	1.01 (1.00-1.02)	.087	1.00 (0.98-1.02)	.997

[1] Frailty was defined by a score of ≥5 on the Clinical Frailty Scale (CFS); [2] Fatigue was defined by a score of ≥27on the Checklist individual Strength (CIS); [3] Anxiety and depression symptoms were defined by a score of ≥ 8 on the Hospital Anxiety and Depression Scale (HADS); [4] Abnormal cognitive function was defined by a score of >43 on the Cognitive Failure Questionnaire (CFQ)

Supplementary file 6. Quality of life before and one year after ICU admission

	Medical					Urgent surgical					Elective surgical				
Quality of life	**Pre-ICU**		***1-year post-ICU***		***P-value***	**Pre-ICU**		***1-year post-ICU***		***P-value***	**Pre-ICU**		***1-year post-ICU***		***P-value***
(SF-36 subdomains), mean (SD)															
• Physical function	62.3	(33.6)	63.0	(30.7)	.531	71.0	(30.6)	66.9	(29.4)	.015*	65.2	(27.5)	74.2	(24.5)	<.001*
• Role physical	52.0	(46.0)	50.3	(43.8)	.407	58.6	(45.7)	46.6	(43.8)	.001*	43.0	(44.8)	62.2	(42.4)	<.001*
• Role emotional	74.5	(40.5)	73.8	(39.3)	.727	76.9	(39.3)	70.4	(41.7)	.048*	69.3	(42.1)	80.5	(34.7)	<.001*
• Vitality	57.5	(24.1)	57.7	(21.3)	.880	62.2	(23.8)	59.0	(20.4)	.031*	57.8	(21.9)	64.6	(20.4)	<.001*
• Mental health	76.1	(19.2)	74.8	(18.4)	.067	77.1	(18.2)	73.8	(18.9)	.007*	74.5	(18.4)	79.4	(16.3)	<.001*
• Social function	70.4	(29.2)	72.1	(25.0)	.155	75.6	(26.7)	71.0	(24.9)	.008*	70.7	(25.5)	80.0	(21.7)	<.001*
• Bodily pain	72.5	(28.2)	74.8	(24.1)	.044*	73.6	(29.1)	74.5	(25.5)	.678	73.4	(25.8)	81.0	(21.6)	<.001*
• General health	51.8	(25.8)	51.2	(21.1)	.519	59.7	(24.4)	54.6	(22.5)	.001*	55.4	(20.6)	59.9	(21.3)	<.001*
• PCS	42.0	(12.4)	42.4	(11.7)	.323	45.1	(11.6)	42.6	(11.1)	.004*	42.6	(10.9)	46.6	(10.1)	<.001*
• MCS	49.4	(11.2)	48.9	(10.8)	.395	49.9	(10.8)	48.0	(10.9)	.020*	47.8	(11.0)	50.7	(9.5)	<.001*

CHAPTER 5

CHANGES IN FRAILTY AMONG ICU SURVIVORS AND ASSOCIATED FACTORS: RESULTS OF A ONE-YEAR PROSPECTIVE COHORT STUDY USING THE DUTCH CLINICAL FRAILTY SCALE

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ABSTRACT

Purpose Frailty is an important predictor for the prognosis of intensive care unit (ICU) patients. This study examined changes in frailty in the year after ICU admission, and its associated factors.

Materials and methods Prospective cohort study including adult ICU patients admitted between July 2016-December 2017. Frailty was measured using the Clinical Frailty Scale (CFS), before ICU admission, at hospital discharge, and three and 12 months after ICU admission. Multivariable linear regression was used to explore factors associated with frailty changes.

Results Frailty levels changed among 1300 ICU survivors, with higher levels at hospital discharge and lower levels in the following months. After one year were 42% of the unplanned, and 27% of the planned patients more frail. For both groups were older age, longer hospital length of stay, and discharge location associated with being more frail. Male sex, higher education level and mechanical ventilation were associated with being less frail in the planned patients.

Conclusion One year after ICU admission, 42% and 27% of the unplanned and planned ICU patients, respectively, were more frail. Insight in the associated factors will help to identify patients at risk, and may help in informing patients and their family members.

Registration NCT03246334 (clinical trials.gov)

INTRODUCTION

Long-term physical, mental and cognitive health problems are common among patients who survived their intensive care unit (ICU) stay (1-3). The underlying causes of these long-term problems are not fully understood, although they are generally thought to result from a complex relationship between the severity of critical illness, ICU treatment, post-ICU factors, and patient's pre-existing health, including the presence of comorbidities and frailty (4-6).

Frailty can be seen as a reflection of overall function. It is a recognizable state of increased vulnerability, due to decline in reserve and function, comprising the ability to cope with every day or acute stressors (7). Frailty is characterized by a combination of decreased mobility and activity, weakness, reduced muscle mass, poor nutritional status and diminished cognitive function (7-9). There is a bidirectional relation between frailty and critical illness: frailty is a risk factor for critical illness (1), but critical illness may also lead to frailty (10), because the frailty deficits of weight loss, undernutrition, muscle wasting and weakness can develop or worsen rapidly in critically ill patients, regardless of the specific critical illness diagnosis (11). Frail ICU patients are more susceptible to adverse events, such as infections, and have a higher risk of ICU-, hospital- and long-term mortality compared to non-frail patients (4, 7-9, 12, 13). After hospital discharge, frail patients are more functionally dependent, and have more disabilities, a lower quality of life, and a worse psychosocial and physical recovery compared to those who are not frail (4, 9-12, 14). Besides, frailty significantly impact healthcare utilization, due to unplanned hospital (re) admissions, increased ICU and hospital length of stay, and institutionalization (7-9, 15).

Consequently, frailty has become an important predictor for the prognosis of critically ill patients (7, 14). Therefore, it is suggested to screen for frailty at ICU admission, to identify patients who are at risk, to provide clinicians with prognostic information and to help informed decision making with patients and families (7, 11). However, frailty should be considered as a dynamic state as changes in frailty are common (16), and is believed to be manageable and even potentially reversible, through targeted interventions such as exercise and nutrition (4, 11, 17). Understanding of frailty changes during and after the ICU may help the decision making about interventions to prevent frailty among individuals at risk, and to reduce the vulnerability among those who are frail. Changes in frailty have often been investigated in community-dwelling older people (18). However, to our knowledge, changes in frailty in ICU patients and

factors associated with these changes have never been examined.

Therefore, the aims of this study were 1) to examine differences between frail and non-frail patients before ICU admission; 2) to determine changes in frailty in the year after ICU admission; and 3) to explore which factors were associated with changes in frailty.

METHODS

Study design and participants

Data from one university medical centre were obtained from an ongoing multicentre prospective cohort study (MONITOR-IC study), in which long-term outcomes of ICU patients are assessed up to five years after ICU admission (ClinicalTrials.gov: NCT03246334). Patients were included when they were 16 years or older, expected to survive the ICU, and admitted for at least 12 hours to the ICU between July 11, 2016 and December 31, 2017. Patient were excluded when they had a life expectancy of less than 48 hours, or could not read and speak the Dutch language.

Information regarding the MONITOR-IC study, such as outcome measures and used instruments, are previously published in detail (19). The study has been approved by the research ethics committee of the Radboud University Medical Center, CMO region Arnhem-Nijmegen (2016-2724). All patients, or their legal representative, provided written informed consent.

Data collection

Frailty was assessed using the Dutch Clinical Frailty Scale (CFS) (20) (for the English and Dutch CFS see Supplementary file 1 and 2 respectively). A description of the translation process can be found in Supplementary file 3. The CFS is a nine-item scale with pictographs and a description of the frailty domains, cognition, mobility, function and comorbidities (21, 22), of which the score ranges from 1 ('Very fit') to 9 ('Terminally ill'). Patients were classified as 'Non-frail' (CFS score 1-4) or 'Frail' (score 5-9) (7).

Patients, or proxies in case patients were not able to fill in the questionnaire by themselves, were asked to rate their frailty by completing a self-administrated paper-based or online questionnaire (depending on their preferences) the day before ICU admission (T0), at hospital discharge (T1), and three (T2) and 12 months (T3) after ICU admission. The baseline questionnaire (T0), in which patients were asked to rate their health before ICU admission,

was provided when patients were asked for informed consent. This was before ICU admission for planned admissions, and as soon as possible after ICU admission for unplanned admissions. Then patients were asked to rate their health retrospectively, recalling their situation before the ICU admission. Telephone and e-mail reminders were used in case of nonresponse.

Patient's demographics, including age, gender, education level, marital status and household composition were retrieved from the baseline questionnaire. Chronic diagnosis, admission type (classified as elective surgical, medical or acute surgical), planned admission, Acute Physiology and Chronic Health Evaluation (APACHE) IV score, mechanical ventilation days, and ICU and hospital length of stay (LOS) were retrieved from the patient's electronic health record. Discharge location was retrieved from the T1 questionnaire.

Statistical analysis

Baseline characteristics were presented as means with standard deviations (SD) for normally distributed continuous variables, medians with inter-quartile ranges (IQR) for not-normally distributed continuous variables, and counts with percentages for categorical variables. Differences in characteristics between non-frail and frail patients were analysed by using the independent-samples t-test or Mann-Whitney test for respectively normally distributed and not-normally distributed variables, and chi-square test or Fisher's exact test for categorical variables.

To explore which factors were associated with changes in frailty 12 months after ICU admission, linear regression analyses were performed. The dependent variable was the frailty change score, which was created by subtracting the CFS score of T0 from the T3 score for each patient. All patient variables (age, gender, education, marital status, household composition and chronic diagnosis) and ICU variables (admission type, APACHE IV score, mechanical ventilation, ICU LOS, hospital LOS and discharge location), were entered in a multivariable linear regression model. Normal distribution of residuals was checked using histograms and normal probability plots, and the homogeneity of variance (homoscedasticity) using a plot of standardized residuals versus predicted values. Multicollinearity was assessed using the indicators Variance Inflation Factor (VIF) and Tolerance statistics, with a score of >10 and a value <0.1 respectively, as an indication for multicollinearity. There was a strong correlation between the variables 'days of mechanical ventilation' and 'ICU LOS'. Therefore, the variable 'days of mechanical ventilation' was

replaced by the variable 'mechanically ventilated (yes/no)'. Outliers were tested using the standardized residuals. Cooks' distance (<1) was used to determine if outliers had a significant influence on the model (23). No significant outliers were found.

Because the majority of the included patients had a planned ICU admission, mainly after elective surgery, the analysis were performed for planned and unplanned patients separately.

Complete-cases (patients that completed both the CFS T0 and T3 questionnaire), were included in the linear regression analyses. Patient- and ICU characteristics were compared between complete-cases and non-responders (patients that filled in the T0, but not the T3), and complete-cases and non-survivors (patients that filled in the T0 and died within one year after ICU admission). All statistical analyses were performed using SPSS IBM statistical software (version 25). Values of p <.05 were considered statistically significant.

RESULTS

Study population

In total, 2922 patients were admitted to the ICU of the university medical centre, of which 1760 patients were included in the study (Figure 1). The most common reasons for exclusion were refusal to participate (n=409), deceased before informed consent (n=210), ICU LOS <12 hours (n=163) or a life expectancy of less than 48 hours (n=140). After informed consent, 460 patients dropped out, mainly because of not completing the baseline questionnaire (n=183) and redrawing from study participation (n=122) (Figure 1). The response rates at hospital discharge, three and 12 months after ICU admission were 90% (n=1170), 76% (n=991) and 65% (n=846) respectively.

The baseline questionnaire was completed by 1300 patients with a mean (SD) age of 61 (14.9) years, 65% (n=843) were male, and 26% (n=337) had one or more chronic diagnoses before admission. Median ICU and hospital LOS were 1 [IQR 1-2] and 9 [IQR 6-15] days respectively (Table 1). At baseline, 20% (n=257) of the questionnaires were completed by proxies, which decreased to 7% (n=57) at 12 months after ICU admission. Two-third of the patients (n=853) had a planned ICU admission, and differed significantly from patients with a unplanned ICU admission (n=447) (Supplementary file 4): patients with a planned admission were for example older, had a shorter ICU and hospital LOS, and had lower hospital and one-year mortality rates, compared to patients with an unplanned ICU admission.

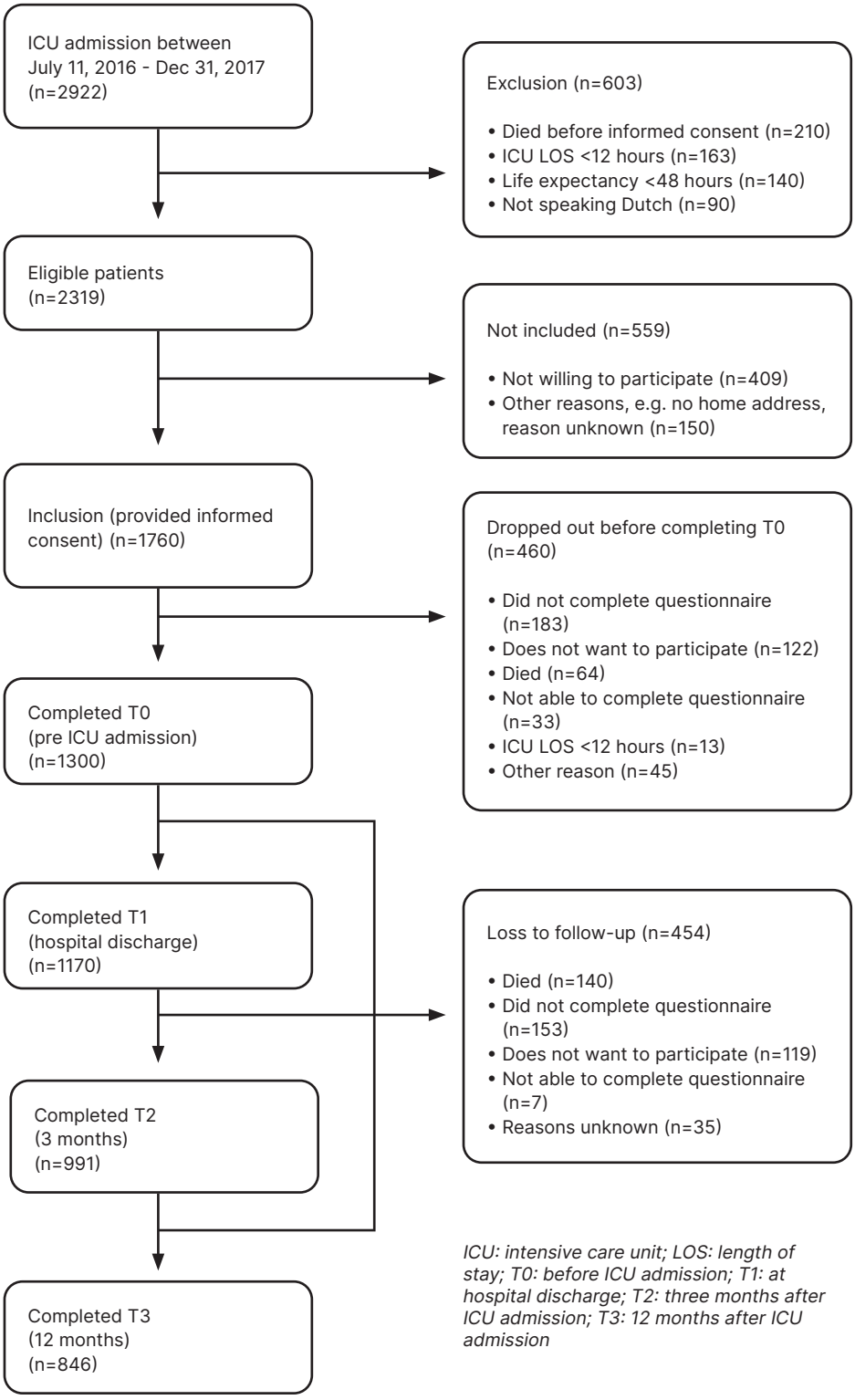
Complete cases (n=846) differed significantly from non-responders (n=338): non responders were more often younger (p<.001), female (p=.009), lower educated (p<.001), and living alone (p=.001). Their CFS baseline score (median 3 [IQR 2-4]) tended to be higher (p=.062) (Supplementary file, Table 1). Also non-survivors (n=116) differed significantly from complete-cases: non-survivors were for instance more often frail (p=.007), older (p=.006), living in a healthcare facility before admission (p=.002), suffering from chronic diagnoses (p<.001), had a higher APACHE IV score (p<.001), and longer ICU and hospital LOS (p<.001) (Supplementary file, Table 2).

Frailty before ICU admission and differences between frail and non-frail patients

The median CFS baseline score among patients with an unplanned ICU admission was 2 [IQR 2-4], representing a state of 'well', 16% of the patients (n=72) were frail and 84% (n=375) non-frail. Among patients with a planned ICU admission, the median CFS baseline score was 3 [IQR 2-3.5] (Supplementary file 4), but less patients were frail (10%, n=81). None of the patients in both groups had a CFS score of 9 ('Terminally ill').

Compared to non-frail patients (CFS 1-4), frail patients (CFS 5-9) were more likely to be female (p<.001), lower educated (p=.027), divorced or widowed (p<.001), living alone or in a healthcare facility (p<.001) and had more often a chronic diagnoses (p<.001). Besides, frail patients had more unplanned ICU admissions (p<.001), were less often mechanically ventilated (p<.001), had longer ICU LOS (p=.032), and a nursing home as discharge location (p=.039) (Table 1). No significant differences were found in age, APACHE IV score and hospital LOS.

Figure 1. Flow diagram of the study population



ICU: intensive care unit; LOS: length of stay; T0: before ICU admission; T1: at hospital discharge; T2: three months after ICU admission; T3: 12 months after ICU admission

Table 1. Characteristics of all included patients, and non-frail and frail patients

	Total group (n=1300)		**Non-frail (CFS 1-4) (n=1147)**		**Frail (CFS 5-9) (n=153)**		**P-value**
Patient characteristics							
CFS score at baseline, median [IQR]	3	[2-4]	2	[2-3]	6	[5-7]	<.001*
Age, yr, mean (SD)	61.4	(14.9)	61.4	(14.7)	61.0	(16.1)	.743
Gender, n (%)							
• Male	843	(64.8)	766	(66.8)	77	(50.3)*	<.001*
• Female	457	(35.2)	381	(33.2)	76	(49.7)*	
Education, n (%)							
• Low	414	(32.4)	351	(31.1)	63	(42.0)*	.027*
• Middle	552	(43.2)	495	(43.9)	57	(38.0)	
• High	312	(24.4)	282	(25.0)	30	(20.0)	
Marital status, n (%)							
• Single	217	(16.9)	188	(16.6)	29	(19.2)	<.001*
• Married	896	(69.7)	810	(71.4)	86	(57.0)	
• Divorced	72	(5.6)	57	(5.0)	15	(9.9)*	
• Widowed	101	(7.9)	80	(7.0)	21	(13.9)*	
Household composition, n (%)							
• Alone	198	(15.5)	164	(14.5)	34	(22.8)*	<.001*
• With someone else[a]	1059	(82.9)	956	(84.7)	103	(69.1)	
• Healthcare facility	21	(1.6)	9	(0.8)*	12	(8.1)*	
One ore more chronic diagnosis[2], n (%)							
• No	963	(74.1)	887	(77.3)	76	(49.7)*	<.001*
• Yes	337	(25.9)	260	(22.7)*	77	(50.3)*	
ICU / clinical characteristics							
Admission type, n (%)							
• Elective surgical	841	(64.7)	767	(66.9)	74	(48.4)*	<.001*
• Medical	307	(23.6)	250	(21.8)	57	(37.3)*	
• Acute surgical	152	(11.7)	130	(11.3)	22	(14.4)	
Planned admission, n (%)							
• No	447	(34.4)	375	(32.7)	72	(47.1)*	<.001*
• Fatigue	853	(65.6)	772	(67.3)	81	(52.9)	
APACHE IV score, mean (SD)	54.1	(21.2)	53.9	(21.5)	55.4	(18.9)	.425

*[1]With someone else: partner, children, parents, etc. [2]Chronic diagnosis are immunological insufficiency, AIDS, haematological malignancy, metastatic neoplasm, cirrhosis, cardiovascular insufficiency, respiratory insufficiency, COPD, chronic dialysis or renal insufficiency. *Significant differences in characteristics between patients who are non-frail and frail. Data are based on the baseline questionnaire and patient's electronic health record.*

Table 1. Continued

	Total group (n=1300)		Non-frail (CFS 1-4) (n=1147)		Frail (CFS 5-9) (n=153)		P-value
Mechanical ventilation (MV)							
• No	393	(30.2)	327	(28.5)	66	(43.1)	<.001*
• Yes	907	(69.8)	820	(71.5)	87	(56.9)	
Days of MV, median [IQR]	1	[0-2]	1	[0-2]	1	[0-2]	.098
ICU LOS, days, median [IQR]	1	[1-2]	1	[1-2]	1	[1-3]	.032*
Hospital LOS, days, median [IQR]	9	[6-15]	9	[6-15]	10	[6-22]	.096
Discharge location, n (%)							
• Home	891	(82.0)	802	(82.9)	89	(74.8)	.039*
• Rehabilitation centre	92	(8.5)	77	(8.0)	15	(12.6)	
• Nursing home	24	(2.2)	18	(1.9)	6	(5.0)*	
• Other	79	(7.3)	70	(7.2)	9	(7.6)	
Hospital mortality, n (%)	6	(0.5)	5	(0.4)	1	(0.7)	.529
One year mortality, n (%)	116	(8.9)	92	(8.0)	24	(15.7)	.003*

*[1]With someone else: partner, children, parents, etc. [2]Chronic diagnosis are immunological insufficiency, AIDS, haematological malignancy, metastatic neoplasm, cirrhosis, cardiovascular insufficiency, respiratory insufficiency, COPD, chronic dialysis or renal insufficiency. *Significant differences in characteristics between patients who are non-frail and frail. Data are based on the baseline questionnaire and patient's electronic health record.*

Changes in frailty during 12 months after ICU admission

Patients with an unplanned ICU admission

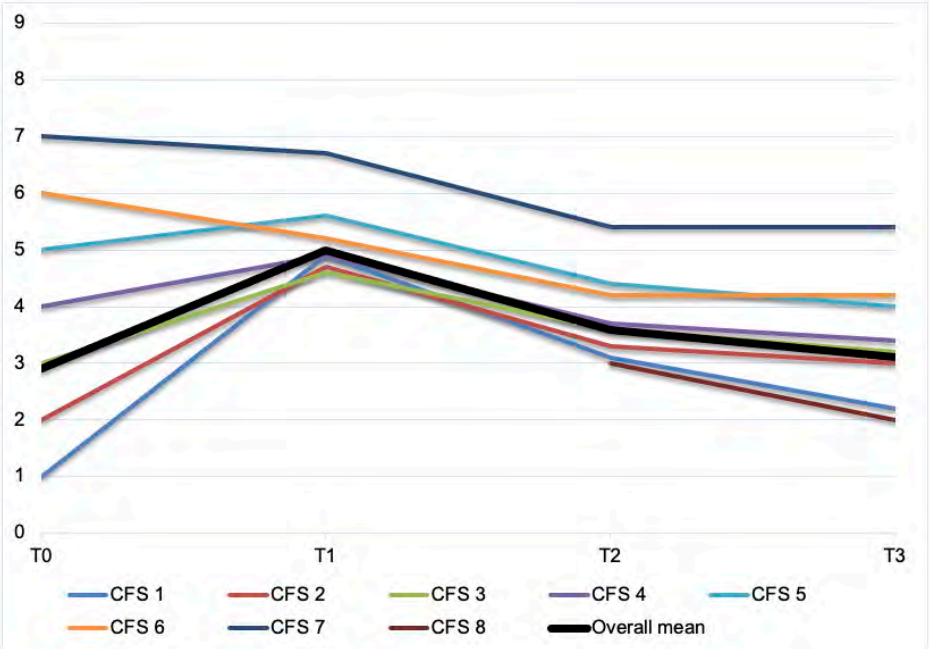
Frailty levels changed significantly after ICU admission: CFS median baseline scores increased from 2 [IQR 2-4] to 5 [IQR 3-6] at hospital discharge, and decreased to 3 [IQR 2-5] after three months and 12 months [IQR 2-4]. The percentage of frail patients (CFS score of 5-9) increased from 16% at ICU admission to 53% at hospital discharge, and decreased to 18% and 10% at three and 12 months, respectively (Supplementary file 6). After 12 months, 23% of the patients were less frail, 42% more frail and 35% experienced the same frailty level as before the ICU admission (Supplementary file 7a and 7b). Changes in frailty differed between frail and non-frail patients: the more frail patients were at baseline, the more they improved during the next 12 months (Figure 2a and 3a). After 12 months, 11% of the non-frail patients transitioned to the frail category, whereas 46% of the frail patients transitioned to the non-frail category.

Patients with a planned ICU admission

Frailty levels in patients with a planned ICU admission changed as well. Although their median CFS baseline score was higher (3 [IQR 2-3.5]) compared to patients with an unplanned admission, they were less frail in the months following ICU admission: 4 [IQR 3-5] at hospital discharge, 3 [IQR 2-3] after three months, and 2 [IQR 2-3] after 12 months. The percentages of frail patients was lower as well: 10% at baseline, 32% at hospital discharge, and 8% and 4% at three and 12 months respectively (Supplementary file 6). After 12 months, 32% of the patients were less frail, 27% more frail, and 41% experienced the same level of frailty as before ICU admission (Supplementary file 7a and 7c). Like the unplanned admitted patients, patients with a higher baseline score (indicating being more frail) were more likely to improve during the next 12 months (Figure 2b and 3b). Of the non-frail patients, 5% transitioned to the frail category, whereas of the frail patients, 80% transitioned to the non-frail category.

Differences in frailty changes were also seen in several subgroups, for example in gender, education level, admission types and ICU LOS (Supplementary file 8).

Figure 2a. Mean CFS scores over time indicated per baseline CFS score: unplanned ICU admission

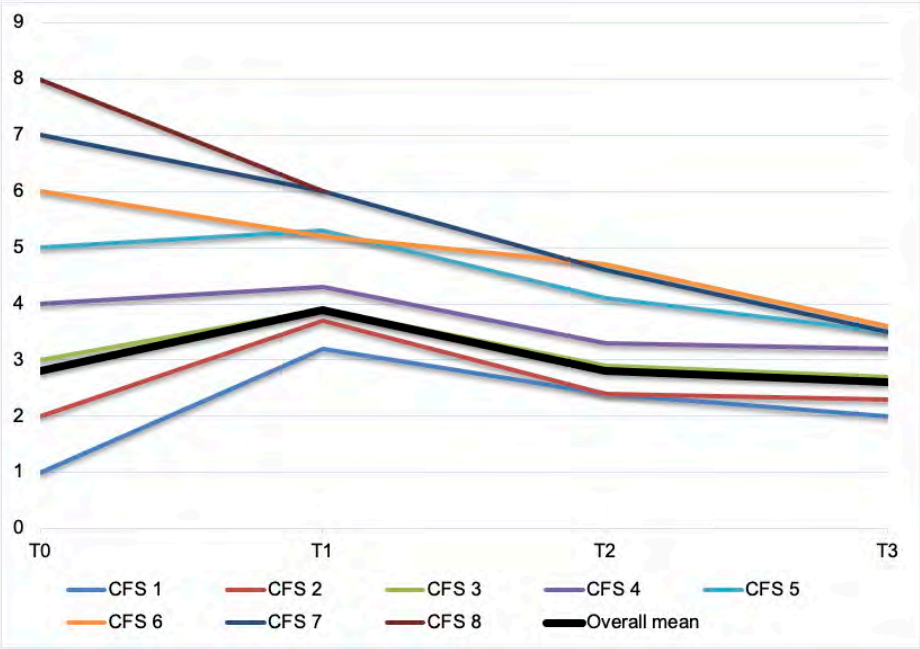


Number of patients per time point per baseline category: T0,T1,T2,T3

CFS 1: 97, 86, 72, 62
CFS 2: 138, 122, 97, 87
CFS 3: 92, 78, 64, 56
CFS 4: 48, 42, 33, 29
CFS 5: 18, 17, 13, 8
CFS 6: 27, 21, 17, 12
CFS 7: 26, 22, 16, 12
CFS 8: 1, 0, 1, 1
CFS 9: 0

T0: before ICU admission, T1: at hospital discharge, T2: three months after ICU admission, T3: 12 months after ICU admission

Figure 2b. Mean CFS scores over time indicated per baseline CFS score: planned ICU admission



Number of patients per time point per baseline category: T0,T1,T2,T3

CFS 1: 109, 100, 90, 74
CFS 2: 296, 272, 241, 212
CFS 3: 235, 223, 192, 160
CFS 4: 132, 115, 97, 88
CFS 5: 38, 34, 29, 23
CFS 6: 19, 18, 13, 11
CFS 7: 22, 19, 16, 11
CFS 8: 2, 0, 1, 1
CFS 9: 0

T0: before ICU admission, T1: at hospital discharge, T2: three months after ICU admission, T3: 12 months after ICU admission

Figure 3a. Frailty status 12 months after ICU admission compared to the frailty status before the ICU admission (indicated per CFS baseline score): unplanned ICU admission

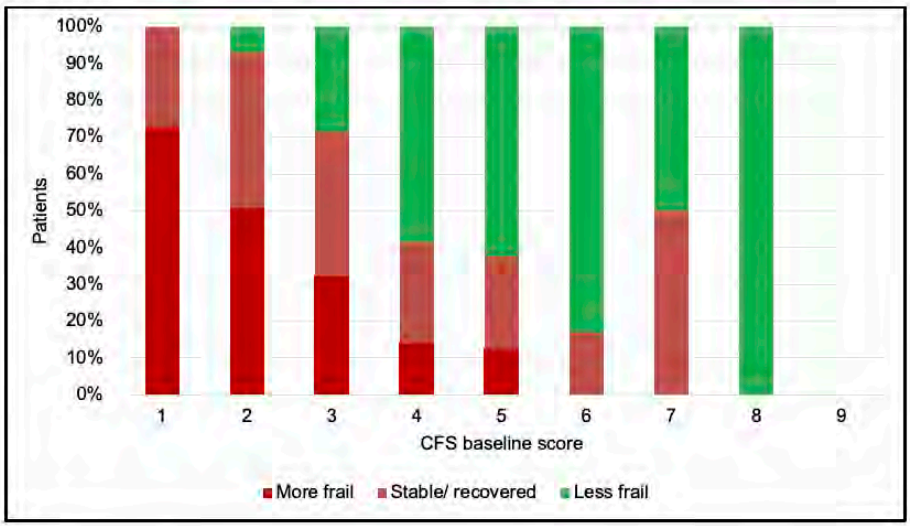
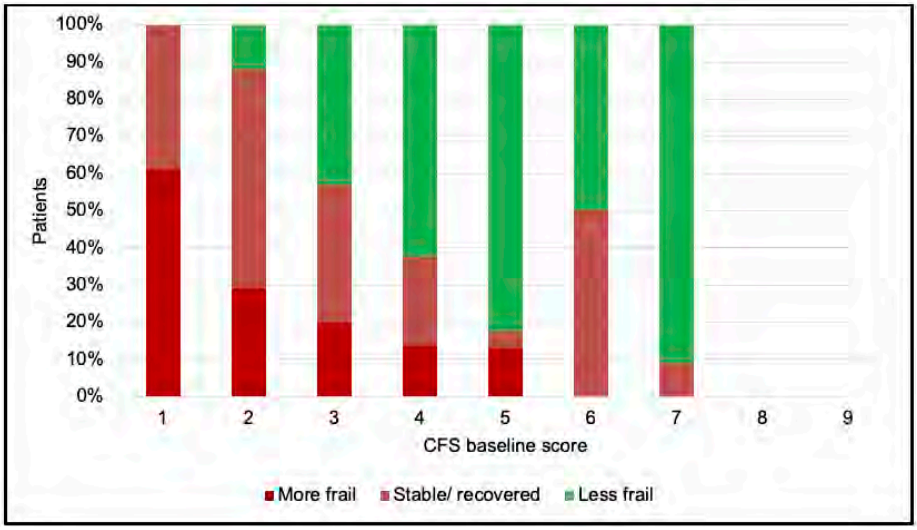


Figure 3b. Frailty status 12 months after ICU admission compared to the frailty status before the ICU admission (indicated per CFS baseline score): planned ICU admission



Factors associated with changes in frailty

Patients with an unplanned ICU admission

The only factor significantly associated with being *less frail* after 12 months, was a higher frailty score at baseline (*b*= -634; p<.001) (Table 2). Factors that were significantly associated with being *more frail*, were older age (*b*= .019; p=.013), longer hospital LOS (*b*= .022; p=.001), and being discharged to a revalidation centre (*b*= .630; p=.020).

Patients with an planned ICU admission

Factors significantly associated with being *less frail* after 12 months, were a higher frailty baseline score (*b*= -.756; p<.001), male sex (*b*= -.207; p=.045), higher education level (*b*= -.447; p<.001) and mechanical ventilation (*b*= -.338; p=.002 (Table 2). Factors that were significantly associated with being *more frail* at 12 months, were longer ICU (b= .035; p=.036) and hospital LOS (*b*= .019; p=.010), and being discharged to a nursing home (*b*= 1.367; p=.005) or another location (*b*= .364; p=.046).

The variables in both models explained 49% of the variance in frailty change.

Table 2. Factors associated with changes in frailty scores for patients with an unplanned and planned ICU admission

	Unplanned ICU admission (n=232)				Planned ICU admission (n=494)			
	B	**SE**	**95% CI for B**	**P**	**B**	**SE**	**95% CI for B**	**P**
Constant	.994	.655	[-.30; 2.29]	.131	1.622	.357	[.92; 2.32]	<.001*
CFS baseline (T0)	-.634	.059	[-.75; -.52]	<.001*	-.756	.038	[-.83; -.68]	<.001*
Age	.019	.008	[.00; .03]	.013*	.009	.005	[.00; .02]	.052
Gender (female ref)								
• Male	-.275	.178	[-.63; .08]	.124	-.207	.103	[-.41; -.00]	.045*
Education (low ref)								
• Medium	.053	.211	[-.36; .47]	.804	-.144	.112	[-.36; .08]	.199
• High	.017	.229	[-.44; .47]	.941	-.447	.125	[-.69; -.20]	<.001*
Marital status (unmarried ref)								
• Married	-.408	.308	[-1.02; .20]	.186	.158	.170	[-.18; .49]	.354
• Divorced	-.082	.425	[-.92; .76]	.848	.239	.264	[-.28; .76]	.365
• Widowed	-.718	.499	[-1.70; .27]	.152	-.518	.280	[-1.07; .03]	.065
Household composition (alone ref)								
• Together	-.066	.370	[-.80; .66]	.858	-.298	.226	[-.74; .15]	.188
• Healthcare facility	1.296	.675	[-.04; 2.63]	.056	.721	.784	[-.82; 2.26]	.358
Chronic diagnosis (no ref)								
• Yes	-.162	.217	[-.59; .27]	.457	.174	.113	[-.05; .40]	.125
Admission type (elective surgical)								
• Medical	.417	.377	[-.33; 1.16]	.270	-.600	.361	[-1.31; .11]	.097
• Acute surgical	.179	.393	[-.60; .95]	.649	-.102	.467	[-1.02; .82]	.828

Abbreviations: B: unstandardized regression coefficients; CI: confidence interval; CFS: clinical frailty scale; SE: standard error; Ref: reference group

*Linear regression model, with the CFS mean change score (T0-T3) as outcome. Data are unstandardized regression coefficients with 95% confidence intervals and p-values (*statistically significant). Note: negative regression coefficients indicate patients become less frail, positive regression coefficient indicate patients become more frail*

Table 2. Continued

	Unplanned ICU admission (n=232)				Planned ICU admission (n=494)			
	B	**SE**	**95% CI for B**	**P**	**B**	**SE**	**95% CI for B**	**P**
APACHE IV score	-.003	.003	[-.01; .00]	.356	.003	.004	[-.00; .01]	.448
Mechanically ventilated (no ref)								
• Yes	-.294	.198	[-.69; .10]	.140	-.338	.110	[-.55; -.12]	.002*
ICU LOS	.009	.015	[-.02; .04]	.532	.035	.017	[.00; .07]	.036*
Hospital LOS	.022	.007	[.01; .04]	.001*	.019	.007	[.00; .03]	.010*
Discharge location (home ref)								
• Revalidation centre	.630	.269	[.10; 1.16]	.020*	-.448	.273	[-.99; .01]	.101
• Nursing home	.663	.482	[-.29; 1.61]	.171	1.367	.479	[.43; 2.31]	.005*
• Other	.453	.300	[-.14; 1.05]	.133	.364	.182	[.01; .72]	.046*

Abbreviations: B, unstandardized regression coefficients; CI, confidence interval; CFS, clinical frailty scale; SE, standard error; Ref, reference group

*Linear regression model, with the CFS mean change score (T0-T3) as outcome. Data are unstandardized regression coefficients with 95% confidence intervals and p-values (*statistically significant). Note: negative regression coefficients indicate patients become less frail, positive regression coefficient indicate patients become more frail*

Box 1. Examples of patients whose frailty level was declined, recovered or improved after 12 months

Declined

A married man, in his sixties, with a middle level of education, was admitted to the ICU after a planned thoracotomy for oesophageal cancer. His APACHE IV score was 52. He was mechanically ventilated on the ICU for 2 days, and stayed 13 days in the hospital. He was very fit before ICU admission (CFS = 1), but vulnerable at hospital discharge (CFS = 4). Although he became less frail in the following months, he became terminally ill 12 months after ICU admission (CFS = 9).

Recovered

A young, low educated, unmarried woman, was admitted to the ICU after a planned craniotomy. Her APACHE IV score was 29. She stayed 1 day in the ICU without mechanical ventilation, and 5 days in the hospital. Before ICU admission she was very fit (CFS =1). At hospital discharge she was more frail (CFS = 3), but after three months she was already very fit again.

Improved

A high educated married man, in his fifties, was unexpectedly admitted to the ICU due to an endocrine and metabolic disorder. His APACHE IV score was 52. He spent one day on the ICU, without mechanical ventilation, and 21 days in the hospital. Before ICU admission he was severely frail (CFS = 8), but improved significantly in the months after discharge. After 3 and 12 months his frailty scores were respectively 3 and 2.

DISCUSSION

In this prospective cohort study, including 1300 patients, we found that 16% of the unplanned and 10% of the planned patients were frail before their admission. Frail patients were more likely to be female, lowered educated, divorced or widowed, diagnosed with a chronic condition, and living alone or in a healthcare facility compared to non-frail patients. Additionally, frail patients had a longer ICU LOS and were more frequently discharged to a nursing home facility. After ICU admission the frailty levels changed: patients were more frail at hospital discharge, and less frail in the following months, although opposite changes were seen between frail and non-frail patients. Different patterns were also seen between patients with an unplanned and planned ICU admission: although patients with an unplanned admission were less frail before admission, they were more frail in the following months compared to patients with a planned admission. Besides, almost 50% of the patients with an unplanned admission and 25% of the patients with a planned admission were more frail after 12 months. Factors associated with changes in frailty differed as well between both groups. In patients with an unplanned admission was a higher CFS baseline score associated with being becoming less frail, and were older age, a longer ICU LOS, and being discharged to a revalidation centre associated with becoming more frail after 12 months. In patients with a planned admission were a higher CFS baseline score, being highly educated, and mechanical ventilation associated with becoming *less frail*. Longer ICU and hospital LOS, and being discharged to a nursing home were associated with being *more frail*.

Since a few years is frailty recognized as an important prognostic determinant for critically ill patients, and are associations with adverse short and long-term outcomes examined (7, 8, 24). Frailty rates in patients being admitted to the ICU differ considerably between studies, ranging from 13 to 53% (25). In a meta-analysis of 10 observational cohort studies including patients admitted to the ICU (7), a pooled frailty prevalence of 30% was found. This is higher compared to the rates found in our study (16% and 10% for the unplanned and planned patients, respectively), which is probably due to the exclusion of terminally ill patients in our study. Nevertheless, the differences between frail and non-frail patients found in our study, are consistent with previous studies, showing that frail patients at ICU admission are significantly more often female (9, 12, 26-29), widowed (9, 12), lower educated (9, 12, 26, 27), living with support or in a healthcare facility (9, 12, 26, 30), have more

often a medical ICU admission (9, 27-29, 31) and a nursing home as discharge location (7, 27, 29, 30). Although it might be expected that frail patients are older, have higher APACHE scores and longer hospital length of stay (9, 31), we did not find significant differences between frail and non-frail patients, although contradictory findings are reported by other studies (26, 29, 30, 32). Changes in frailty among critically ill patients over time have not been examined before. Nonetheless, changes in frailty among community-dwelling older people have extensively been examined, corroborating as well that frailty is a dynamic state. A meta-analysis, including more than 42.000 participants from 16 studies, analysed transitions between frailty states, and showed that over a period of four year, frailty worsened in 29%, maintained the same in 57%, and improved in 14% participants (18). In our study, patients became more frail at hospital discharge and less frail in the following months, although differences were seen between patients with an unplanned and planned ICU admission: 42% of the patients with an unplanned admission were more frail after one year, compared to 27% of the patients with a planned admission. These differences are not remarkable. A study that compared older patients admitted to the ICU after acute (unplanned admission) versus elective surgery (planned admission), showed that elective surgery patients are less sick, have shorter ICU LOS, lower mortality and better outcomes compared to patients after acute surgery (33).

Factors associated with changes in frailty in non-ICU patients, are age (34, 35), gender (35, 36), education level (34, 35) and hospital LOS (36). Other interesting reported factors, not investigated in our study, are limitations in daily living, low albumin levels, lower cognition, loss of vision, polypharmacy, smoking, obesity, and conditions such as COPD, diabetes, cancer, cardiovascular diseases, stroke and osteoarthritis (34, 35, 37). Remarkably, we found that frail patients were more likely to improve over time than non-frail patients, whereas other studies suggested that frail patients were less likely to re-achieve their baseline function (22) and were more likely to die (36), while non-frail patients tended to remain healthy (36) and recovered completely from acute illness (22). This sounds more reasonable, and this contradictory finding could be a result of the exclusion of terminally ill patients in our study and the complete case analysis, in which the non-survivors and non-responders, with both higher frailty rates before ICU admission, were not included.

Implications

Frailty is common among ICU patients (7, 24, 29), and unmistakably associated with adverse health outcomes, prolonged recovery, higher mortality and higher healthcare utilizations (7, 9, 12, 27). Screening for frailty in ICU patients, to identify and recognize those who are at risk, will increase clinical awareness of patient's vulnerability, stratification of patients at risk, prognostication, and informed decision making (10, 15, 27, 29, 38-41). In addition, it will lead to better informed patients and families, regarding the prognosis for survival, expectations of recovery, and expected resource use (22, 41). Although there is no consensus on which screening instrument to use in the ICU (7, 8, 25, 39), since commonly used instruments are not feasible in the IC, due to time constraints and measurements impossible to perform (7, 30, 39, 40), simple and rapid frailty screening instruments, such as the CFS, can be used (25, 39, 42, 43). However, frailty screening instruments should be robust and properly validated (25). The validity and reliability of the CFS should be further tested and improved (39), for example by the comparison with a gold standard, the comprehensive geriatric assessment carried out by a specialist in geriatric medicine (24). Additionally, the CFS is a subjective frailty assessment, often relying on information from proxies, which can lead to an underestimation of frailty (25, 39, 40). In two inter-reliability studies, an agreement in frailty assessment was found in half of the cases (30, 44). Clear instructions, simplifying the wording, and training of ICU professionals, might improve the reliability. Additionally, we should keep in mind that screening can cause false reassurance, whereby identification of non-frailty could be wrongly interpreted as indicating they are less likely to develop frailty in the future. In our study we showed that many patients who were identified as non-frail at ICU admission, were more frail after one year, especially in patients with an unplanned admission.

It is important that critical care healthcare professionals are aware that the diminished reserve in frail patients may increase the adverse effects of routine critical care treatment, such as bed rest, polypharmacy, sedation and mechanical ventilation (7, 13), and that the reduced resilience in frail patients may make their recovery more difficult and prolonged (7). By efficient weaning strategies (8), minimization of unnecessary sedation (7-10), screening for delirium (8, 9), reduction of polypharmacy (9, 43), adequate nutritional support, (4, 7, 9, 10, 43, 45), cognitive training (4, 45) and early mobilization and exercises (4, 7-9, 43, 45, 46) frailty progression among ICU patients could be prevented and positive outcomes maximized.

Limitations

This study has certain limitations. First, our study was conducted in one university medical centre, in which the majority of the ICU patients were admitted after elective surgery. Because of this case-mix, and consequently the limited generalizability of the findings to other ICUs, we separated the analysis for patients with an unplanned and planned ICU admission. Second, selection bias is likely due to the considerable number of patients lost to follow-up, which is a major challenge in long-term outcome studies in critical care (47, 48). Although loss to follow-up cannot be eliminated (47), we tried to minimize it by the use of telephone and e-mail reminders, providing patients the option to fill in the questionnaire on paper or online, and ask proxies to fill in the questionnaires when patients were unable to do it. Third, 20% of the baseline CFS score were completed by proxies instead of the patients themselves, especially in patients with an unplanned admission (40% compared to 10% in the planned admissions). Because family members tend to underestimate the frailty levels of their loved one (40), CFS scores could be underrated. Fourth, bias of the results is also possible due to our decision for the complete-case analysis. There is a lack of consensus on how to deal in statistical analyses with patients who die during follow-up, as they could not be considered as a missing (49). Like most studies, we decided to exclude them from the analysis (49). By describing the characteristics and differences between the complete-case patients, the non-survivors and non-responders, we tried to get insight into the magnitude and direction of the selection bias. Significant higher baseline CFS scores were found in the non-survivors, which could explain the improvements in frailty in especially the patients who were frail at ICU admission. And fifth, the explored factors in this study that were associated with changes in frailty, were mainly patient demographic factors. Unfortunately, we were not able to include more clinical factors such as delirium, sepsis, use of sedatives and other medications, because these data were not available. It is likely that these factors might have an influence on the changes in frailty as well.

Conclusion

In conclusion, frailty levels changed following ICU admission, with higher frailty levels at hospital discharge, and lower levels at 12 months. After one year, 42% of the patients with an unplanned admission and 27% of the patients with a planned admission were more frail. For both groups were older age, longer hospital length of stay, and discharge location associated with being more

frail. In the planned ICU patients were male sex, higher education level and mechanical ventilation associated with being less frail. Insight in the associated factors will help to identify patients at risk, and may guide in clinical decision making and informing patients and their family members.

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Supplementary file 1. Clinical Frailty Scale (English version)

1. Very fit - People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age. ☐

2. Well - People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally. ☐

3. Managing well - People whose medical problems are well controlled, but are not regularly active beyond routine walking. ☐

4. Vulnerable – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day. ☐

5. Mildly frail - These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications).Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework. ☐

6. Moderately frail – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing. ☐

7. Severely frail – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months). ☐

8. Very severely frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness. ☐

9. Terminally ill - Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail. ☐

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common symptoms in mild dementia include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal. In moderate dementia, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting. In severe dementia, they cannot do personal care without help.

Supplementary file 2. Clinical Frailty Scale (Dutch version)

1. Zeer fit - Mensen die krachtig, actief, energiek en gemotiveerd zijn. Deze mensen oefenen/trainen regelmatig. Ze behoren tot de fitste mensen van hun leeftijd. ☐

2. Fit - Mensen die geen actieve ziektesymptomen hebben, maar die minder fit zijn dan in categorie 1. Ze bewegen of trainen vaak, of zijn meer actief tijdens seizoensgebonden activiteiten. ☐

3. Zelfredzaam - Mensen met medische problemen die goed onder controle zijn, maar die niet regelmatig actief zijn, anders dan de dagelijkse wandelingen. ☐

4. Risico voor kwetsbaarheid – Mensen die, hoewel ze niet afhankelijk zijn van anderen voor de dagelijkse hulp, vaak klachten hebben die hun dagelijkse activiteiten beperken. Een veelgehoorde klacht is: 'traag', en/of moe zijn gedurende de dag. ☐

5. Licht kwetsbaar - Deze mensen zijn vaak duidelijk trager (met lopen of denken) en hebben hulp nodig bij complexere dagelijkse activiteiten (financiën, vervoer, zwaar huishoudelijk werk, medicatie). Typisch is dat door de lichte kwetsbaarheid het winkelen, alleen buiten wandelen, maaltijdbereiding en huishoudelijk werk hen in toenemende mate belemmert. ☐

6. Matig kwetsbaar – Mensen hebben hulp nodig bij alle activiteiten buitenshuis en bij het huishouden. Binnenshuis hebben ze vaak problemen met traplopen en is er hulp nodig bij het douchen en eventueel minimale hulp (aansporen) bij het aankleden. ☐

7. Ernstig kwetsbaar – Mensen die volledig afhankelijk bij hun persoonlijke verzorging, ongeacht de reden (fysiek of mentaal). Ze lijken stabiel en er is geen hoog risico op overlijden (binnen 6 maanden). ☐

8. Zeer ernstig kwetsbaar – Mensen zijn volledig afhankelijk, het einde van het leven nadert. Typisch is dat ze niet meer kunnen herstellen, zelfs niet van een milde ziekte. ☐

9. Terminaal - Het einde van het leven nadert. Deze categorie is alleen van toepassing op mensen met een levensverwachting van minder dan 6 maanden en die niet op een andere manier duidelijk kwetsbaar zijn. ☐

In geval van aanwezigheid van (milde) dementie

De graad van kwetsbaarheid in de scorelijst hierboven, correspondeert met de graad van kwetsbaarheid bij dementie. Veel voorkomende symptomen bij milde dementie zijn o.a. het vergeten van de details van een recente gebeurtenis, maar de gebeurtenis zelf herinneren ze wel, ze herhalen dezelfde vraag/ verhaal en trekken zich terug uit het sociale leven. Bij matige dementie worden de recente gebeurtenissen slecht onthouden, hoewel ze schijnbaar de gebeurtenissen uit het verleden in het leven goed kunnen herinneren. Persoonlijke zorg is mogelijk met aansporing. Patiënten met ernstige dementie zijn volledig zorgafhankelijk.

Supplementary file 3. Dutch translation of the Clinical Frailty Scale

The translation and adaptation of the Clinical Frailty Scale (CFS) was performed according to the guidelines for the process of cross-cultural adaptation of self-report measures[1], consisting of the following steps.

Step 1: Initial translation Permission was obtained from the authors of the original version of the Rockwood Clinical Frailty Scale to use the instrument for translation. Additionally, a team was established for the translation process of which MvdB (nurse and researcher in the ICU) and PD (intensive care physician) were both project managers. The CFS was translated from English into Dutch by two independent forward translators (BD and GM), with mother tongue Dutch and professional proficiency in English. Both are ICU nurses and BD is a researcher as well. An explanation of the concepts of frailty was provided to the two forward translators.

Step 2: Synthesis of the translations The two translators discussed their translations together. Reconciliation was carried out via discussion with a third reviewer (MvdB), generating the first version (CFS-NL version 1).

Step 3: Back translation The CFS-NL version 1 was conceptually translated back into English, the source language, by an independent native English speaker (JP), with a medical background (physiotherapist in the ICU).

Step 4: Expert committee The backward translation was compared to the source questionnaire to identify any discrepancies and to check for equivalence. During the process, no consensus was reached on the best translation for item four 'Vulnerable'. Therefore, a survey was held among geriatricians, and ICU physicians, residents and nurses of the university medical centre, considered to be experts in the ICU, frailty or in both. In the survey, the participants could choose between three possible Dutch translations, which were selected by the research group: 'bedreigd', 'potentieel fragiel' and 'risico op kwetsbaarheid'. The participants could indicated the best translation with three points, the second best translation with two points and the least appropriate translation with one point. The proposed translations with the highest score was considered as most suitable. In total 47 persons were invited to participate in the survey, of which 36 responded (13 intensive care physicians, 10 nurses, 8 residents and 5 geriatricians). 'Risico op kwetsbaarheid' was considered the most suitable translation (40% of total points) of the item 'Vulnerable', and as such, this translation was used in the Dutch translation of the CFS. The options 'potentieel fragiel' and 'bedreigd' had respectively 34% and 26% of the total points given by the responders. Adaptations were made to the first version and a second version was generated (CFS-NL version 2).

Step 5: Test of the prefinal version The last step was the use and evaluation of the translated CFS-NL version 2 in ICU practice. The evaluation with 98 patients did not result in new information for which the translation needed to be adjusted/updated.

BD = Boukje Dijkstra; GM = Grietje Marten- van Stijn; JP = Joanne Postma-Rowden†; MvdB = Mark van den Boogaard; PD = Peter Dieperink

[1] *Beaton DE, Bombardier C, Guillemin F, Bosi Ferraz M. Guidelines for the Process of Cross-Cultural Adaptation of Self-Report Measures. Spine 2000; 25(24):3186-91*

Supplementary file 4. Characteristics of patients with an unplanned and planned ICU admission

	Unplanned admission (n=447)		Planned admission (n=853)		P-value
Patient characteristics					
CFS score at baseline, median [IQR]	2	[2-4]	3	[2-3.5]	.154
• Non frail, n (%)	375	(84)	772	(90)	<.001*
• Frail, n (%)	72	(16)	81	(10)	
Age, mean (SD) in years	57.7	(16.6)	63.4	(13.4)	<.001*
Gender, n (%)					
• Male	265	(59.3)	578	(67.8)	.002*
• Female	182	(40.7)	275	(32.2)	
Education, n (%)					
• Low	140	(31.9)	274	(32.7)	.807
• Middle	195	(44.4)	357	(42.6)	
• High	104	(23.7)	208	(24.8)	
Marital status, n (%)					
• Single	91	(20.6)	126	(14.9)	.003*
• Married	279	(63.1)	617	(73.1)	
• Divorced	30	(6.8)	1.2	(5.0)	
• Widowed	42	(9.5)	59	(7.0)	
Household composition, n (%)					
• Alone	74	(17)	124	(14.7)	.001
• With someone else[1]	347	(79.6)	712	(84.6)	
• Healthcare facility	15	(3.4)	6	(0.7)	
One or more chronic diagnosis[2], n (%)					
• No	322	(72.0)	641	(75.1)	.231
• Yes	125	(28.0)	212	(24.9)	
ICU/ clinical characteristics					
Admission type, n (%)					
• Elective surgical	29	(6.5)	812	(95.2)	<.001*
• Medical	272	(60.9)	35	(4.1)	
• Acute surgical	146	(32.7)	6	(0.7)	
APACHE IV score, mean (SD)	62.5	(26.9)	49.7	(15.6)	<.001*

[1] With someone else: partner, children, parents, etc.
[2]Chronic diagnosis are immunological insufficiency, AIDS, haematological malignancy, metastatic neoplasm, cirrhosis, cardiovascular insufficiency, respiratory insufficiency, COPD, chronic dialysis or renal insufficiency
**Significant differences in characteristics between patients with an unplanned and planned ICU admission.*
Data are based on the baseline questionnaire and patient's electronic health record.

Supplementary file 4. Continued

	Unplanned admission (n=447)		Planned admission (n=853)		P-value
Mechanical ventilation (MV)					
• No	125	(28.0)	268	(31.4)	.204
• Yes	322	(72.0)	585	(68.6)	
Days of MV, median [IQR]	2	[0-5]	1	[0-2]	<.001*
ICU LOS, days, median [IQR]	2	[1-6]	1	[1-1]	<.001*
Hospital LOS, days, median [IQR]	14	[8-25]	8	[5-12]	<.001*
Discharge location, n (%)					
• Home	254	(69.2)	637	(88.6)	<.001*
• Rehabilitation centre	63	(17.2)	29	(4.0)	
• Nursing home	17	(4.6)	7	(1.0)	
• Other	33	(9.0)	46	(6.4)	
Hospital mortality, n (%)	5	(1.1)	1	(0.1)	.020*
One year mortality, n (%)	51	(11.4)	65	(7.6)	.025*

[1] With someone else: partner, children, parents, etc.
[2]Chronic diagnosis are immunological insufficiency, AIDS, haematological malignancy, metastatic neoplasm, cirrhosis, cardiovascular insufficiency, respiratory insufficiency, COPD, chronic dialysis or renal insufficiency
**Significant differences in characteristics between patients with an unplanned and planned ICU admission.*
Data are based on the baseline questionnaire and patient's electronic health record.

Supplementary file 5. Missing data

Data was missing in the analysis. This was due to patients who died during the first year, loss to follow up, withdrawal or a intermitted missing. Because the missing data could bias the results, baseline characteristics were compared between two groups:

1) Complete cases (completed T0 and T3) versus non-responders (patients alive at follow-up but excluded from the analysis because of missing data)

2) Complete cases versus non-survivors (patients who died during the first year)

Supplementary file 5.1. Differences in characteristics between complete cases and non-responders

	Completed cases (n=846)		**Non-responders (n=338)**		**P-value**
Patient characteristics					
CFS score at baseline, median [IQR]	2	[2-3]	3	[2-4]	.062
Age, mean (SD) in years	62.0	(14.0)	58.3	(17.1)	<.001*
Gender, n (%)					
• Male	568	(67.1)	200	(59.2)	
• Female	278	(32.9)	138	(40.8)	
Education, n (%)					
• Low	235	(28.1)	131	(39.7)*	.009*
• Middle	362	(43.4)	140	(42.4)	
• High	238	(28.5)	59	(17.9)*	
Marital status, n (%)					
• Single	120	(14.3)*	88	(26.3)*	<.001*
• Married	623	(74.4)	189	(56.4)*	
• Divorced	45	(5.4)	22	(6.6)	
• Widowed	49	(5.9)	36	(10.7)*	
Household composition, n (%)					
• Alone	111	(13.2)	70	(21.3)*	<.001*
• With someone else[1]	720	(85.8)	252	(76.6)	
• Healthcare facility	8	(1.0)	7	(2.1)	

[1]With someone else: partner, children, parents, etc. [2]Chronic diagnosis are immunological insufficiency, AIDS, haematological malignancy, metastatic neoplasm, cirrhosis, cardiovascular insufficiency, respiratory insufficiency, COPD, chronic dialysis or renal insufficiency
**Significant differences in characteristics between the complete cases (patients who completed the T0 and T3 questionnaire), and the non-responders (patients who did not completed the T3 questionnaire, but were alive). Data are based on the baseline questionnaire and patient's electronic health record.*

Supplementary file 5.1. Continued

	Completed cases (n=846)		Non-responders (n=338)		P-value
One or more chronic diagnosis, n (%)[2]					
• No	653	(77.2)	247	(73.1)	.135
• Yes	193	(22.8)	91	(26.9)	
ICU/ clinical characteristics					
Admission type, n (%)					
• Elective surgical	566	(66.9)	211	(62.4)	.338
• Medical	183	(21.6)	82	(24.3)	
• Acute surgical	97	(11.5)	45	(13.3)	
Planned admission, n (%)					
• No	267	(31.6)	129	(38.2)	.030
• Yes	579	(68.4)	209	(61.8)	
APACHE IV score, mean (SD)	53.6	(20.5)	52.3	(20.4)	.337
Mechanical ventilation (MV)					
• No	235	(27.8)	117	(34.6)	.020*
• Yes	611	(72.2)	221	(65.4)	
ICU LOS, days, median [IQR]	1	[1-2]	1	[1-2]	.473
Hospital LOS, days, median [IQR]	9	[6-15]	9	[6-15]	.727
Discharge location, n (%)					
• Home	617	(82.7)	209	(82.0)	.665
• Rehabilitation centre	58	(7.8)	25	(9.8)	
• Nursing home	13	(1.7)	5	(2.0)	
• Other	58	(7.8)	16	(6.3)	

[1]With someone else: partner, children, parents, etc. [2]Chronic diagnosis are immunological insufficiency, AIDS, haematological malignancy, metastatic neoplasm, cirrhosis, cardiovascular insufficiency, respiratory insufficiency, COPD, chronic dialysis or renal insufficiency
**Significant differences in characteristics between the complete cases (patients who completed the T0 and T3 questionnaire), and the non-responders (patients who did not completed the T3 questionnaire, but were alive). Data are based on the baseline questionnaire and patient's electronic health record.*

Supplementary file 5.2. Differences in characteristics between complete cases and non-survivors

	Completed cases (n=846)		**Non-survivors (n=116)**		**P-value**
Patient characteristics					
CFS score at baseline, median [IQR]	2	[2-3]	3	[2-4]	.007*
Age, mean (SD) in years	62.0	(14.0)	65.8	(12.0)	.006*
Gender, n (%)					
• Male	568	(67.1)	75	(64.7)	.594
• Female	278	(32.9)	41	(35.3)	
Education, n (%)					
• Low	235	(28.1)	48	(42.5)*	<.001*
• Middle	362	(43.4)	50	(44.2)	
• High	238	(28.5)	15	(13.3)*	
Marital status, n (%)					
• Single	120	(14.3)*	9	(7.9)	.004*
• Married	623	(74.4)	84	(73.7)	
• Divorced	45	(5.4)	5	(4.4)	
• Widowed	49	(5.9)	16	(14.0)*	
Household composition, n (%)					
• Alone	111	(13.2)	17	(15.5)	.002*
• With someone else[1]	720	(85.8)	87	(79.1)	
• Healthcare facility	8	(1.0)	6	(5.5)*	
One or more chronic diagnosis, n (%)[2]					
• No	653	(77.2)	63	(54.3)*	.000*
• Yes	193	(22.8)	53	(45.7)*	
ICU/ clinical characteristics					
Admission type, n (%)					
• Elective surgical	566	(66.9)	64	(55.2)	.002*
• Medical	183	(21.6)	42	(36.2)*	
• Acute surgical	97	(11.5)	10	(8.6)	
Planned admission, n (%)					
• No	267	(31.6)	51	(44.0)*	.008*
• Yes	579	(68.4)	65	(56.0)	

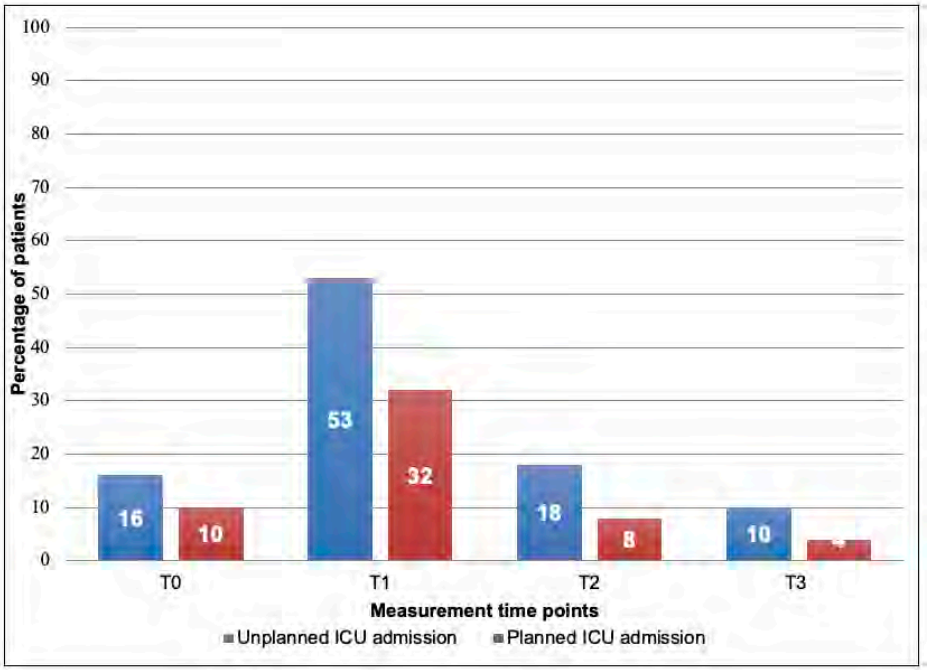
*[1]With someone else: partner, children, parents, etc. [2]Chronic diagnosis are immunological insufficiency, AIDS, haematological malignancy, metastatic neoplasm, cirrhosis, cardiovascular insufficiency, respiratory insufficiency, COPD, chronic dialysis or renal insufficiency *Significant differences in characteristics between the complete cases (patients who completed the T0 and T3 questionnaire), and the non-survivors (patients who died during 12 months after their ICU admission). Data are based on the baseline questionnaire and patient's electronic health record.*

Supplementary file 5.2. Continued

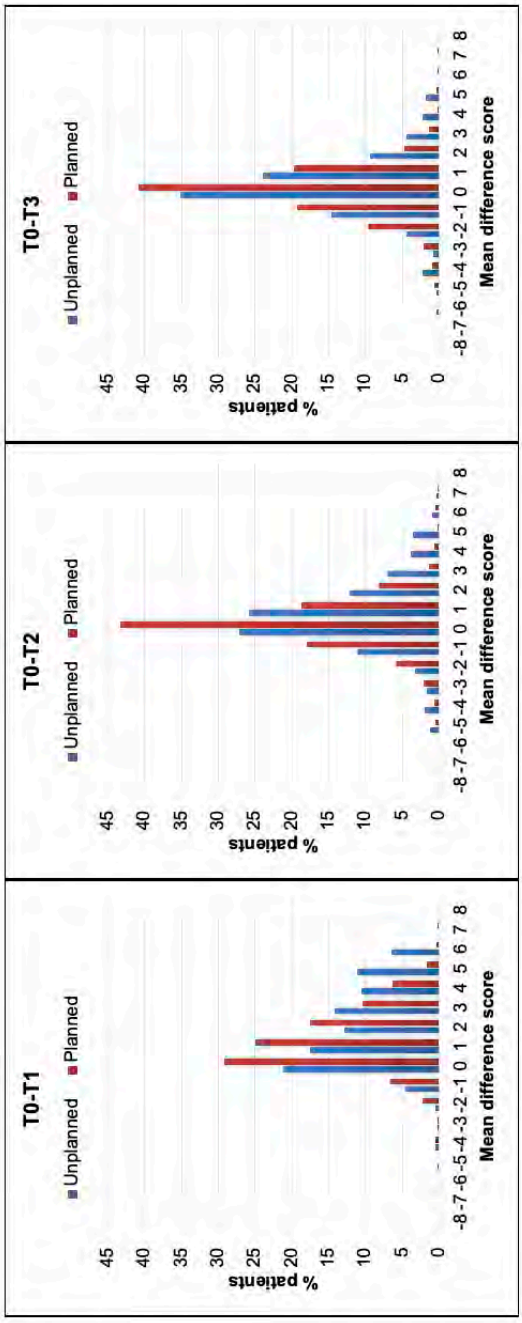
	Completed cases (n=846)		Non-survivors (n=116)		P-value
APACHE IV score, mean (SD)	53.6	(20.5)	62.9	(26.5)	<.001*
Mechanical ventilation (MV)					
• No	235	(27.8)	41	(35.3)	.101
• Yes	611	(72.2)	75	(64.7)	
ICU LOS, days, median [IQR]	1	[1-2]	2	[1-4.75]	<.001*
Hospital LOS, days, median [IQR]	9	[6-15]	13	[8-23]	<.001*
Discharge location, n (%)					
• Home	617	(82.7)	65	(76.5)	.015*
• Rehabilitation centre	58	(7.8)	9	(10.6)	
• Nursing home	13	(1.7)	6	(7.1)*	
• Other	58	(7.8)	5	(5.9)	

*[1]With someone else: partner, children, parents, etc. [2]Chronic diagnosis are immunological insufficiency, AIDS, haematological malignancy, metastatic neoplasm, cirrhosis, cardiovascular insufficiency, respiratory insufficiency, COPD, chronic dialysis or renal insufficiency *Significant differences in characteristics between the complete cases (patients who completed the T0 and T3 questionnaire), and the non-survivors (patients who died during 12 months after their ICU admission). Data are based on the baseline questionnaire and patient's electronic health record.*

Supplementary file 6. Percentage of patients being frail(CFS score 5-9) at different time points



Supplementary file 7a. Changes in frailty between baseline and different time points. Unplanned versus planned ICU admission



T0: before ICU admission; T1: at hospital discharge; T2: three months after ICU admission; T3: 12 months after ICU admission
*Negative mean difference score means patients are **less** frail compared to their baseline score; a positive mean difference score means patients are **more** frail compared to their baseline score*

Supplementary file 7b and 7c.

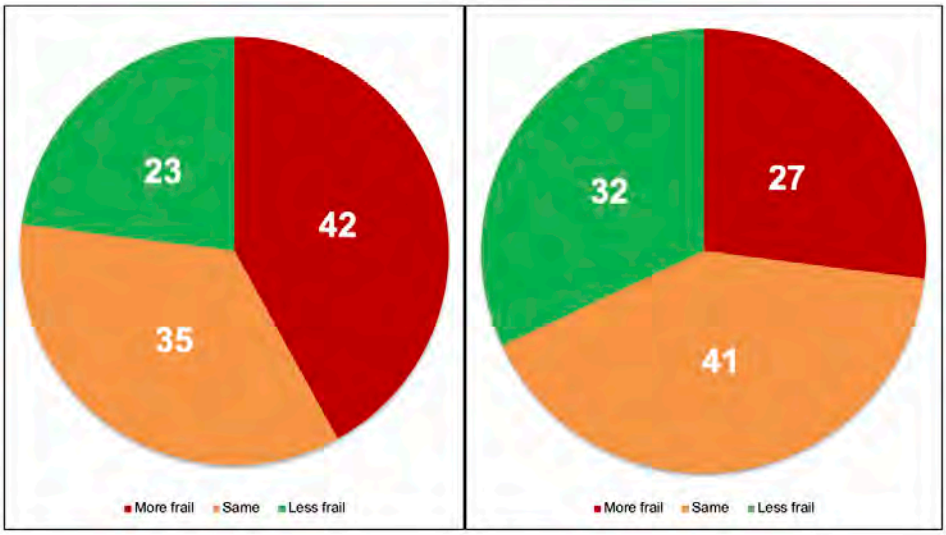
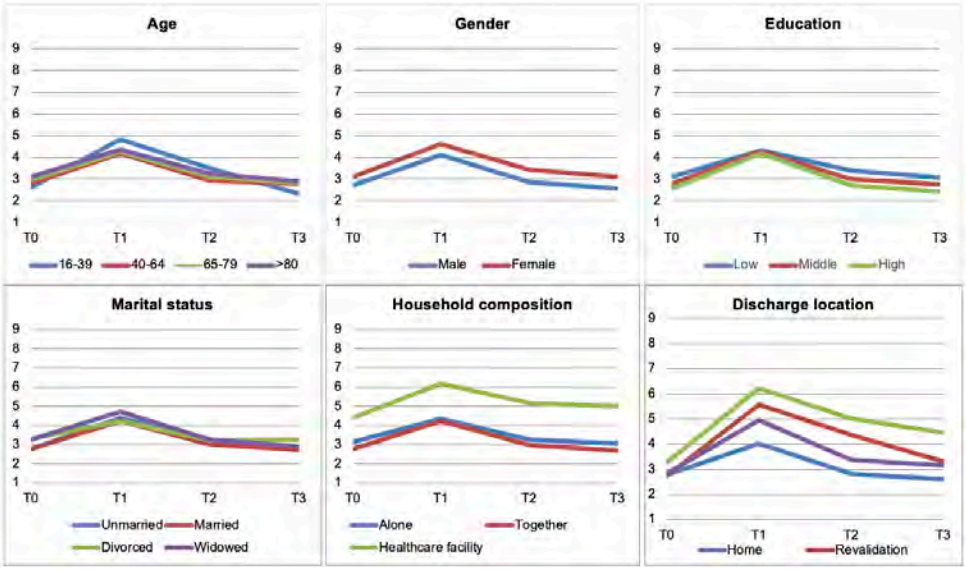


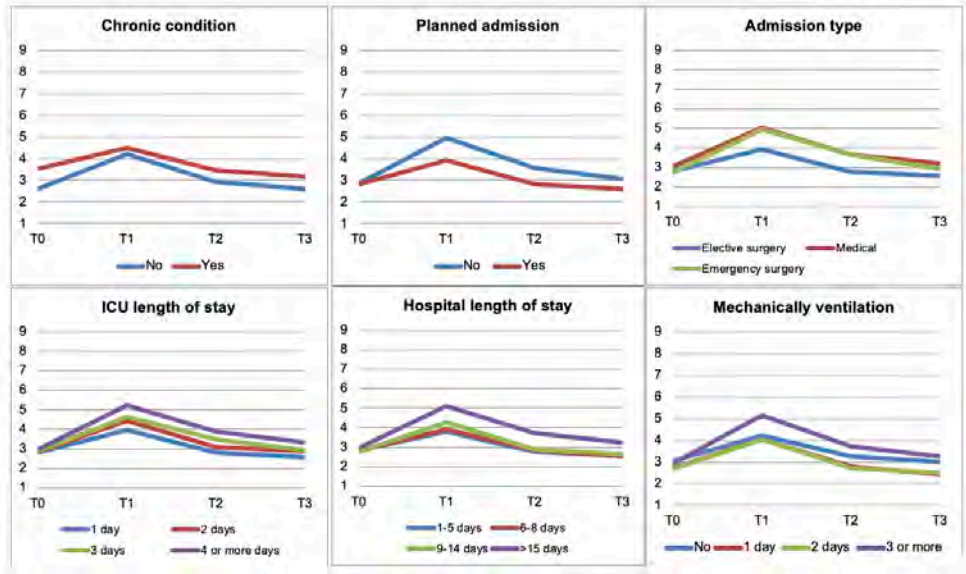
Figure 7b. Changes in frailty status among patients with an unplanned ICU admission after 12 months compared to the frailty status before their ICU admission.

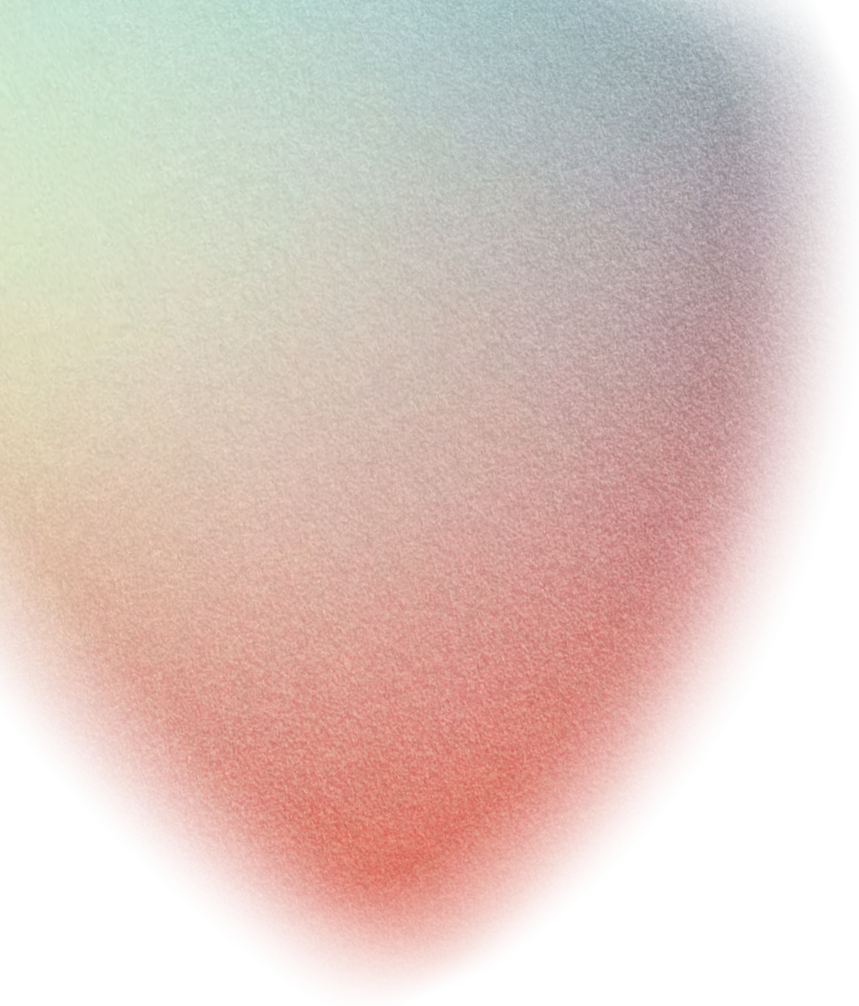
Figure 7c. Changes in frailty status among patients with a planned ICU admission after 12 months compared to the frailty status before their ICU admission.

Supplementary file 8. Subgroup patient characteristic: frailty changes during 12 months



Supplementary file 8b. Subgroup clinical and ICU characteristics: Frailty changes during 12 months





CHAPTER 6

REDUCED QUALITY OF LIFE IN ICU SURVIVORS - THE STORY BEHIND THE NUMBERS: A MIXED METHODS STUDY

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ABSTRACT

Purpose To gain insight into the daily functioning of ICU survivors who reported a reduced quality of life (QoL) one year after ICU admission.

Materials and methods A two-phase mixed method study design. QoL was assessed using the SF-36 questionnaire before admission and after one year (Phase 1). Participants reporting a reduced QoL were invited for an in-depth interview (Phase 2). Interview data were coded thematically using the PROMIS framework.

Results Of the 797 participants, 173 (22%) reported a reduced QoL, of which 19 purposively selected patients were interviewed. In line with their questionnaire scores, most participants described their QoL as reduced. They suffered from physical, mental and/or cognitive problems, impacting their daily life, restricting hobbies, work, and social activities. A new balance in life, including relationships, had to be found. Some interviewees experienced no changes in their QoL; they were grateful for being alive, set new life priorities, and were able to accept their life with its limitations.

Conclusion Reduction in QoL is due to physical, mental, and cognitive health problems, restricting participants what they want to do. However, QoL was not only affected by the critical illness, but also by factors including independency, comorbidity, and life events.

Registration NCT03246334 (clinical trials.gov)

INTRODUCTION

Although a major goal of the intensive care unit (ICU) is to ensure patients' survival, for patients it is essential to survive with the highest possible quality of life (QoL) (1, 2). Nevertheless, recent years it became evident that, in the months and years following ICU admission, the QoL in ICU survivors is significantly lower compared to the matched normal population (1, 3-8). With the increasing number of ICU survivors every year (9), it is important to discuss with ICU patients their presumed future QoL after ICU discharge (10-12). Insight into how patients' QoL is affected, and why patients experience their QoL as reduced is therefore of utterly importance (1, 7, 13-15).

To assess QoL in ICU survivors, generic validated instruments, such as the 36-item short form health survey (SF-36) and EuroQoL 5 Dimensions (EQ-5D), are used (14, 16-18). However, it is unknown whether these instruments reflect QoL adequately (10, 19), and how scores should be interpreted (16, 18). Additionally, important aspects for ICU survivors are not measured (7, 14), including mental and cognitive health (18, 20, 21), social functioning (22), and return to normal living and work (20, 23). By using questionnaires only, patients are unable to offer their own perspective on their experiences, as the responses are restricted to questions and topics that are specifically evaluated (24). The use of a mixed methods design, in which quantitative and qualitative methods are integrated, can provide additional information and clinical useful insights (16, 25). Individual interviews can explain the statistical results by exploring ICU survivors' views in more depth, by getting insight into what is most relevant to them in their everyday lives, and their values, beliefs and concerns (16, 24, 25).

Therefore, the aim of this study is to identify and purposively select ICU survivors, who experience a reduced QoL one year after ICU admission, for a follow-up in-depth qualitative study to get more insight into their daily functioning and their story behind the numbers.

METHODS AND RESULTS

This is an ancillary study of the MONITOR-IC study; an ongoing prospective multicenter cohort study (26). For the present study, the participant selection model was used, a variant of the explanatory design (Supplementary file 1). In this two-phased mixed methods design, quantitative information (Phase 1) is used to identify and purposively select participants for a follow-up in-depth

qualitative study (Phase 2) (25, 27). In 'Phase 1' of this study, QoL was assessed using questionnaires before and one year after ICU admission. Participants who reported a reduced QoL were interviewed in 'Phase 2'.
The study has been approved by the research ethics committee of the Radboud university medical center, CMO region Arnhem-Nijmegen, The Netherlands (2016-2724). Each participant provided written informed consent for the study.

Phase 1: Quantitative data

1.1 Data collection

The MONITOR-IC study is extensively described in the study protocol (26). In short; adult patients (≥16 years) of four hospitals were included when admitted to the ICU (≥12 hours) between August 2018 and June 2019. Patients with a short life expectancy (≤48 hours) or receiving palliative care were excluded. Included patients, or their proxies, completed a QoL questionnaire at baseline, addressing their QoL prior to ICU admission, and one year following ICU admission. QoL was assessed using the SF-36 (28). Scores were summed together into two summary scores: Physical Component Score (PCS) and Mental Component Score (MCS), ranging from 0-100, with higher scores indicating a better QoL.
Patient demographics, such as gender and age, were addressed in the baseline questionnaire. Clinical variables, for example severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE]-IV), and ICU and hospital lengths of stay (LOS), were retrieved from the electronic health record.

1.2 Data analysis

Patients that completed both the baseline and one-year SF-36 questionnaires were included in the descriptive analysis. QoL change score were calculated by subtracting the SF-36 PCS and MCS baseline scores from the one-year scores at patient level.

1.3 Results

Of the 1220 included patients, 794 completed both SF-36 questionnaires (Table 1 and Supplementary file 1). An improvement in PCS and MCS scores was seen in 248 (31%), *and* a decline in 173 patients (22%) with a median (IQR) PCS *and* MCS score of -7.0 (-11.9; -2.9) and -6.3 (-11.5; -2.8), respectively (Supplementary file 2).

Table 1. Characteristics of patients who experienced a reduced QoL

Patient characteristics	Total group of patients (n=794)		Patients with a reduced QoL, Δ score till Q3 (n=102)		Interview participants (n=19)	
Gender, n (%)						
• Female	246	(31.0)	29	(28.4)	5	(26.3)
• Male	548	(69.0)	73	(71.6)	14	(73.7)
Age in years, mean (SD)	63.5	(12.3)	62.9	(12.7)	67.2	(9.0)
Education, n (%)*						
• Low	232	(29.6)	26	(25.7)	4	(22.2)
• Medium	336	(42.8)	44	(43.6)	4	(22.2)
• High	217	(27.6)	31	(30.7)	10	(55.6)
Marital status, n (%)						
• Unmarried/single	111	(14.0)	11	(10.8)	0	(0)
• Married	575	(72.5)	78	(76.5)	14	(73.7)
• Divorced	43	(5.4)	6	(5.9)	2	(10.5)
• Widowed	64	(8.1)	7	(6.9)	3	(15.8)
Household composition, n (%)						
• Alone	127	(16.2)	14	(13.9)	4	(21.1)
• With someone else	652	(83.4)	87	(86.1)	15	(78.9)
• Healthcare facility	3	(0.4)	0	(0)	0	(0)
One or more chronic condition, n (%)	206	(25.9)	21	(20.6)	3	(15.8)
Δ QoL, median (IQR)						
• PCS	0.9	(-5.2; 7.6)	-10.3	(-14.2; -6.5)	-12.4	(-16.4; -6.4)
• MCS	1.0	(-4.5; 7.1)	-9.9	(-16.4; -5.0)	-13.0	(-17.7; -6.3)
ICU characteristics						
Admission type, n (%)						
• Medical	241	(30.4)	41	(40.2)	8	(42.1)
• Urgent surgical	100	(12.6)	25	(24.5)	5	(26.3)
• Elective surgical	453	(57.1)	36	(35.3)	6	(31.6)
APACHE-IV score, mean (SD)	54.5	(20.6)	60.0	(26.4)	74.4	(25.6)
ICU LOS in days, median (IQR)	1	(1-3)	2	(1-6)	4	(1-10)
Hospital LOS in days, median (IQR)	8	(6-14)	12	(6.8-21.3)	12	(8-21)

Δ = delta PCS and MCS score: one year minus baseline score. IQR: interquartile range; SD: standard deviation

**Low: Primary education, pre-vocational education, lower general secondary or assistant training at secondary vocational level*

Medium: Upper general secondary, (basic) vocational training and middle management and specialist training

High: University or university of applied sciences

Phase 2: Qualitative data

This phase is described according to the Consolidated Criteria for Reporting Qualitative Studies (COREQ) (29).

2.1 Participant selection

For the interview study, patients with the largest reduction in QoL were selected using the third quartile values (Q3) of delta PCS *and* MCS scores as cut-off (≤-2.9 and ≤-2.8, respectively) (Supplementary file 2). Participants were purposively sampled on gender, age and admission type.

2.2 Data collection

An invitation letter and informed consent form were sent to the participants. They were not informed that they were invited because of their reduced QoL. After informed consent, semi-structured interviews were performed by the main researcher (WG) trained in conducting and analyzing interviews, and by an ICU nurse/nursing science student (MdG). The first two interviews were conducted by WG and MdG together. The interview location, at home or in the hospital, was chosen by the participant. Seven interviews were conducted by (video)phone due to the COVID-19 outbreak. Interviews lasted between 35 and 108 minutes and took place between February and Augusts 2020, median 17 months (range 14-18) after ICU admission.

A topic list, consisted of open-ended questions about patients' physical, mental, cognitive, and social functioning was used during the interviews (Supplementary file 3), and developed using international literature (22, 30) and expertise of the research team.

2.3 Data analysis

Interviews were audio-taped and transcribed verbatim by a professional transcriptionist. After the first interviews, data analysis started using thematic analysis. The interviews were coded independently by WG and MdG by coding and categorizing themes based on the three domains of the Patient Reported Outcomes Measurements Information System (PROMIS) framework (31): physical, mental, and social health, aspects of QoL often used in healthcare research (32). Codes were compared until consensus was reached. Discrepancies were discussed with a third researcher (MZ). Participant recruitment continued until no new themes were identified (data saturation). Data were analyzed using Atlas.ti software V.8.0. (ATLAS.ti Scientific Software Development Company, GmbH, Berlin, Germany).

2.4 Results

Of the 173 patients with a reduced QoL, 102 (59%) patients had delta PCS and MCS values till Q3 (Supplementary file 2). Invitation letters were sent to 53 patients, of which 19 patients (36%) responded. The 19 participants were older, higher educated, suffering less from chronic conditions, and had a higher APACHE-IV score and ICU LOS than the total group of ICU survivors (n=794) and survivors with the largest reduction in QoL (n=102) (Table 1 and 2).
Participants' daily functioning is described below, according to the domains of the PROMIS framework.

Physical health

Common problems mentioned were muscle weakness, fatigue, shortness of breath, and decreased stamina. Participants were quickly tired and *"no longer the same"* [#2]. Loss of sight, hearing and taste, increased sleeping problems (due to nightmares and pain) and skin problems, such as itching skin ("*It drives me crazy!*" [#11]) were experienced. Some were continuously aware of their symptoms, including pain and sensory changes: one participant felt his mechanical heart valve constantly 'ticking'. Participants indicated several causes of the physical problems, including the critical illness or event, treatment, complications, medication side effects, age, and comorbidities.
Participants were daily confronted with their physical limitations: "*Once, I made a list with things I couldn't do anymore. That was a lot. Really hard to see*" [#11]. Due to, for example, fatigue and muscle weakness, daily activities were limited and took much more time: "*What I used to do in one day, will take me more than a week now*" [#11]. Participants needed household support, and the ones being unable to walk or drive, had to adapt their house and/or car to become independent again and to unburden their partner. One participant had to move, because his property was not wheelchair accessible. To cope with their limited energy, participants conserve energy by taking a nap during the day and planning their activities carefully: "*I'm fully aware of my energy levels, and try to spend my energy wisely. That's why I get homecare, to help me dress, an irrelevant activity, leading to nothing, and only takes a lot of energy*" [#8]. Some were careful with their health, trying to listen to their body, while others found that difficult, because they have lost trust in their body: "*my body betrayed me*" [#9].

Table 2. Characteristics of the 19 interview participants

Nr.*	Gender	Age in years	ICU admission	Admission diagnosis	APACHE-IV score	ICU LOS in days	Hospital LOS in days	Δ PCS	Δ MCS
#1	Male	66	Elective surgical	Surgery for oesophageal cancer	47	2	8	-11.2	-16.8
#2	Male	61	Medical	Cardiac arrest	114	10	20	-12.9	-10.7
#3	Male	58	Elective surgical	Coronary artery bypass grafting (CABG)	39	1	8	-8.5	-6.3
#4	Male	58	Urgent surgical	Thoracic aortic aneurysm	53	2	8	-5.9	-24.0
#5	Male	76	Elective surgical	Bullectomy	58	1	11	-6.4	-16.3
#6	Male	72	Elective surgical	Thoracic aortic aneurysm	60	1	6	-15.3	-21.1
#7	Female	70	Elective surgical	Aortic valve replacement	55	1	12	-26.4	-1.1
#8	Male	57	Urgent surgical	Surgery for extremity/face trauma	110	54	61	-35.7	-10.6
#9	Male	52	Medical	Cardiac arrest	127	4	17	-3.4	-29.8
#10	Female	69	Elective surgical	CABG alone, coronary artery bypass grafting	78	5	12	-12.9	-4.5
#11	Male	74	Urgent surgical	Surgery for pelvis/extremity trauma	73	3	59	-21.7	-25.3
#12	Male	68	Medical	Chest/abdomen trauma	57	5	18	-11.3	-13.0
#13	Male	72	Medical	Pneumonia	84	2	7	-6.1	-4.7
#14	Male	77	Medical	Pneumonia (fungal)	54	14	35	-16.4	-15.3
#15	Male	77	Elective surgical	Surgery for inflammatory bowel disease	77	4	9	-8.7	-4.5
#16	Male	48	Urgent surgical	Thoracic aortic aneurysm, with dissection	52	1	5	-4.3	-8.2
#17	Female	78	Medical	Sepsis	112	27	27	-12.4	-17.7
#18	Female	71	Medical	Sepsis (pulmonary)	120	14	21	-21.1	-7.0
#19	Female	73	Medical	Airway obstruction	44	8	12	-14.1	-14.4

**The numbers in the first column are used for the quotations in the result section.*

Mental health

Although participants could not recall what exactly happened during ICU stay, some had delusional memories, often caused by delirium: "*I wanted to crawl under my bed*" [#5]. They could not share their anxiety and fear, because "*she [nurse] was part of the conspiracy. It was horrible*" [#10]. ICU events were stressful (e.g. the repeatedly placement of a tunneled dialysis catheter: "*It was absolutely horrendous*" [#18]), and participants felt powerless, due to being physically restrained, incontinent, dependent, or unable to communicate. Some were still concerned about their future, recovery, and possible recurrence of the critical event. Frustration, disappointment, and symptoms of depression were experienced, primarily because of being limited in daily activities, overestimating their abilities, and being unable to reach (new) goals.

Further, mood changes were mentioned. Some were emotionally more 'flattened', probably due to medication side-effects ("*I used to be a very emotional human being. Now, I really don't care*" [#8]), or as another participant said: "*I haven't cried for a long time. Nor that I laughed. I'm more like a 'flatliner' now*" [#9]. Conversely, others became more emotional, experiencing outbursts of tears and increased frustration and irritability ("having a short fuse").

Nearly all participants experienced a deterioration in cognitive functioning since the ICU: "*Many people say 'you're doing well', but people close to me, like my children, know very well there is a huge contrast; in analyzing problems, remembering stuff, and speed of talking and thinking. There's a world of difference*" [#8]. Executive function deficits were reported, and keeping track, having an overview, and learning new tasks has become difficult: "*Before [ICU admission], I always saw things as a challenge and opportunity. Now, I think... do I really have to?*" [#4]. Others experienced difficulties in their (short-term) memory: "*I can't remember things, for example my pin*" [#10]. Also problems in concentration and attention were reported, and cognitive task became energy- and time-consuming: "*I'm unable to concentrate. After my morning shift, I'm totally exhausted*" [#2]. Reduced processing speed in speaking and thinking limited their abilities to react in group conversations, and losing their train of thoughts: "*If I want to react on something, the conversation is already another fifteen minutes further*" [#1].

The way participants coped with the long-lasting impairments and daily consequences differed. Some reported difficulties in accepting the reality.

Their self-image had changed ("*My life is a mess…This is a B-category human*" [#8]), seeing themselves as vulnerable. They did not have a goal in life anymore, nor future plans, since they were more concerned about the present. However, most were resigned to their situation ("*There is no point in thinking about 'what If'*"), mentioning they had to 'deal with it' and their life was still 'worth it'. Others had an enormous drive to continue: "*I've to try to eliminate my impairment by being active. What comes out as the max, I'll accept that. This isn't going to ruin my life*" [#11].
Positive aspects were also reported, including an increased awareness of the fragility of life, which put things into perspective: "*Nobody is indispensable*" (2). Participants experienced their life as enriched, appreciated more what they have, were grateful for being alive, and set new life priorities: "*My life was turned upside down, which made me realize what's most important in life. My job wasn't part of that*" [#11].

Social health
The impact of the health problems on participants' daily living is profound: they had less time for, or even had to give up, their hobbies, mainly due to physical problems and time-consuming daily activities. Also cognitive problems were involved: "*I'd really like to remember my dance steps. If I'd forget something else, groceries for example, I really wouldn't care. But if I've to quit dancing… that would really hurt*" [#10]. Others were hesitant to pick up their hobbies again, or had to search for new hobbies, although some found that difficult: "*Sometimes people say, 'find a new hobby'… If that's what I wanted, I'd already have done it in the past*" [#8]. Participants who were able to pick up their (new) hobbies, stated it gives them joy, relaxation and helped them to 'clear their mind'.

Work-related problems were mainly due to cognitive impairments. Many were not able to work on their previous level: "*I used to do projects in the category 'difficult to very difficult'. I was able to do that. That was unique. But all those things, remembering everything, every detail, every discussion with a client or supplier… I don't even have to think about that anymore. I'd completely panic*" [#8]. Participants had to make adjustments in their working activities or hours, leading to feelings of guilt to their colleagues, and less fulfilment and social interactions. Some even had given up their job. Others mentioned that, since their critical illness, work has become "*totally less important*" [#4], because "*there are so many things more fun than my job*" [#8].

The critical illness also had a major impact on their family: "*She [partner] and my two sons resuscitated me*" [#9]. Tensions were common, particularly due to emotionally changed participants. A new balance had to be found since they spend more time at home or became dependent on their partner, altering the roles. Further, communication difficulties were mentioned ("*Our conversations are different now. Much is now related to my handicap*" [#8]) and some participants or partner did not wanted to talk about the event or ICU admission. Conversely, other said their critical illness brought them closer to their partner, realizing what is most important in life. They appreciated their partner more ("*My wife is partially my caregiver. I've so much more respect for her. I put her on a pedestal*" [#8]), and wanted to spent more time with them. Although many experienced support from friends, stating their friendships have become closer, others suffered from social isolation: they were physically unable to visit their friends, or experienced difficulties in paying attention in conversations due to fatigue and cognitive problems ("*I find it hard to find words, and they've little patience to listen… So I'm quiet*" [#17]).

2.5 Interpretation quantitative and qualitative data

Most participants described their QoL as reduced, in line with their questionnaire scores. They experienced daily physical, mental and/or cognitive impairments, and subsequently the inability to do what they wanted to do: "*My quality of life depends of course on what I could and did. That's all impossible now*" [#11]. The contrast between their life before and after the ICU admission was for many confronting. However, some were still hoping it might improve: "*There's an upward trend, I think it will be okay. But it isn't what I expected of my life, and how it was*" [#9]. The QoL reduction was not always due to critical illness or ICU admission: pre-existing comorbidities and life events, such as the death of a loved one, affected their QoL as well. Others experienced no changes in QoL, despite their reduced scores on the questionnaires, primarily because they were able to accept their life with its limitations. Some reported their QoL as different, but unchanged. One participant described his QoL as improved: his pre-ICU health condition was poor (Kahler's disease), limiting his ability to live a meaningful life. Since the post-ICU treatment, his condition has improved.

DISCUSSION

In this mixed methods study, quantitative data was used to identify and purposively select ICU survivors, who experienced a reduced QoL, for a follow-

up in-depth interview to hear their story behind the numbers. One year after ICU admission, participants experienced several physical, mental and cognitive problems. They were continuously aware of these problems, limiting their mobility, hobbies, and independency. They were concerned about their future, depressed and disappointed because of being unable what they wanted to do, and cognitive problems restricted their employment and participation in social activities. Despite these problems, most participants were resigned to their situation.

In line with other studies, interviewees indicated that their QoL is affected by the critical illness and long-lasting physical, mental, and cognitive problems, broadly termed as post-intensive syndrome (PICS) (4, 22, 30, 33-35). Similar to our results, social health is also found to be an important contributing factor to impaired QoL (16, 22, 36, 37), as social roles and relationships are often abruptly changed due to critical illness (22, 30). Besides, QoL is strongly determined by the inability to perform valued tasks (10), including the return to work (7, 35, 38, 39). Other significant (ICU) associated factors are illness severity (3) and prolonged mechanical ventilation (7). In addition, some subgroups of ICU patients, with for instance renal failure (1), severe ARDS, or trauma having worse reductions in QoL (7). There is also increasing evidence that reduced QoL may also reflect a poor pre-ICU health status and QoL (7, 15, 38, 40). Nonetheless, in our study only a few participants related their reduced QoL to their pre-existing condition.
In agreement with findings in previous studies (22, 30), positive emotions, including gratitude and a positive outlook, were mentioned as well. Some participants described their QoL as the same or even better, despite rating their QoL in the questionnaires as reduced. This discrepancy can, for example, be explained by the fact that patients' health status might have been improved in the period between completion of the one-year questionnaire and interview (5, 36). Although we tried to minimize this period, several months in between could not be prevented. Besides, patients' QoL might have been improved due to the development of active coping strategies (6, 17, 41). Furthermore, due to the critical illness, and the necessity to adapt to the disease and situation, participants might have changed their internal standards, values and conceptualization of QoL, a phenomenon called 'response shift' (10, 14, 17). Participants stated, for instance, they appreciated their life more, set new life priorities, and wanted to spend more time with their family.

Implications

It is difficult to say how ICU patients will recover and what their future QoL will be (10, 14). Issues of survivorship are subsequently rarely addressed during or after ICU stay, leaving the survivors and their family members unprepared for the future (42). However, future QoL and functional outcomes are highly valued by patients and their families (20, 43). As ICU survivors are physically, mentally, cognitively, and socially vulnerable after ICU discharge (35), it is important to inform the patients and their family members about their life after the ICU, and the new long-lasting impairments they might experience (10), enabling them to reclaim ownership of their lives (44).

Limitations

This study has some limitations. First, selection bias could have resulted from non-response: interview participants had higher median delta PCS and MCS scores, higher mean APACHE-IV scores, and median ICU LOS, were older, higher educated, and more often living alone compared to the group from which they were selected. Second, due to the purposive sampling method used in this study, researcher bias might be possible, because the sampling criteria for the interviews were based on our judgement (45). On the other hand, by selecting participants based on their age, gender and admission type we tried to study and explain the reduction in QoL from different perspectives. Third, due to the COVID-19 outbreak, seven interviews were conducted by (video)phone, making it more difficult for the interviewer to anticipate and to build 'rapport' with participants (46). Some participants also mentioned they were more careful since COVID-19, perceiving themselves as more vulnerable. And fourth, Q3 values of delta PCS and MCS scores were used to select participants. Whether these values are clinically important is unknown (15, 47).

Conclusion

One year after ICU admission, over one fifth of the ICU survivors experienced a reduced QoL, mainly due to physical, mental and/ or cognitive problems, and subsequently the inability to do what they wanted or used to do, including hobbies, employment and social activities. QoL was not only influenced by the critical illness and ICU admission, but also by factors including acceptance, independency, comorbidities, age, and major life events. A discrepancy was seen between the reported QoL in the questionnaires and interviews. Understanding the impact of critical illness on QoL and patient values is

paramount to formulate a personalized recovery plan, and to adequately advise and talk to patients and their relatives about what their lives are likely to be after discharge.

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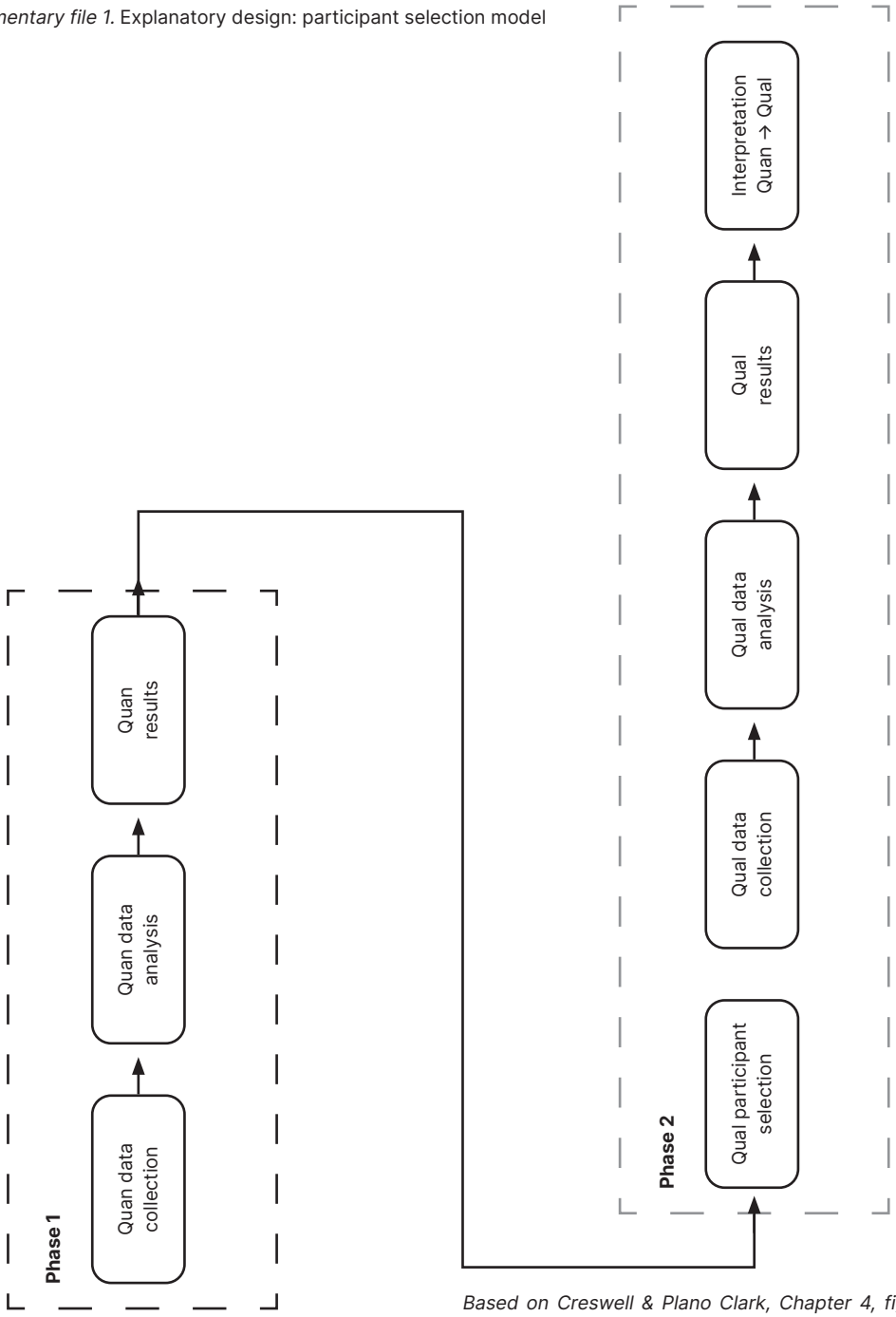
Supplementary file 1. Explanatory design: participant selection model



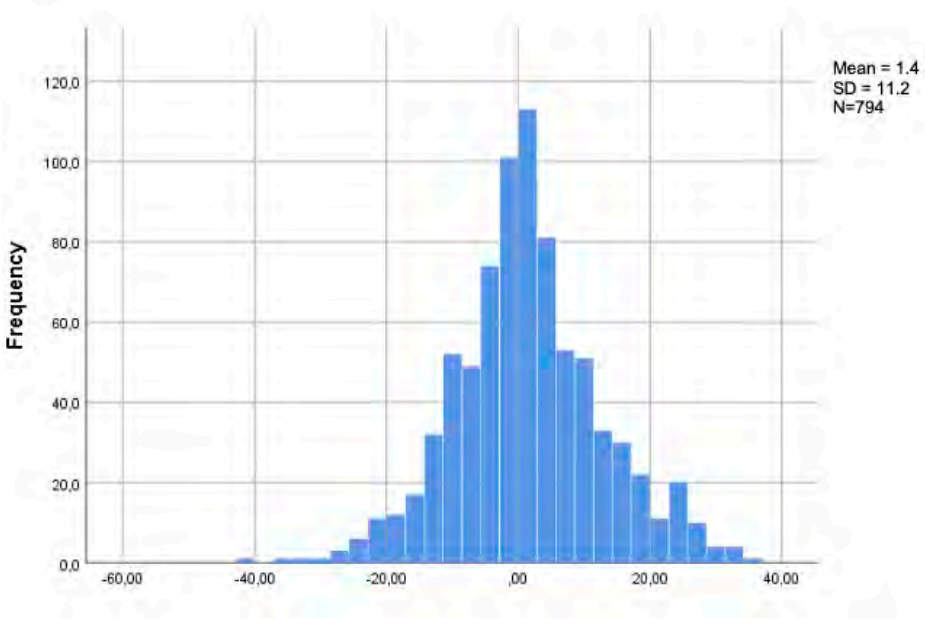
Based on Creswell & Plano Clark, Chapter 4, figure 4.3 [27] Qual: qualitative phase; Quan: quantitative phase

Supplementary file 2. Histograms SF-36 PCS and MCS delta scores

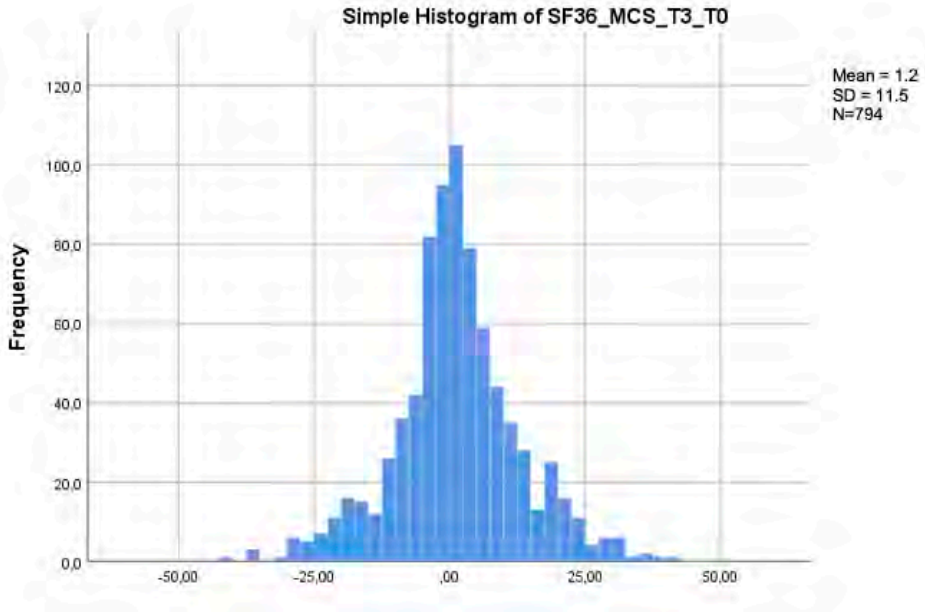
One year after ICU admission - pre-ICU

Complete cases (n=794)

SF-36 delta PCS (one year-baseline score)

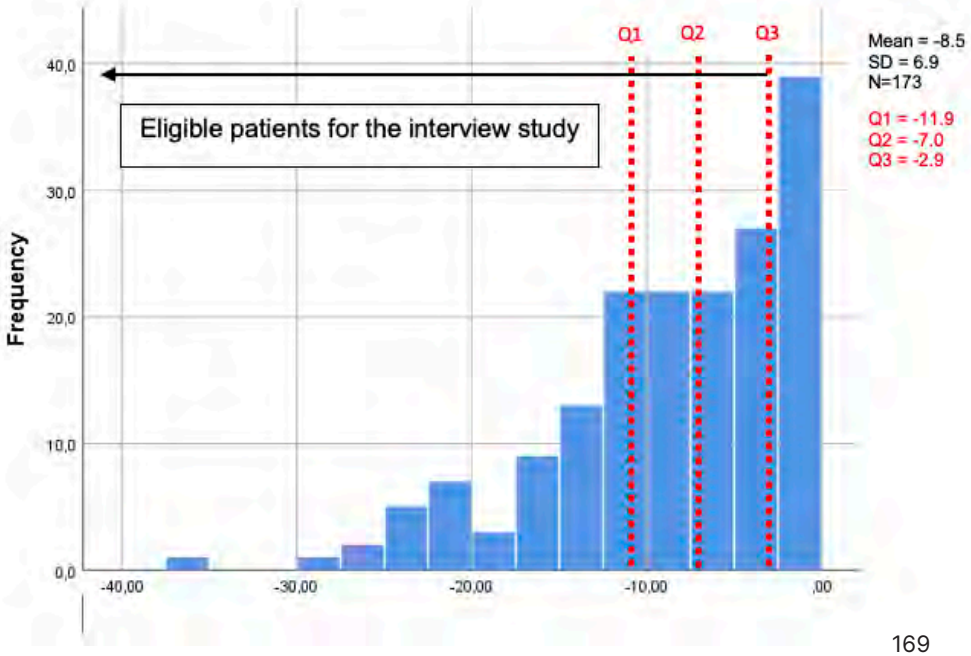


SF-36 delta PCS (one year-baseline score)

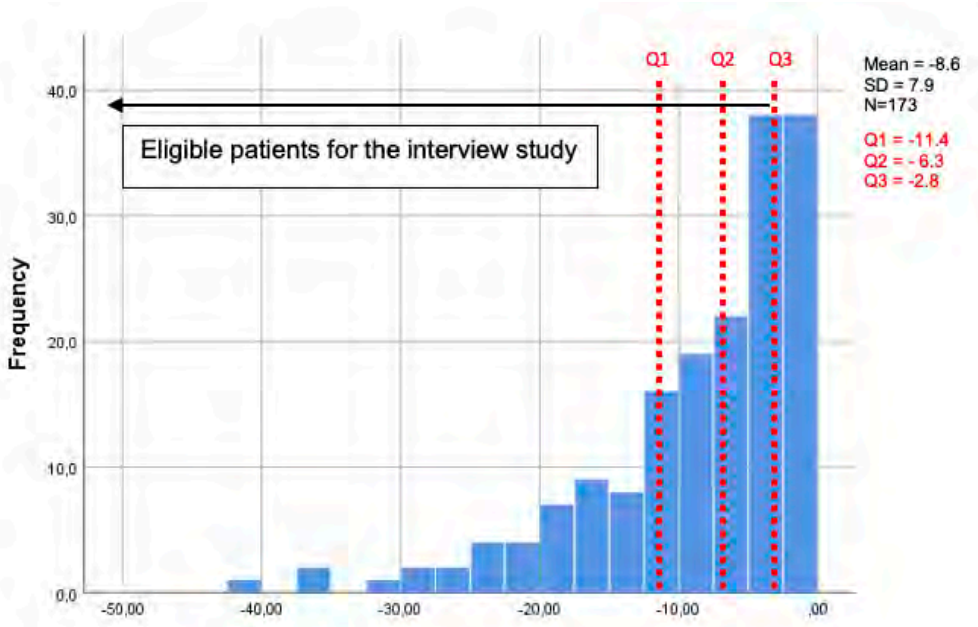


Patients with reduced QoL (n=173)

SF-36 delta PCS (one year-baseline score)



SF-36 delta PCS (one year-baseline score)



Supplementary file 3. Topic list interview study

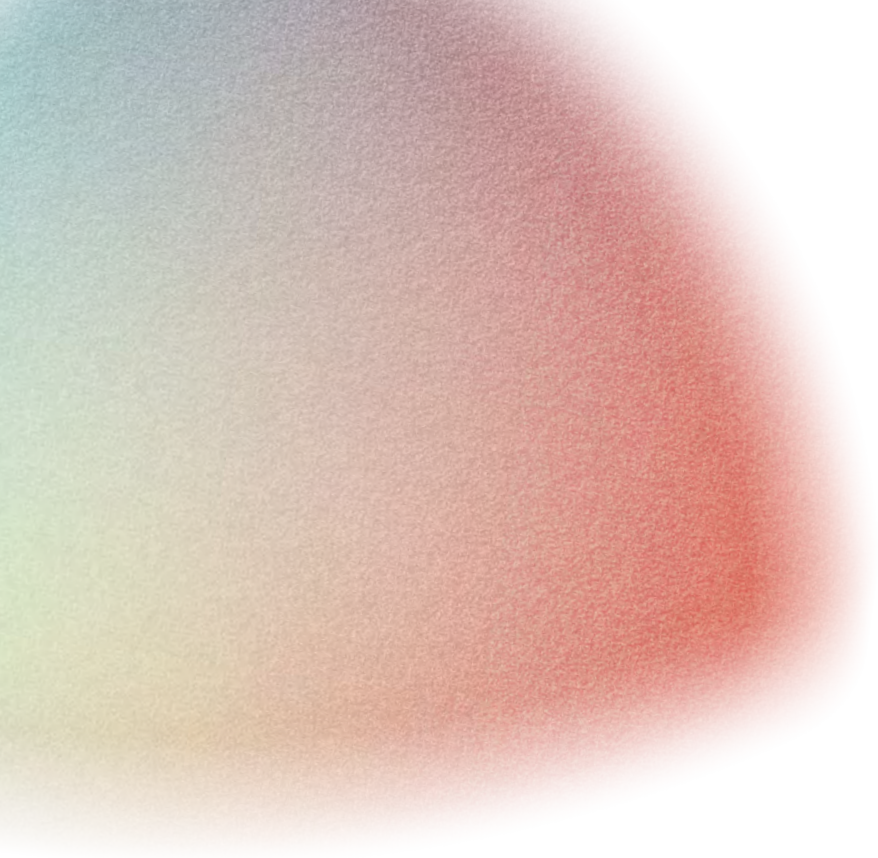
Can you tell me about why you were admitted to the ICU one year ago?
How would you describe your health now?
How has your health changed from before you were admitted to the ICU?

Physical health
Do you experience physical problems (pain, fatigue, sleeping problems, stiffness joints/ muscle weakness)?
How much energy do you have during the day?

Mental health
How is your mood now? (depression, anxiety, anger, stress)
How is this different from before your ICU admission
Do you have unwanted memories or thoughts about your ICU admission?
Do you avoid certain things because it reminds you of the ICU admission?
Do you have problems with your memory (concentration, paying attention, planning and organization, taking initiatives)?

Social health
How would you describe a typical day now? (employment, hobbies)
How , if at all, have your relationships changed with your family and friends since the ICU admission? (Partner, children, friends)

Quality of life
How is your quality of life now compared to before the ICU admission?
What is a good day for you?
What is a bad day for you?
What is the biggest change in your life since your ICU admission?
What do you miss most?
Would you like something to change about your life as it is now?
How do you see the future?



CHAPTER 7

NONPHARMACOLOGIC INTERVENTIONS TO PREVENT OR MITIGATE ADVERSE LONG-TERM OUTCOMES AMONG ICU SURVIVORS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Wytske Geense, Mark van den Boogaard, Johannes van der Hoeven, Hester Vermeulen, Gerjon Hannink, Marieke Zegers

Critical Care Medicine, 2019

ABSTRACT

Objective ICU survivors suffer from long-lasting physical, mental and cognitive health impairments, also called "postintensive care syndrome". However, an overview of the effectiveness of interventions to prevent or mitigate these impairments is lacking. The aim of this study is to assess the effectiveness of non-pharmacologic interventions.

Data Sources PubMed, CINAHL, PsycINFO, Embase, and Cochrane Library were systematically searched from inception until July 19, 2018.

Study Selection (Non)randomized clinical trials, controlled before-after studies, and interrupted-time series were included. Outcomes of interest included physical, mental and cognitive outcomes, quality of life, and outcomes as social functioning and functional status, measured after hospital discharge.

Data Extraction Two independent reviewers selected studies, extracted data, and assessed the risk of bias. Pooled mean differences and standardized mean differences were calculated using random-effect meta-analyses.

Data Synthesis After screening 17,008 articles, 36 studies, including 10 pilot studies, were included (n=5,165 ICU patients). Interventions were subdivided into six categories: 1) exercise and physical rehabilitation programs; 2) follow-up services; 3) psychosocial programs; 4) diaries; 5) information and education; and 6) other interventions. Many outcomes favored the interventions, but significant differences were only found for diaries in reducing depression (two studies, n=88; standardized mean difference, 0.68; 95% CI, 0.14-1.21) and anxiety (two studies, n=88; standardized mean difference, 0.44; 95% CI, 0.01-0.87) and exercise programs in improving the Short Form Health Survery-36 Mental Component Score (seven studies, n=664; mean difference, 2.62; 95% CI, 0.92-4.32).

Conclusions There is thin evidence that diaries and exercise programs have a positive effective on mental outcomes. Despite outcomes favoring the intervention group, other commonly used nonpharmacologic interventions in daily ICU practice are not supported by conclusive evidence from this meta-analysis. To improve recovery programs for ICU survivors, more evidence is needed from robust intervention studies using standardized outcomes.

Registration PROSPERO NCT01738620

INTRODUCTION

The number of patients admitted to the ICU is increasing, as well as the patients who survive their critical illness (1). The road to recovery is long, and patients' outcomes after ICU discharge are of growing concern (1-3). Many studies demonstrate that ICU survivors suffer from a wide range of physical (e.g. pain, fatigue) (4), mental (e.g. anxiety, depression) (5-7), and cognitive problems (e.g. memory and planning problems) (8). These problems, also called "postintensive care syndrome" (PICS), can last for months to even years (1). Although it is estimated that over half of all ICU survivors experience physical, mental, or cognitive health problems, the exact prevalence of PICS is unknown (9). PICS can adversely affect patients' health-related quality of life (HRQoL) (10) and their ability to participate in social roles and activities, including hobbies and return to work (11). Additionally, it results in higher healthcare utilization due to hospital readmissions, homecare support, and long-term care admissions (12). The causal factors of PICS are not fully understood yet, but are generally thought to be a combination of patient characteristics, pre-ICU health status, severity of critical illness, ICU treatment, and post-ICU factors (13).

Development, implementation, and evaluation of effective interventions, aiming to prevent or mitigate adverse long-term outcomes and to improve quality of life, are utterly important (14, 15). Although still in its infancy, a wide range of interventions has been developed, such as diaries, early mobilization, electrical muscle stimulation, and post-ICU follow-up clinics (13, 16), and the number of interventions is rapidly increasing every year. To summarize the effects of these interventions so far, several systematic reviews have been published. However, reviews often examined effects of one specific intervention (17-22), or evaluated only one of the outcome domains of PICS (23, 24). Additionally, most of the reviews described patient outcomes till hospital discharge and did not focus on the long-term outcomes (25-28). Given the increasing numbers of ICU survivors and rapid development of various interventions, it is important to evaluate the current status and to provide recommendations for the improvement of interventions for ICU survivors.

Therefore, the aim of this systematic review and meta-analysis was to assess the effectiveness of nonpharmacologic interventions to prevent or mitigate adverse long-term outcomes among ICU survivors.

MATERIALS AND METHODS

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines statement (29) (Supplementary file 1). The protocol is registered in International prospective register of systematic reviews (PROSPERO) (NCT01738620) (30).

Data Sources and Searches

Databases of PubMed, CINAHL, PsycINFO, Embase, and Cochrane Central Register of Controlled Trials were systematically searched from inception to September 19, 2017 and updated to July 19, 2018. Reference lists of included studies and relevant systematic reviews were scanned to identify studies that were missed in the database search.

The search strategy included a combination of medical subject headings and title abstract terms consisting of four parts: *Population and Setting* (e.g. "Critical Care", "Intensive care units"); *Intervention* (e.g. "Counseling", "Rehabilitation"); *Outcome* (e.g. "Anxiety", "Quality of Life") and Design (e.g. "Clinical Trials") using the Cochrane Effective Practice and Organization of Care study designs guidance (31). The detailed search strategy per database is provided in Supplementary file 2.

Study Selection

Studies were considered eligible for inclusion if they met the following criteria (Supplementary file 3):

- Adult patients admitted to the ICU for at least 12 hours. Studies that included patients in the PICU, postanesthesia care unit, or coronary care unit were excluded.
- Interventions performed before, during, or after ICU admission and aimed to prevent or mitigate long-term adverse outcomes. Pharmacologic and nutritional interventions were excluded.
- Outcomes measured after hospital discharge. Physical (e.g. pain, fatigue), mental (e.g. anxiety, depression), or cognitive (e.g. memory, attention) outcomes were included, as well as quality of life and outcomes such as social functioning and daily activities. Outcomes related to healthcare utilization, costs, length of stay, ICU and hospital mortality, and readmissions were excluded.
- The study design was a randomized controlled trial (RCT), non-RCT (NRCT), controlled before-after, or interrupted time series.

No language restrictions were used.

Data Extraction and Quality Assessment

Titles, abstracts, and subsequently full-text articles were screened by two independent authors (W.W.G., M.v.d.B./M.Z.). Disagreements were resolved by discussion, and when no consensus was reached, a third author arbitrated (M.v.d.B./M.Z.). Excluded full-text studies were listed with reason for exclusion (Supplementary file 4). From the included studies, data were extracted on a standardized data collection form (Supplementary file 5), including the methods (e.g. design, setting), participants (e.g. number of patients, age), interventions (e.g. components, comparisons), outcomes, and time points reported.

The quality of the included studies was independently assessed by two authors (W.W.G,. M.v.d.B./M.Z.) using the Cochrane Collaboration's risk of bias tool (32) (Supplementary file 6). Any disagreement was resolved by discussion or involving a third author (M.v.d.B./M.Z.). Risk of bias was assed as "low risk", "high risk", or "unclear risk" in seven domains of potential bias: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel for each outcome), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), selective reporting, and other sources of bias (32).

Data Synthesis and Analysis

Patient outcomes were categorized into five domains: "Physical health", "Mental health", "Cognitive health", "Quality of life", and "Other outcomes". Follow-up time was categorized into three different time categories: 1) between hospital discharge and 3 months after hospital discharge; 2) between 3 and 6 months after hospital discharge; and 3) more than 6 months after hospital discharge.

Within each domain (e.g. mental health), outcomes were pooled (e.g. depression) per time category (e.g. between 3 and 6 mo after hospital discharge). Pooled mean differences (MDs) or standardized MDs (SMDs) with 95% confidence intervals (CI) were estimated using random-effects models (32). Hedges'g instead of Cohen's D was used as a measure of SMD, because it includes an adjustment for small sample sizes (<20) (32). Statistical heterogeneity was assessed using chi-square test and I2 statistics (32). Subgroup analyses were performed on intervention category (e.g. diaries), when two or more independent comparisons per outcome could be included. Additional analyses were performed on outcome level, in which per study, the time category with the largest MD or SMD was included. All analysis were performed on an intention-to-treat basis.

In case of multiple treatment groups, relevant groups were combined to create a single pairwise comparison, as recommended by the Cochrane Handbook (32). If an outcome was measured with two or more instruments in one study (e.g. handgrip left and right hand), pooled means and SDs were calculated. Due to their inaccuracy, reported medians and interquartile ranges (IQRs) were not converted into means and SDs (32). When numerical outcome data were missing, or medians and IQRs were presented instead of means and SDs, corresponding authors were contacted. In case of no response, studies were not included in the meta-analyses. Publication bias was addressed by means of a funnel plot, if at least 15 studies could be included (33).

The data were analyzed in R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and package "meta" (version 4.9-2) (34).

RESULTS

The initial search yielded 17,008 citations. After removing duplicates, 12,708 titles and abstracts and subsequently 135 full-text articles were screened. One additional study was identified by manual check of the reference lists, resulting in a final set of 36 included studies (Figure 1).

Characteristics of included studies

The 36 included studies (35-70) (Table 1) consisted of two NRCTs (48, 53) and 34 RCTs, including 10 pilot studies (35, 37, 38, 40, 49-51, 56, 67, 69). Twenty studies were single center studies (35, 36, 38, 39, 44, 45, 48, 49, 51, 53, 56, 57, 59, 60, 64-69). A total of 5,165 patients were included, ranging from 10 to 231 in the intervention groups and from 8 to 196 in the control groups.

Risk of bias

Most studies had a "low risk" of bias for random sequence generation (81%) and allocation concealment (58%). A high proportion had an "unclear risk" for blinding of participants (72%) and incomplete data (50%) and a "high risk" for other sources of bias (42%) (for the risk of bias summary table and graph, see Supplementary file 7 and 8, respectively).

Publication bias

The presence of publication bias could not be assessed due to the low number of studies that were included in the meta-analysis.

Interventions

The interventions were subdivided into six categories: 1) "Exercise and physical rehabilitation programs" (20 studies); 2) "Follow-up services" (five studies); 3) "Psychosocial programs" (three studies); 4) "Diaries" (three studies); 5) "Information and education" (two studies); and 6) "Other interventions", including an Awakening and Breathing, Coordination, Delirium monitoring and management, and Early mobilization education program, use of earplugs and eye masks, and use of structured mirrors. Interventions were carried out before hospital admission (one study), during ICU (16 studies), post-ICU discharge (eight studies), and post-hospital discharge (11 studies). A description of the interventions is provided in Supplementary file 9.

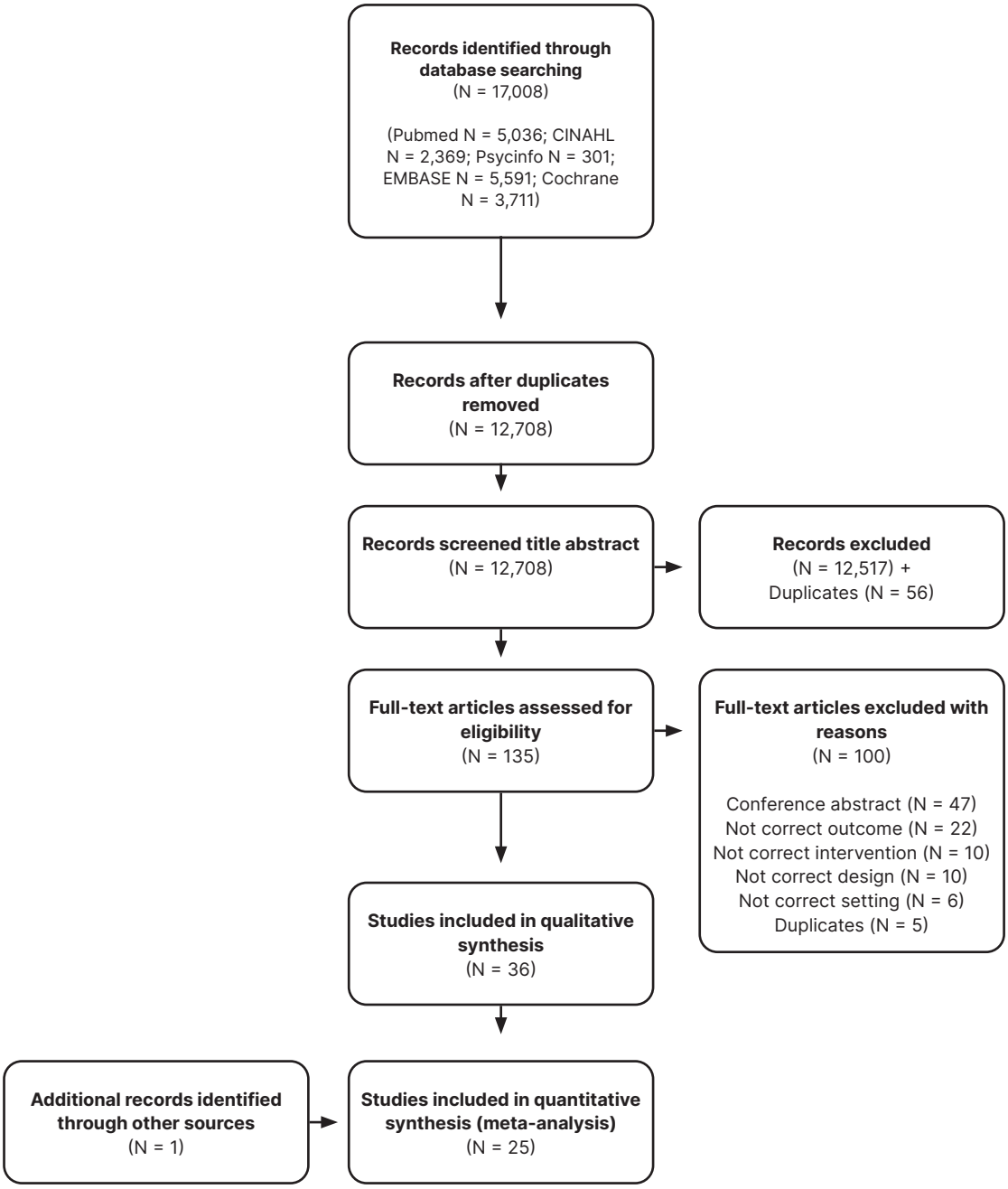
Outcomes

An overview of the used outcomes and instruments is presented in Supplementary file 10, and in Supplementary file 11 the reported outcomes per study are described.

One study (63) reported outcomes in all five domains, and 12 studies (33%) reported outcomes in one domain only (Table 1). Quality of life was most frequently reported (26 studies, 72%) and cognitive outcomes the least (four studies, 11%). Outcomes were measured with 73 different instruments, including seven different instruments to evaluate posttraumatic stress disorder (PTSD) and six to evaluate quality of life. Forty-nine instruments (67%) were only used once (Supplementary file 10). In most studies, patients' outcomes were measured between hospital discharge and 3 months after hospital discharge and between 3 and 6 months after hospital discharge (respectively 81% and 56%), whereas outcomes after 6 months were only reported in eight studies (22%).

Physical health Ten RCTs (37, 40, 44, 46, 59-61, 65, 66, 70) reporting physical outcomes were included in the meta-analyses, all evaluating exercise and physical rehabilitation programs. Although most of the pooled SMDs favored the intervention group, exercise and rehabilitation programs were not associated with differences in walking distance (five RCTs) (40, 44, 46, 66, 70), muscle strength (four RCTs) (40, 60, 65, 66), physical performance (three RCTs) (44, 60, 61), balance (two RCTs) (61, 66), or oxygen uptake (two RCTs) (37, 59) (Supplementary file 12).

Figure 1. PRISMA Flow Diagram



Mental health A total of 13 studies was included in the meta-analyses, reporting depression (11 RCTs and two NRCTs) (35, 37, 40-43, 48, 52, 53, 55, 57, 66, 67), anxiety (10 RCTs and two NRCTs) (37, 40-43, 48, 52, 53, 55, 57, 66, 67), PTSD (five RCTs and two NRCTs) (41, 42, 48, 52, 53, 55, 67), or coping (two RCTs) (41, 67). Pooled data from two diary studies (48, 57) showed significant differences in depression (n=88; SMD, 0.68; 95% CI, 0.14-1.21; P≤ 0.01; I2=15%, P= 0.28) (Figure 2) and anxiety (n=88; SMD, 0.44; 95% CI, 0.01-0.87; P= 0.05; I2=0%, P= 0.87) (Figure 3) between hospital discharge and 3 months after discharge. One of the two studies had a high risk of bias (48).

Exercise and physical rehabilitation programs, follow-up services, and psychosocial programs were not associated with differences in depression, anxiety, PTSD, and coping skills at the different time categories. No significant differences were found either in the analysis based on the largest SMDs reported within the studies (Supplementary file 12).

Figure 2. Forest plot depression

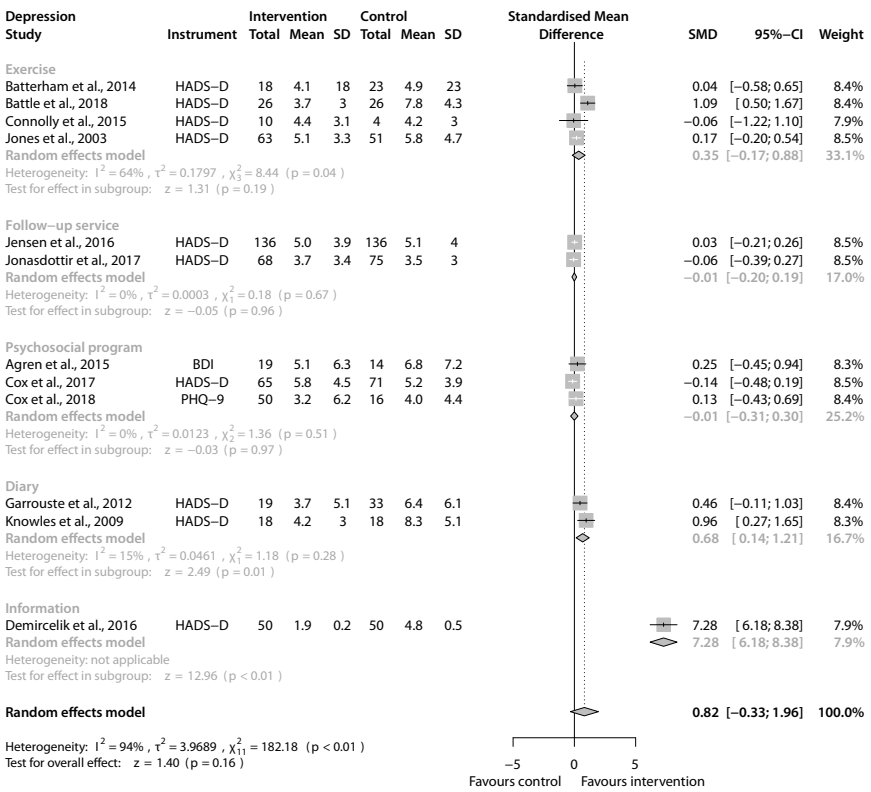


Figure 3. Forest plot anxiety

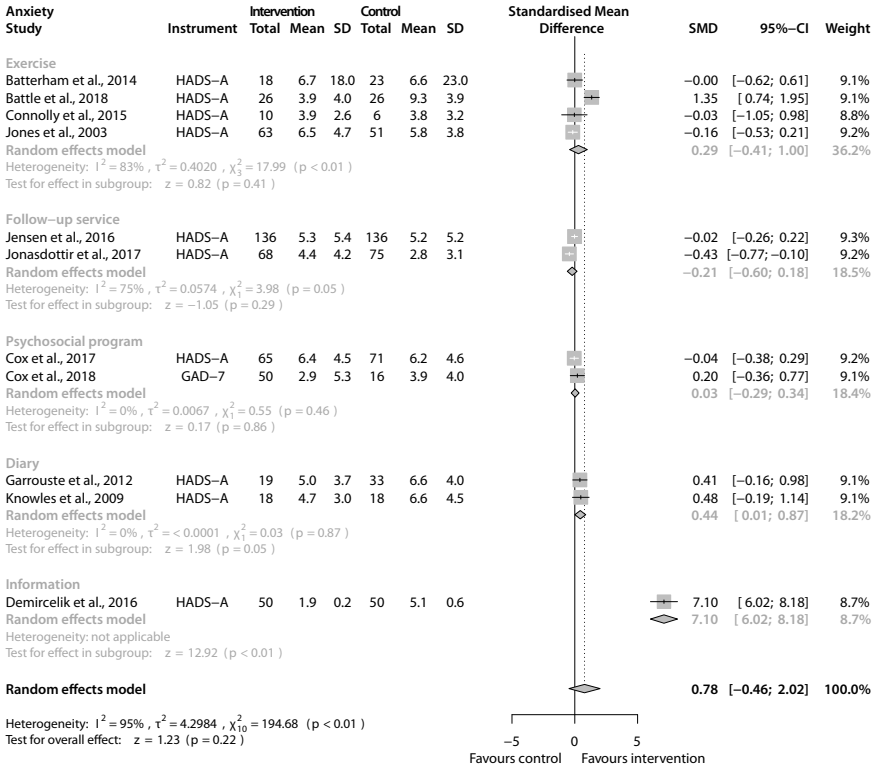
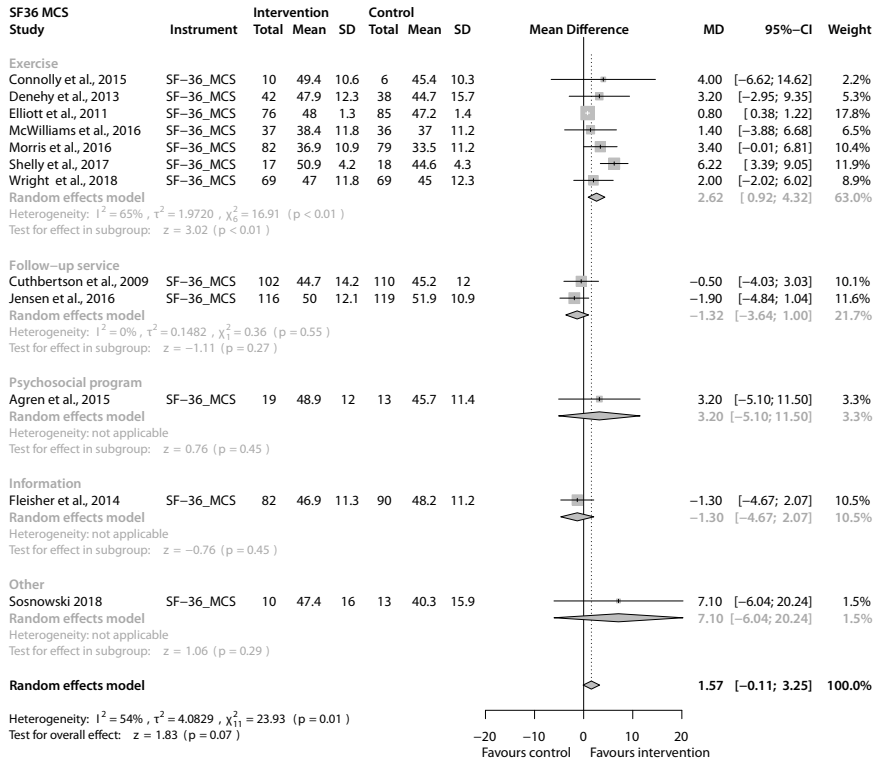


Figure 4. Forest plot SF-36 MCS



Cognitive health Four RCTs (38, 51, 60, 63) reported cognitive health outcomes. Due to reported medians, and heterogeneity in interventions and time of measurement, data could not be pooled.

Quality of life A total of 17 RCTs was included in the meta-analyses evaluating five different intervention categories. Data was pooled separately for the Short From Health Survery-36 (SF-36) physical component score (PCS) and mental component score (MCS) (both 12 studies) (35, 40, 42, 44, 46, 47, 52, 59, 60, 64, 69, 70) and EQ-5D visual analogue scale (VAS) (5 studies) (37, 41, 49, 50, 67) and EQ-5D index (5 studies) (37, 42, 49, 50, 70). Exercise and physical rehabilitation programs, follow-up services, and psychosocial programs were not associated with improvements in the quality of life at the three different time categories (Supplementary file 12). Only in the analysis based on the largest SMDs reported within the studies, exercise and physical rehabilitation programs were associated with a significant improvement in the SF-36 MCS (seven RCTs; n=664; MD, 2.62; 95% CI 0.92-4.32]; P <0.01; I2 =65% P≤0.01 (Figure 4) (Supplementary file 12)).

Other outcomes Fifteen studies measured other outcomes than the above mentioned (Supplementary file 10 and 11). Exercise and physical rehabilitation programs (two RCTs) (50, 65) may make little or no difference to daily activities (Supplementary file 12).

DISCUSSION

In this comprehensive systematic review with multiple meta-analyses, the use of diaries was associated with a significant reduction in depression and anxiety, and the use of exercise and physical rehabilitation programs with a significant improvement in the mental component score of the SF-36 quality of life questionnaire. These results should be interpreted with caution: the effects for diaries are based on only two studies, with one (48) having methodological limitations, and the SF-36 MCS improvement for early exercise and physical rehabilitation programs is very small (MD, 2.62; 95% CI 0.92-4.32). Previous systematic reviews did not show conclusive evidence for interventions such as early rehabilitation and mobilization programs (17, 19, 20, 71), ICU follow-up clinics (72, 73), or interventions primarily focused on reducing cognitive impairments (23), and psychological distress (24). Conflicting results were seen for the use of ICU diaries (74, 75).

This lack of compelling evidence emphasizes the importance to continue with the development, implementation, and evaluation of interventions to prevent or mitigate long-term adverse outcomes among ICU survivors. There are possible explanations for this lack of evidence on the effectiveness of interventions.

First, the increasing awareness in the international critical care community on adverse long-term outcomes among ICU survivors (13) and the necessity for preventive interventions (16) have led to a comprehensive implementation of interventions in daily practice, such as follow-up clinics and diaries. Although it is widely accepted and intuitive that these interventions are effective, research in this field is still in its early stages. Rigorous evaluation studies are lagging behind the rapid development of interventions. In this systematic review, only 36 studies were found worldwide, evaluating the long-term effects of a wide range of interventions.

Second, methodological limitations (e.g. incomplete presented data) and considerable heterogeneity in interventions, populations, reported outcomes, and instruments (17, 20, 74, 76-78) limited the ability to assess the effectiveness of interventions and to provide precise estimates of treatment effects.

Third, although ICU survivors often experience a combination of physical, mental, and cognitive problems (79), the focus in rehabilitation programs is usually on patients' physical recovery (80, 81). The majority of the studies in this review were exercise and physical rehabilitation programs, and

consequently most of the outcomes measured were physical health outcomes. Cognitive outcomes were rarely assessed (10% of the studies), neither were outcomes such as return to work or daily activities, although patients consider these outcomes as important (82). Because of the large variety of physical outcomes, options to pool were limited. Analyses that could be performed included small numbers of studies. No statistically significant differences were evident for any of the physical outcomes.

Based upon these findings, the following recommendations are made for future studies in developing and evaluating interventions aimed to prevent or mitigate adverse long-term outcomes among ICU survivors.

First, the use of a core outcome set (COS) is highly recommended to limited the considerable heterogeneity in outcomes and outcome measures, causing inconsistencies in outcome reporting, and difficulties in comparing and combining results (83). A COS is an agreed standardized collection of outcomes, which can serve as a minimum standard to ensure that essential outcomes are consistently assessed using the same instruments (13, 20, 26, 76, 84). Although the development of a COS could be a challenge, because physicians and researchers, often primary stakeholders in designing research, have different perspectives than patients on what important outcomes are (82), an encouraging initiative is already taken by Needham et al., (85), who developed a COS to evaluate long-term outcomes of acute respiratory failure survivors.

Second, although qualitative evaluations are rarely used (71, 73, 86), the use of mixed methods, in which quantitative and qualitative research are integrated, is highly recommended to provide a broader picture of the effectiveness of interventions (87). Qualitative research (e.g. interview or focus group studies to explore experiences of study participants with the intervention) can clarify the outcomes of the quantitative evaluation.

Third, given the link between physical, mental, and cognitive outcomes, and combination of problems patients experience, interventions should not focus on one domain only, but should be coordinated more across the various domains (1). Combined cognitive and physical rehabilitation programs appear, for example, feasible and possibly effective in improving cognitive performance and functional outcomes (38, 51).

Fourth, large scale, rigorous adequately powered RCTs with appropriate methodologic quality and clearly reported interventions and control conditions

must be conducted to enable future replication and generalizability (17, 20, 27, 88).

Fifth, because it is likely that patients respond differently to interventions (89), subgroup analyses on, for example, age, different types and severity of conditions (e.g. sepsis), or timing of interventions (e.g. during ICU admission or after hospital discharge) are essential to identify patients who benefit from interventions (1, 13, 71, 88). Because the relevance of a one-size-fits-all approach is doubtful (81, 86), tailored interventions are needed to individualize therapy.

Sixth, adjustment of patient's pre-ICU health status in studies is necessary, although it is rarely done (90). Adverse long-term outcomes are caused by a complex mix of factors (13), making it a challenge to design effective interventions (89). Patients' pre-ICU health status is probably the most important factor (91) and personal characteristics such as coping and resilience may be modifiable through post-ICU interventions (86).

Seventh, in most of the studies, the emphasis is placed on effect evaluation to determine if the intervention was successful. However, conducting a process evaluations is highly recommended to understand the results from of the program, how the programs affects the outcomes, and how and why the program was (un)successful. A programs' lack of success could, for example, be attributed to any number of program-related reasons, such as poor program design, poor or incomplete program implementation, or failure to reach insufficient numbers of the target audience (92).

Besides these recommendations for future research, it is important to emphasize that, with the increasing knowledge of the long-term consequences of ICU stay, discharge from the ICU no longer signifies the endpoint of critical illness (93). Professionals need to go beyond saving lives of critically ill patients by utilizing practices and interventions to prevent and decrease physical, mental, and cognitive adverse long-term outcomes. Causes underlying the adverse outcomes are multifactorial (13). Therefore, it is likely that multicomponent interventions are needed to adequately address multiple adverse outcomes. During ICU admission, risk factors can be reduced by early mobilization and by minimizing pain, sedation, delirium, and length of mechanical ventilation (3). After ICU and hospital discharge, the prevention and treatment of the adverse outcomes should continue, by rehabilitation programs, social support, ICU follow-up clinics, and psychologic programs. Although in medicine "the benefit of doubt" is rarely given to unproven treatments, we want to emphasize

that, despite the lack of conclusive evidence, critical care professionals should continue initiating and testing structured interventions to ensure the best possible outcomes of our ICU patients because in this case, the "absence of evidence is not evidence of absence."

Several limitations need to be addressed. First, there was considerable heterogeneity in populations, interventions, outcomes, instruments, and time of follow-up, limiting the ability to pool data. Data was sometimes not reported, or presented in medians and percentages, whereas means and SDs were necessary for meta-analyses. Unfortunately, only a few authors responded to the request to provide their data.

Second, 10 of the 36 included studies were pilot studies and many studies had small sample sizes, being underpowered to detect an intervention effect. Some researchers argue for excluding small studies from meta-analyses (94). However, in view of the aim to give a state-of-the-art overview of the available evidence of the wide range of interventions, and a new research field with mainly small studies with no conclusive results, excluding smaller studies would be inappropriate.

Third, the aim was to assess the effectiveness of interventions on the long-term outcomes among ICU survivors. However, long-term outcomes were only assessed in eight studies.

Fourth, pharmacologic and nutritional intervention studies were excluded, although early parental nutrition and daily interruption of sedation might have an effect on the long-term outcomes (16).

Conclusions

There is thin evidence that diaries and exercise programs have a positive effect on mental outcomes of ICU survivors. Despite outcomes favoring the intervention groups, other commonly used nonpharmacologic interventions in daily ICU practice are not supported by conclusive evidence from this meta-analysis. Due to considerable heterogeneity in interventions, outcomes, instruments, and follow up time, comparing and analyzing data were difficult. To improve recovery programs for ICU survivors, robust intervention studies using standardized outcomes are highly recommended.

Acknowledgements

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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3,4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6,7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supp. 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7, Supp. 3

rom: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Supplementary file 1. Continued.

Section/topic	#	Checklist item	Reported on page #
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8, Supp. 5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7,8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8, Supp. 6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10,11 Table 1, Supp. 9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10, e-Sup 7, Supp. 8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-13 Table 2, Figure 2,3,4, Supp. 10, Supp. 11

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Supplementary file 1. Continued.

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12,13, Table 2, Figure 2,3,4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10, Supp. 7,8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 2
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA (no funding)

rom: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Supplementary file 2. Search strategy per database

Pubmed

((((((PICS [tiab] AND ("Critical Care Nursing"[Mesh] OR "Critical Care"[Mesh:NoExp] OR "Critical Illness"[Mesh] OR "Intensive Care Units"[Mesh:NoExp] OR critical care [tiab] OR critical ill [tiab] OR critical illn* [tiab] OR critically ill [tiab] OR critically illn* [tiab] OR ICU [tiab] OR ICUs [tiab] OR intensive care [tiab])))) OR (("post intensive care syndrome" [tiab] OR "post icu syndrome" [tiab] OR "post ic syndrome" [tiab])))) OR (((((("Clinical Trial" [Publication Type] or "Clinical Trials as Topic"[Mesh] or "Comparative Study" [Publication Type] or "Controlled Clinical Trial" [Publication Type] or "Controlled Clinical Trials as Topic"[Mesh] or "Evaluation Studies as Topic"[Mesh] or "Evaluation Studies" [Publication Type] or "Non-Randomized Controlled Trials as Topic"[Mesh] or "Random Allocation"[Mesh] or "Randomized Controlled Trial" [Publication Type] or "Randomized Controlled Trials as Topic"[Mesh] or comparative study [tiab] or control group [tiab] or control groups [tiab] or non-randomised [tiab] or non-randomized [tiab] or random [tiab] or randomised [tiab] or randomised-controlled [tiab] or randomized [tiab] or randomized-controlled [tiab] or randomly [tiab] or RCT [tiab] or repeated measures [tiab] or time series [tiab] or trial [tiab]))))) AND ((((((((("Activities of daily living"[Mesh] or "Return to work"[Mesh] or activities of daily living[tiab] or ADL[tiab] or ADLs[tiab] or Basic ADL [tiab] or Instrumental ADL [tiab] or IADL[tiab] or return to work[tiab] or unemployment[tiab] or functional status [tiab] or financial problems[tiab]))))) OR (("Social participation"[Mesh] or autonomy[tiab] or autonomies[tiab] or social activities [tiab] or social contact[tiab] or social contacts [tiab] or role in family [tiab] or relationship [tiab] or relationships [tiab])))) OR (("Quality of life"[Mesh] or health related quality of life[tiab] or hrqol[tiab] or life quality[tiab] or quality of life[tiab] or well being[tiab] or life satisfaction [tiab])))) OR (("Spirituality"[Mesh] or spiritualit*[tiab] or coping[tiab] or acceptance[tiab] or future prospects [tiab])))) OR (("Anxiety"[Mesh] or "Attention"[Mesh] or "Cognition"[Mesh] or "Depression"[Mesh] or "Memory"[Mesh] or "Problem solving"[Mesh] or "Stress disorders,Traumatic"[Mesh] or Anxiety[tiab] or Anxieties[tiab] or Cognitive deficit [tiab] or Cognitive deficits[tiab] or Cognitive disorder [tiab] or Cognitive disorders [tiab] or Cognitive dysfunction [tiab] or Cognitive dysfunctions[tiab] or Cognitive function[tiab] or Cognitive functions [tiab] or Cognitive impairment[tiab] or Cognitive impairments [tiab] or Cognitive symptom [tiab] or Cognitive symptoms [tiab] or Depression[tiab] or Depressions [tiab] or Depressive [tiab] or Distress [tiab] or Executive function [tiab] or Executive functioning [tiab] or Memory [tiab] or Mental function [tiab] or Mental dysfunction [tiab] or Mental disorder [tiab] or Mental symptoms [tiab] or Nervousness [tiab] or Post traumatic [tiab] or posttraumatic [tiab] or PTSD [tiab] or PTSS [tiab] or Stress disorder [tiab] or Stress disorders [tiab])))) OR ((("Fatigue"[Mesh] OR "Mobility limitation"[Mesh] OR "Muscle Weakness"[Mesh] OR "Pain"[Mesh] OR "recovery of function"[Mesh] OR dyspnoe [tiab] OR Physical decline[tiab] OR Physical disability [tiab] OR Physical disabilities [tiab] OR Physical disorder [tiab] OR Physical disorders [tiab] OR Fatigue [tiab] OR ICUAW [tiab] OR ICU acquired weakness [tiab] OR Muscle weakness [tiab] OR muscle weaknesses [tiab] OR Muscular weakness [tiab] OR muscular weaknesses [tiab] OR Neuropathy [tiab] OR polyneuropathy [tiab] OR atrophy [tiab] OR Pain [tiab] OR Pains [tiab] OR Physical activity[tiab] OR Physical activities [tiab] OR Physical impairment [tiab] OR Physical functioning [tiab] OR Physical function [tiab] OR Sleep [tiab] OR Sleeping [tiab] OR Sexual dysfunction [tiab] OR Weight loss [tiab])))) AND ((("Aftercare"[Mesh] OR "Counseling"[Mesh] OR "Exercise Therapy"[Mesh] OR

"Occupational Therapy"[Mesh] OR "Physical Therapy Modalities"[Mesh] OR "Psychotherapy"[Mesh] OR "Rehabilitation" [Subheading] OR "Rehabilitation"[Mesh] OR Anxiety management [tiab] OR Consultation [tiab] OR Consultations [tiab] OR Counseling [tiab] OR Counselling [tiab] OR diaries [tiab] OR diary [tiab] OR early exercise [tiab] OR early mobilisation [tiab] OR early mobilization [tiab] OR exercise [tiab] OR exercises [tiab] OR exercise therap* [tiab] OR exercises [tiab] OR Intervention [tiab] OR interventions [tiab] OR Mobilit* [tiab] OR occupational therapy [tiab] OR Physical therap* [tiab] OR Physiotherap* [tiab] OR Psychoeducation [tiab] OR psycho-education [tiab] OR Psychosocial support group [tiab] OR Program* [tiab] OR Psychotherap* [tiab] OR recover*[tiab] OR Rehabilitation [tiab] OR therapies [tiab] OR therapy[tiab] OR therapeutic [tiab] OR training [tiab])))) AND ((("Critical Care Nursing"[Mesh] OR "Critical Care"[Mesh:NoExp] OR "Critical Illness"[Mesh] OR "Intensive Care Units"[Mesh:NoExp] OR critical care [tiab] OR critical ill [tiab] OR critical illn* [tiab] OR critically ill [tiab] OR critically illn* [tiab] OR ICU [tiab] OR ICUs [tiab] OR intensive care [tiab])))

CINAHL

#1 (MH "Critical Care Nursing+") OR (MH "Critical Care") OR (MH "Critical Illness") OR (MH "Intensive Care Units") OR "critical care" OR "critical ill" OR "critical illn*" OR "critically ill" OR "critically illn*" OR "ICU" OR "ICUs" OR "intensive care"

#2(MH "After Care") OR (MH "Counseling+") OR (MH "Therapeutic Exercise+") OR (MH "Occupational Therapy+") OR (MH "Physical Therapy+") OR (MH "Psychotherapy+") OR (MH "Rehabilitation+") OR "anxiety management" OR "consultation" OR "consultations" OR "counseling" OR "counselling" OR "diaries" OR "diary" OR "early exercise" OR "early mobilisation" OR "early mobilization" OR "exercise" OR "exercises" OR "exercise therap*" OR "intervention" OR "interventions" OR "mobility*" OR "occupational therap*" OR "physical therap*" OR "physiotherap*" OR "program" OR "psychotherap*" OR "psychoeducation" OR "psycho-education" OR "psychosocial support group" OR "recover*" OR "rehabilitation" OR "therapies" OR "therapy" OR "therapeutic" OR "training"

#3(MH "Fatigue+") OR (MH "Muscle Weakness") OR (MH "Pain+") OR "fatigue" OR "mobility limitation" OR "muscle weakness" OR "pain" OR "recovery of function" OR "dyspnoe" OR "physical decline" OR "physical disability" OR "physical disabilities" OR "physical disorder" OR "physical disorders" OR "ICUAW" OR "ICU acquired weakness" OR "muscle weakness" OR "muscle weaknesses" OR "muscular weakness" OR "muscular weaknesses" OR "neuropathy" OR "polyneuropathy" OR "atrophy" OR "pain" OR "pains" OR "physical activity" OR "physical activities" OR "physical impairment" OR "physical functioning" OR "physical function" OR "sleep" OR "sleeping" OR "sexual dysfunction" OR "weight loss"

#4(MH "Anxiety+") or (MH "Attention+") or (MH "Cognition+") or (MH "Depression+") or (MH "Memory+") or (MH "Problem Solving+") or (MH "Stress Disorders, Post-Traumatic+") or "anxiety" or "Anxieties" or "Cognitive deficit" or "Cognitive deficits" or "Cognitive disorder" or "Cognitive disorders" or "Cognitive dysfunction" or "Cognitive dysfunctions" or "Cognitive function" or "Cognitive functions" or "Cognitive impairment" or "Cognitive impairments" or "Cognitive symptom" or "Cognitive symptoms" or "Depression" or "Depressions" or "Depressive" or "Distress" or "Executive function" or "Executive functioning" or "Memory" or "Mental function" or "Mental dysfunction" or "Mental disorder" or "Mental symptoms" or "Nervousness" or "Post traumatic" or "posttraumatic" or "PTSD" or "PTSS" or "Stress disorder" or "Stress disorders"

#5 (MH "Spirituality") or spiritualit* or coping or acceptance or future prospects

#6(MH "Quality of Life+") or "Health related quality of life" or "Hrqol" or "life quality" or "quality of life" or "well being" or "life satisfaction"
#7"Autonomy" or "Autonomies" or "Social activities" or "Social contact" or "Social contacts" or "Role in family" or "Relationship" or "Relationships"
#8(MH "Activities of Daily Living+") or "Activities of daily living" or "ADL" or "ADLs" or "Basic ADL" or "Instrumental ADL" or "IADL" or "return to work" or "Unemployment" or "Functional status" or "Financial problems"
#9S3 OR S4 OR S5 OR S6 OR S7 OR S8
10#(MH "Clinical Trials+") or (MH "Comparative Studies") or (MH "Evaluation Research+") or (MH "Random Assignment") or (MH "Randomized Controlled Trials") or "before after" or "before and after" or "comparative study" or "control group" or "control groups" or "non-randomised" or "non-randomized" or "placebo" or "random" or "randomised" or "randomised-controlled" or "randomized" or "randomized-controlled" or "randomly" or "RCT" or "repeated measures" or "time series" or "treatment group" or "treatment groups" or "trial"
11#S1 AND S2 AND S9 AND S10
12#"post intensive care syndrome" or "post icu syndrome" or "post ic syndrome"
13#PICS
14#S1 AND S13
15# S12 OR S14
#16 S11 OR S15

PsycINFO
#1Intensive Care/ or critical care.ab,ti. or critical ill.ab,ti. or critical illn*.ab,ti. or critically ill.ab,ti. or critically illn*.ab,ti. or ICU.ab,ti. or ICUs.ab,ti. or intensive care.ab,ti.
#2exp AFTERCARE/ or exp COUNSELING/ or exp physical therapy/ or exp Occupational Therapy/ or exp Psychotherapy/ or exp REHABILITATION/ or anxiety management.ab,ti. or Consultation.ab,ti. or Consultations.ab,ti. or counselling.ab,ti. or counseling.ab,ti. or diaries.ab,ti. or diary.ab,ti. or early exercise.ab,ti. or early mobilisation.ab,ti. or early mobilization.ab,ti. or exercise.ab,ti. or exercises.ab,ti. or exercise therap*.ab,ti. or Intervention.ab,ti. or interventions.ab,ti. or mobilit*.ab,ti. or occupational therap*.ab,ti. or Physical therap*.ab,ti. or Physiotherap*.ab,ti. or Program*.ab,ti. or Psychotherap*.ab,ti. or Psychoeducation.ab,ti. or Psycho-education.ab,ti. or Psychosocial support group.ab,ti. or recover*.ab,ti. or Rehabilitation.ab,ti. or therapies.ab,ti. or therapy.ab,ti. or therapeutic.ab,ti. or training.ab,ti.
#3exp FATIGUE/ or exp PAIN/ or dyspnoe.ab,ti. or Physical decline.ab,ti. or Physical disability.ab,ti. or Physical disabilities.ab,ti. or Physical disorder.ab,ti. or Physical disorders.ab,ti. or Fatigue.ab,ti. or ICUAW.ab,ti. or ICU acquired weakness.ab,ti. or Muscle weakness.ab,ti. or muscle weaknesses.ab,ti. or Muscular weakness.ab,ti. or muscular weaknesses.ab,ti. or Neuropathy.ab,ti. or Polyneuropathy.ab,ti. or Atrophy.ab,ti. or Pain.ab,ti. or pains.ab,ti. or Physical activity.ab,ti. or Physical activities.ab,ti. or Physical impairment.ab,ti. or Physical functioning.ab,ti. or Physical function.ab,ti. or Sleep.ab,ti. or sleeping.ab,ti. or Sexual dysfunction.ab,ti. or Weight loss.ab,ti.
#4exp ANXIETY/ or exp ATTENTION/ or exp COGNITION/ or exp ATTENTION/ or exp "DEPRESSION (EMOTION)"/ or exp MEMorY/ or exp Problem Solving/ or exp Posttraumatic Stress Disorder/ or anxiety.ab,ti. or anxieties.ab,ti. or Cognitive deficit.ab,ti. or Cognitive deficits.ab,ti. or Cognitive

disorder.ab,ti. or Cognitive disorders.ab,ti. or Cognitive dysfunction.ab,ti. or Cognitive dysfunctions.ab,ti. or Cognitive function.ab,ti. or Cognitive functions.ab,ti. or Cognitive impairment.ab,ti. or Cognitive impairments.ab,ti. or Cognitive symptom.ab,ti. or Cognitive symptoms.ab,ti. or Depression.ab,ti. or depressions.ab,ti. or depressive.ab,ti. or distress.ab,ti. or executive function.ab,ti. or executive functioning.ab,ti. or memory.ab,ti. or mental function.ab,ti. or mental dysfunction.ab,ti. or mental disorder.ab,ti. or mental symptoms.ab,ti. or nervousness.ab,ti. or post traumatic.ab,ti. or posttraumatic.ab,ti. or PTSD.ab,ti. or PTSS.ab,ti. or stress disorder.ab,ti. or stress disorders.ab,ti.
#5exp SPIRITUALITY/ or spiritualit*.ab,ti. or coping.ab,ti. or acceptance.ab,ti. or future prospects.ab,ti.
#6exp "Quality of Life"/ or health related quality of life*.ab,ti. or hrqol.ab,ti. or life quality*.ab,ti. or quality of life*.ab,ti. or well being*.mp. or life satisfaction*.ab,ti. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
#7(Autonomy or autonomies or social activities* or social contact* or social contacts* or role in family* or relationship or relationships).ab,ti.
#8exp "Activities of Daily Living"/ or exp Reemployment/ or activities of daily living*.ab,ti. or ADL.ab,ti. or ADLs.ab,ti. or Basic ADL*.ab,ti. or Instrumental ADL*.ab,ti. or IADL.ab,ti. or return to work*.ab,ti. or unemployment.ab,ti. or functional status*.ab,ti. or financial problem*.ab,ti.
#9 3 or 4 or 5 or 6 or 7 or 8
#10exp Clinical Trials/ or exp Treatment Effectiveness Evaluation/ or exp EXPERIMENT CONTROLS/ or exp Experimental Design/ or comparative study.ab,ti. or control group.ab,ti. or control groups.ab,ti. or non-randomised.ab,ti. or non-randomized.ab,ti. or random.ab,ti. or randomised.ab,ti. or randomised-controlled.ab,ti. or randomized.ab,ti. or randomized-controlled.ab,ti. or randomly.ab,ti. or RCT.ab,ti. or repeated measures.ab,ti. or time series.ab,ti. or trial.ab,ti.
#11 1 and 2 and 9 and 10
#12 (Post intensive care syndrome or post icu syndrome or post ic syndrome).ab,ti.
#13 PICS.ab,ti.
#14 1 and 13
#15 12 or 13
#16 11 or 15

Embase

#1 exp intensive care nursing/ or intensive care/ or exp critical illness/ or intensive care unit/ or (critical care or critical ill or critical illn* or critically ill or critically illn* or ICU or ICUs or intensive care).ab,ti.
#2 exp Aftercare/ or exp Counseling/ or exp Occupational Therapy/ or exp Physiotherapy/ or exp Psychotherapy/ or exp rehabilitation/ or exp Therapy/ or anxiety management, Consultation, Consultations, counselling, counseling, diaries, diary, early exercise, early mobilisation, early mobilization, exercise, exercises, exercise therap*, Intervention, interventions, mobilit*, occupational therap*, Physical therap*, Physiotherap*, Program*, Psychotherap*, Psychoeducation, Psychoeducation, Psychosocial support group, recover*, Rehabilitation, therapies, therapy, therapeutic, training.ab,ti.
#3exp Fatigue/ or exp Muscle weakness/ or exp Pain/ or exp Convalescence/ or dyspnoe, Physical

decline, Physical disability, Physical disabilities, Physical disorder, Physical disorders, Fatigue, ICUAW, ICU acquired weakness, Muscle weakness, muscle weaknesses, Muscular weakness, muscular weaknesses, Neuropathy, Polyneuropathy, Atrophy, Pain, pains, Physical activity, Physical activities, Physical impairment, Physical functioning, Physical function, Sleep, sleeping, Sexual dysfunction, Weight loss.ab,ti.
#4exp Anxiety/ or exp Attention/ or exp Cognition/ or exp Depression/ or exp Memory/ or exp Problem solving/ or exp posttraumatic stress disorder/ or anxiety, anxieties, Cognitive deficit, Cognitive deficits, Cognitive disorder, Cognitive disorders, Cognitive dysfunction, Cognitive dysfunctions, Cognitive function, Cognitive functions, Cognitive impairment, Cognitive impairments, Cognitive symptom, Cognitive symptoms, Depression, depressions, depressive, distress, executive function, executive functioning, memory, mental function, mental dysfunction, mental disorder, mental symptoms, Nervousness, post traumatic, posttraumatic, PTSD, PTSS, stress disorder, stress disorders.ab,ti.
#5 (spiritualit* or coping or acceptance or future prospects).ab,ti.
#6 exp "quality of life"/ or health related quality of life, hrqol, life quality, quality of life, well being, life satisfaction.ab,ti.
#7 exp social participation/ or autonomy, autonomies, social activities, social contact, social contacts, role in family, relationship, relationships.ab,ti.
#8exp Daily life activity/ or exp Return to work/ or activities of daily living, ADL, ADLs, Basic ADL, Instrumental ADL, IADL, return to work, unemployment, functional status, financial problem.ab,ti.
#9 3 or 4 or 5 or 6 or 7 or 8
#10 Clinical trial/ or exp Comparative study/ or exp Controlled Clinical Trial/ or exp Evaluation Study/ or exp Randomization/ or Randomized Controlled Trial/ or (before after, before and after, comparative study, control group, control groups, non-randomised, non-randomized, placebo, random, randomised, randomised-controlled, randomized, randomized-controlled, randomly, RCT, repeated measures, time series, treatment group, treatment groups, trial).ab,ti.
#11 1 and 2 and 9 and 10
#12 (Post intensive care syndrome or post icu syndrome or post ic syndrome).ab,ti.
#13 PICS.ab,ti.
#14 1 and 13
#15 12 or 14
#16 11 or 15

Cochrane Center Register of Controlled Trials
1 ([mh "Critical Care Nursing"] or [mh ^"Critical Care"] or [mh "Critical Illness"] or [mh "Intensive Care Units"]) or ("Critical care" or "Critical illn*" or "Critical ill" or "Critically ill" or "Critically illn*" or ICU or ICUs or "Intensive care"):ti,ab,kw
#2 ([mh Aftercare] or [mh Counseling] or [mh "Exercise Therapy"] or [mh "Occupational Therapy"] or [mh "Physical Therapy Modalities"] or [mh Psychotherapy] or [mh Rehabilitation] or [mh Rehabilitation]) or ("Anxiety management" or Consultation or Consultations or Counseling or Counselling or diaries or diary or early exercise or "early mobilisation" or "early mobilization" or exercise or exercises or "exercise therapy" or Intervention or interventions or mobilit* or "occupational therap*" or "Physical therap*" or Physiotherap* or Program* or Psychotherap* or Psychoeducation

or Psycho-education or "Psychosocial support group" or Recover* or Rehabilitation or therapies or therapy or therapeutic or training):ti,ab,kw
#3 ([mh Fatigue] or [mh "Mobility limitation"] or [mh "Muscle Weakness"] or [mh Pain] or [mh "Recovery of function"]) or (dyspnoe or "Physical decline" or "Physical disability" or "Physical disabilities" or "Physical disorder" or "Physical disorders" or Fatigue or ICUAW or ICU "acquired weakness" or "Muscle weakness" or "muscle weaknesses" or "Muscular weakness" or "muscular weaknesses" or Neuropathy or polyneuropathy or atrophy or Pain or Pains or "Physical activity" or "Physical activities" or "Physical impairment" or "Physical functioning" or "Physical function" or Sleep or Sleeping or "Sexual dysfunction" or "Weight loss"):ti,ab,kw
#4 ([mh Anxiety] or [mh Attention] or [mh Cognition] or [mh Depression] or [mh Memory] or [mh "Problem solving"] or [mh "Stress Disorders, Post-Traumatic"]) or (Anxiety or Anxieties or "Cognitive deficit" or "Cognitive deficits" or "Cognitive disorder" or "Cognitive disorders" or "Cognitive dysfunction" or "Cognitive dysfunctions" or "Cognitive function" or "Cognitive functions" or "Cognitive impairment" or "Cognitive impairments" or "Cognitive symptom" or "Cognitive symptoms" or Depression or Depressions or Depressive or Distress or "Executive function" or "Executive functioning" or Memory or "Mental function" or "Mental dysfunction" or "Mental disorder" or "Mental symptoms" or Nervousness or "Post traumatic" or posttraumatic or PTSD or PTSS or "Stress disorder" or "Stress disorders"):ti,ab,kw
#5 [mh Spirituality] or (spiritualit* or coping or acceptance or "future prospects"):ti,ab,kw
#6 [mh "Quality of life"] or ("health related quality of life" or hrqol or "life quality" or "quality of life" or "well being" or "life satisfaction"):ti,ab,kw
#7 [mh "Social participation"] or (autonomy or autonomies or "social activities" or "social contact" or "social contacts" or "role in family" or relationship or relationships):ti,ab,kw
#8 ([mh "Activities of daily living"] or [mh "Return to work"]) or ("activities of daily living" or ADL or ADLs or "Basic ADL" or "instrumental ADL" or IADL or "return to work" or unemployment or "functional status" or "financial problems"):ti,ab,kw
#9([mh "Clinical Trials"] or [mh "Controlled Clinical Trial"] or [mh "Evaluation Studies"] or [mh "Randomized Controlled Trial "] or [mh "Random Allocation"]) or ("before after" or "before and after" or "comparative study" or "control group" or "control groups" or "non-randomised" or "non-randomized" or placebo or random or randomised or "randomised-controlled" or randomized or "randomized-controlled" or randomly or RCT or "repeated measures" or "time series" or "treatment group" or "treatment groups" or trial):ti,ab,kw
#10 #3 or #4 or #5 or #6 or #7 or #8
#11 #1 and #2 and #10 and #9
#12 ("post intensive care syndrome" or "post icu syndrome" or "post ic syndrome"):ti,ab,kw
#13 (pics):ti,ab,kw
#14 #13 and #1
#15 #12 or #14
#16 #11 or #15

Supplementary file 3. Titel - abstract selection criteria

Research question: "What are effective non-pharmacologic interventions to prevent or mitigate adverse long-term outcomes among ICU survivors?

0. Inclusion

1. Exclusion, because of the
   - Setting & patient category
   - Intervention
   - Outcomes
   - Study design

   - No abstract available

8. Article needs to be discussed

Setting & patient category

Inclusion
- All adult ICU patients (18 years and older)
- Admitted to the ICU for at least 12 hours

Exclusion
- CCU (Coronary Care Unit); PACU (Post Anesthesia Care Unit); PICU (Pediatric Intensive Care Unit)

Interventions

Inclusion
- Interventions aimed to prevent or mitigate adverse long-term outcomes, conducted before, during or after ICU admission.

Exclusion
- Pharmacologic and nutritional interventions (incl. medication for sedation)

Outcomes

Inclusion
- Measured at patient level
- Measured after hospital discharge
- Quantitative effect sizes should be reported

- Health related quality of life
- Physical symptoms: such as pain, fatigue, short of breath, weakness, loss of body weight, immobility
- Mental symptoms: e.g. anxiety, depression, PTSD
- Cognitive symptoms: e.g. attention, decision making, problem solving, executive function, concentration
- Social functioning, functional status, return to work, daily activities, self-care and coping

Exclusion
- Related health care utilization and costs
- Hospital or ICU readmissions
- Length of stay

Study design

Inclusion
- Randomized controlled trial (RCT), including cluster RCT
- Controlled clinical trial (CCT)/ non-randomized controlled trials (NRCT)
- Controlled before after study (CBA)
- Interrupted time series (ITS) and repeated measure studies

Exclusion
- Qualitative, observational and case reports
- Uncontrolled before-after studies
- Cohort with and without control (retrospective and prospective)
- Cross sectional studies
- Case studies
- Systematic review/ meta-analysis
- Study protocols

Supplementary file 4. List of excluded full-text studies

Original search (till 19.09.2017)

Characteristics of excluded studies (N=42)

Nr	Authors	Year	Title study	Reason for exclusion
1	M. S. T. Ali, D.: Jain, S. K.	2014	The effect of a short-term pulmonary rehabilitation on exercise capacity and quality of life in patients hospitalised with acute exacerbation of chronic obstructive pulmonary disease	No correct setting
2	J. A. K. Alison, P.: King, M. T.: McKinley, S.: Aitken, L. M.: Leslie, G. D.: Elliott, D.	2012	Repeatability of the six-minute walk test and relation to physical function in survivors of a critical illness	No correct design: secondary analysis of primary study Elliott
3	C. G. O. Backman, L.: Sjoberg, F.: Fredrikson, M.: Walther, S. M.	2010	Long-term effect of the ICU-diary concept on quality of life after critical illness	No correct design: control group is retrospective
4	H. M. Bagheri, R.: Alhani, F.	2007	Evaluation of the effect of group counselling on post myocardial infarction patients: determined by an analysis of quality of life	No correct setting: no IC patients
5	S. D. Bench, T.: Heelas, K.: Hopkins, P.: White, C.: Griffiths, P.	2015	Evaluating the feasibility and effectiveness of a critical care discharge information pack for patients and their families: a pilot cluster randomised controlled trial	No correct outcome: not measured after hospital discharge
6	B. M. L. Bissett, I. A.: Neeman, T.: Boots, R.: Paratz, J.	2016	Inspiratory muscle training to enhance recovery from mechanical ventilation: a randomised trial	No correct outcome: not measured after hospital discharge
7	A. W. Boumendil, M.: Quenot, J. P.: Rooryck, F. X.: Makhlouf, F.: Yordanov, Y.: Delerme, S.: Takun, K.: Ray, P.: Kouka, M. C.: Poly, C.: Garrouste-Orgeas, M.: Thomas, C.: Simon, T.: Azerad, S.: Leblanc, G.: Pateron, D.: Guidet, B.	2016	Designing and conducting a cluster-randomized trial of ICU admission for the elderly patients: the ICE-CUB 2 study	No correct intervention: triage
8	S. B. Brunner, D.: Winter, H.: Kneidinger, N.	2016	Feasibility of whole-body vibration as an early inpatient rehabilitation tool after lung transplantation - a pilot study	No correct design: no control group

Nr	Authors	Year	Title study	Reason for exclusion
9	S. B. Calthorpe, E. A.: Holland, A. E.: Kimmel, L.: Webb, M. J.: Hodgson, C.: Gruen, R. L.	2014	An intensive physiotherapy program improves mobility for trauma patients	No correct setting: no ICU patients
10	E. S. M. Cavalcante, R.: Conforti, C. A.: Junior, G. C.: Arena, R.: Carvalho, A. C. C.: Buffolo, E.: Filho, B. L.	2014	Impact of intensive physiotherapy on cognitive function after coronary artery bypass graft surgery	No correct outcome: not measured after hospital discharge
11	L. S. Chlan, K.	2011	Patterns of anxiety in critically ill patients receiving mechanical ventilatory support	No correct intervention: sedation
12	Y. K. Cirak, Z.: Yilmaz Yelvar, G. D.: Erden, I.: Demirkilic, U.	2015	Is physiotherapy effective on the occurrence of postoperative pulmonary complications in patients undergoing coronary artery bypass graft surgery with different pulmonary complication risk profiles? A randomised controlled trial	No correct design
13	C. E. P. Cox, L. S.: Hough, C. L.: White, D. B.: Kahn, J. M.: Carson, S. S.: Tulsky, J. A.: Keefe, F. J.	2012	Development and preliminary evaluation of a telephone-based coping skills training intervention for survivors of acute lung injury and their informal caregivers	No correct design: uncontrolled, prospective pre post study
14	C. E. P. Cox, L. S.: Buck, P. J.: Hoffa, M.: Jones, D.: Walton, B.: Hough, C. L.: Greeson, J. M.	2014	Development and preliminary evaluation of a telephone-based mindfulness training intervention for survivors of critical illness	No correct design: uncontrolled, prospective pre post study
15	M. R. Diby, J. A.: Frick, S.: Heidegger, C. P.: Walder, B.	2008	Reducing pain in patients undergoing cardiac surgery after implementation of a quality improvement postoperative pain treatment program	No correct intervention: pain management
16	C. Du	2016	A Comparative Study of the Efficacy and Psychological States between Patients with Senile Ischemic Heart Failure Undergone ICU and Conventional Therapies	No correct intervention
17	C. S. Dunn, J.: Collett, D.	1995	Sensing an improvement: an experimental study to evaluate the use of aromatherapy, massage and periods of rest in an intensive care unit	No correct outcome: not measured after hospital discharge

Nr	Authors	Year	Title study	Reason for exclusion
18	A. S. Fischer, M.: Altmann, K.: Winkler, A.: Salamon, A.: Themessl-Huber, M.: Mouhieddine, M.: Strasser, E. M.: Schiferer, A.: Paternostro-Sluga, T.: Hiesmayr, M.	2016	Muscle mass, strength and functional outcomes in critically ill patients after cardiothoracic surgery: Does neuromuscular electrical stimulation help? The Catastim 2 randomized controlled trial	No correct outcome: not measured after hospital discharge
19	D. S. Fraser, L.: Forman, W.: Hallen, C.	2015	Original Research: Implementation of an Early Mobility Program in an ICU	No correct outcome: not measured after hospital discharge
20	A. L. T. Freeman-Sanderson, L.: Elkins, M. R.: Phipps, P. R.	2016	Return of Voice for Ventilated Tracheostomy Patients in ICU: A Randomized Controlled Trial of Early-Targeted Intervention	No correct outcome: not measured after hospital discharge
21	S. B. Fumagalli, L.: Lo Nostro, A.: Valoti, P.: Baldereschi, G.: Di Bari, M.: Ungar, A.: Baldasseroni, S.: Geppetti, P.: Masotti, G.: Pini, R.: Marchionni, N.	2006	Reduced cardiocirculatory complications with unrestrictive visiting policy in an intensive care unit: results from a pilot, randomized trial	No correct outcome: not measured after hospital discharge
22	L. T. Gattinoni, G: Pesenti, A: Taccone, P: Mascheroni, D: Labarta, V: Malacrida, R: Giulio, P: Fumagalli, R: Pelosi, P: Brazzi, L: Latini, R	2001	Effect of prone positioning on the survival of patients with acute respiratory failure. see comment summary for patients in Aust J Physiother. 2002;48(3): 237; PMID: 12369564	No correct intervention: sedation
23	W.Gruen	1975	Effects of brief psychotherapy during the hospitalization period on the recovery process in heart attacks	No correct outcome: no quantitative outcomes after hospital discharge
24	W. P. Gruther, Karin: Steiner, Irene: Hein, Cornelia: Hiesmayr, Jörg Michael: Paternostro-Sluga, Tatjana	2017	Can Early Rehabilitation on the General Ward After an Intensive Care Unit Stay Reduce Hospital Length of Stay in Survivors of Critical Illness? A Randomized Controlled Trial	No correct outcome: not measured after hospital discharge
25	R. A. J. Hernandez, D.: Vale, L.: Cuthbertson, B. H.	2014	Economic evaluation of nurse-led intensive care follow-up programmes compared with standard care: the PRaCTICaL trial	No correct design: overlap with Cutherbertson et al., 2009

Nr	Authors	Year	Title study	Reason for exclusion
26	J. C. G. Jackson, T. D.: Gordon, S. M.: Thompson, J. L.: Shintani, A. K.: Thomason, J. W.: Pun, B. T.: Canonico, A. E.: Dunn, J. G.: Bernard, G. R.: Dittus, R. S.: Ely, E. W.	2010	Long-term cognitive and psychological outcomes in the awakening and breathing controlled trial	No correct intervention: sedation
27	C. E. Jones, J.: McCairn, A.: Dowling, S.: McWilliams, D.: Coughlan, E.: Griffiths, R. D.	2015	Improving rehabilitation after critical illness through outpatient physiotherapy classes and essential amino acid supplement: A randomized controlled trial	No correct intervention: nutritional intervention
28	E. S. Karadag, S.: Ozden, D.: Bakir, E.	2017	Effects of aromatherapy on sleep quality and anxiety of patients	No correct outcome: not measured after hospital discharge
29	H. J. L. Kim, Y.: Sohng, K. Y.	2014	Effects of bilateral passive range of motion exercise on the function of upper extremities and activities of daily living in patients with acute stroke	No correct setting: no ICU patients
30	T. C. Mailhot, S.: Cote, J.: Bourbonnais, A.: Cote, M. C.: Lamarche, Y.: Denault, A.	2017	A post cardiac surgery intervention to manage delirium involving families: a randomized pilot study	No correct outcome: not measured after hospital discharge
31	P. M. Melchers, A.: Suhr, L.: Scholten, S.: Lehmkuhl, G.	1999	An Early Onset Rehabilitation Program for Children and Adolescents after Traumatic Brain Injury (TBI): Methods and First Results	No correct setting: patients < 18 years
32	A. N.-C. Neumeier, A.: Malone, D.: Schenkman, M.: Clark, B.: Moss, M.	2017	Prolonged acute care and post-acute care admission and recovery of physical function in survivors of acute respiratory failure: a secondary analysis of a randomized controlled trial	No correct design: secondary analysis of Moss et al., 2016
33	A. W. Parthum, A.: Grassel, E.: Koppert, W.	2006	[Preoperative pain training. No influence on postoperative pain perception in patients undergoing cardiac surgery]	No correct intervention: pain medication
34	I. G. Patsaki, V.: Sidiras, G.: Karatzanos, E.: Mitsiou, G.: Papadopoulos, E.: Christakou, A.: Routsi, C.: Kotanidou, A.: Nanas, S.	2017	Effect of neuromuscular stimulation and individualized rehabilitation on muscle strength in Intensive Care Unit survivors: A randomized trial	No correct outcome: not measured after hospital discharge

Nr	Authors	Year	Title study	Reason for exclusion
35	A. B. Peris, M.: Iozzelli, D.: Migliaccio, M. L.: Zagli, G.: Bacchereti, A.: Debolini, M.: Vannini, E.: Solaro, M.: Balzi, I.: Bendoni, E.: Bacchi, I.: Trevisan, M.: Giovannini, V.: Belloni, L.	2011	Early intra-intensive care unit psychological intervention promotes recovery from post-traumatic stress disorders, anxiety and depression symptoms in critically ill patients	No correct design: no randomization, no baseline measure
36	M. P. Scarpa, E.: Saraceni, E.: Cavallin, F.: Parotto, M.: Alfieri, R.: Nardi, M. T.: Marchi, M. R.: Cagol, M.: Castoro, C.	2017	Randomized clinical trial of psychological support and sleep adjuvant measures for postoperative sleep disturbance in patients undergoing oesophagectomy	No correct outcome: not measured after hospital discharge
37	W. H. B. Sledge, K. E.: Levine, J. M.: Fiellin, D. A.: Chawarski, M.: White, W. D.: O'Connor P, G.	2006	A randomized trial of primary intensive care to reduce hospital admissions in patients with high utilization of inpatient services	No correct setting: no IC patients
38	D. A. Somme, N.: Guerot, E.: Lahjibi-Paulet, H.: Lazarovici, C.: Gisselbrecht, M.: Fagon, J. Y.: Saint-Jean, O.	2010	Loss of autonomy among elderly patients after a stay in a medical intensive care unit (ICU): a randomized study of the benefit of transfer to a geriatric ward	No correct outcome: not measured after hospital discharge
39	T. S. S. Walsh, L. G.: Merriweather, J. L.: Boyd, J. A.: Griffith, D. M.: Huby, G.: Kean, S.: Mackenzie, S. J.: Krishan, A.: Lewis, S. C.: Murray, G. D.: Forbes, J. F.: Smith, J.: Rattray, J. E.: Hull, A. M.: Ramsay, P.	2015	Increased Hospital-Based Physical Rehabilitation and Information Provision After Intensive Care Unit Discharge: The RECOVER Randomized Clinical Trial	No correct intervention
40	C. L. T. Yang, Y. H.: Jiang, X. X.: Meng, F. Y.: Wu, Y. L.: Chen, Q. L.: Ma, L. L.: Wang, L. X.	2012	Pre-operative education and counselling are associated with reduced anxiety symptoms following carotid endarterectomy: a randomized and open-label study	No correct outcome: not measured after hospital discharge
41	O. A. Yosef-Brauner, N.: Ben Shahar, T.: Yehezkel, E.: Carmeli, E.	2015	Effect of physical therapy on muscle strength, respiratory muscles and functional parameters in patients with intensive care unit-acquired weakness	No correct outcome: not measured after hospital discharge
42	S. H. O. Yun, E. G.: Yoo, Y. S.: Kim, S. S.: Jang, Y. S.	2017	Development and Effects of a Transition Nursing Program for Patients and Family Caregivers at a Neurological ICU in Korea	No correct outcome: not measured after hospital discharge

Original search (till 19.09.2017)

Characteristics of conference abstracts (N=34)

Nr	Authors	Year	Title
1	C. E. J. Battle, K.: Hutchings, H. A.: Temblett, P.	2014	Early results of a six-week supervised exercise programme in post-ICU patients
2	N. G. Brummel, Td: Jackson, Jc: Pandharipande, Pp: Morandi, A: Hughes, Cg: Graves, Aj: Shintani, Ak: Gill, Tm: Ely, Ew	2013	A combined cognitive and physical rehabilitation program for survivors of critical illness: Results of the activity and cognitive therapy in the ICU trial
3	N. G. Brummel, Td: Pandharipande, Pp: Jackson, Jc: Hughes, C: Pun, Bt: Boehm, L: Murphy, E: Work, B: Graves, A: Shintani, Ak: Ely, Ew	2013	Efficacy of an early combined cognitive and physical rehabilitation program for cognitive and functional impairment following critical illness: Results of the activity and cognitive therapy in the ICU (ACT-ICU) trial
4	B. T. Connolly, A.: Moxham, J.: Hart, N.	2013	A randomised controlled trial of exercise-based rehabilitation following hospital discharge for survivors of critical illness with intensive care unit-acquired weakness: A pilot feasibility study (clinical trials NCT00976807 www.clinicaltrials.gov)
5	C. E. C. Cox, S. S.: Hough, C. L.: Kahn, J.: White, D. B.: Olsen, M. K.: Somers, T.: Kelleher, S.: Porter, L. S.	2017	Coping skills training to improve psychological distress among critical illness survivors: A randomized clinical trial
6	M. Y. Demircelik, D: Sentepe, E: Keklik, M: Cetin, M: Cetin, Z: Eryonucu, B	2013	The effectiveness of multimedia nursing education on reducing illness-related anxiety and depression in coronary care unit's patients
7	A. C. Demoule, S.: Lavault, S.: Pallanca, O.: Morawiec, E.: Mayaux, J.: Arnulf, I.: Similowski, T.	2016	Impact of earplugs and eye mask on sleep in critically ill patients: A prospective randomized polysomnographic study
8	L. B. Denehy, S.: Skinner, E.: Edbrooke, L.: Haines, K.: Warrillow, S.: Hawthorne, G.: Morris, M. E.	2011	Evaluation of exercise rehabilitation for survivors of intensive care: An assessor blinded randomised controlled trial
9	B. C. Foreman, J: Bazil, C	2013	Melatonin, light & noise reduction to improve sleep in the neurological intensive care unit

Nr	Authors	Year	Title
10	A. T. Freeman-Sanderson, L.: Elkins, M.: Phipps, P.	2015	An intervention to allow early speech in ventilated tracheostomy patients in an Australian intensive care unit (ICU): A randomized controlled trial
11	S. L. Gandotra, J.: Case, D.: Bakhru, R. N.: Gibbs, K.: Berry, M.: Files, D. C.: Morris, P. E.	2017	Recovery trajectories of critically ill patients in a randomized controlled trial of early rehabilitation
12	R. N. Gawlytta, H.: Bottche, M.: Scherag, A.: Knaevelsrud, C.: Rosendahl, J.	2017	Internet-based cognitive-behavioural writing therapy for reducing post-traumatic stress after intensive care for sepsis in patients and their spouses (REPAIR): Results of two pilot cases
13	B. A. B. Goodman, S.: Batterham, A. M.: Wright, J.: Hugill, K.: Howard, P.: Howell, S.: Danjoux, G.	2012	Impact of an aerobic rehabilitation programme on fitness and qol in ICU survivors: An exploratory trial (pix study)
14	J. W. Goodman, W.: Wright, J.: Danjoux, G.: Howell, S.: Martin, D.: Bonner, S.	2013	Project PIX (Post Intensive care exercise): Impact on physical fltness and focus group analysis of quality of life following exercise rehabilitation
15	H. M. Hoenig, M.: Jackson, J.: Siebert, C.: Williams, N.: Clune, J.: Janz, D.: Schiro, E.: Jones, J.: Zoz, J.: Shintani, A.: Ely, W.	2010	The RETURN trial: A pilot study of in-home rehabilitation for ICU survivors
16	J. C. A. Jackson, K. R.: Bauer, R.: Abraham, C. M.: Song, Y.: Greevey, R.: Guillamondegui, O.: Ely, E. W.: Obremskey, W.	2010	The returning to everyday tasks utilizing rehabilitation networks (RETURN) trial: A pilot, feasibility trial including in-home cognitive rehabilitation of ICU survivors
17	J. F. E. Jensen, I.: Bestle, M. H.: Christensen, D. F.: Alklit, A.: Hansen, R. L.: Knudsen, H.: Grode, L. B.: Overgaard, D.	2016	The effectiveness of a recovery program aimed at improving quality of life and sense of coherence in post intensive care patients: A pragmatic multicenter randomized controlled trial, the recovery and aftercare of post intensive care patients (RAPIT) study
18	C. B. Jones, C.: Capuzo, M.: Egerod, I.: Flaatten, H.: Granja, C.: Rylander, C.: Griffiths, R. D.	2009	ICU diaries reduce posttraumatic stress disorder after critical illness: A randomised, controlled trial
19	G. B. Kayambu, R.: Paratz, J.	2015	Early physical rehabilitation in intensive care patients with sepsis syndromes-a randomised controlled trial

Nr	Authors	Year	Title
20	K. O. N. McDowell, B.: Blackwood, B.: Clarke, C.: Gardner, E.: Johnson, P.: Kelly, M.: McCaffrey, J.: Mullan, B.: Murphy, S.: Trinder, J.: Lavery, G.: McAuley, D. F.: Bradley, J. M.	2015	Effectiveness of a programme of exercise on physical function in survivors of critical illness following discharge from the intensive care unit: A randomised controlled trial
21	K. O. N. McDowell, B.: Blackwood, B.: Clarke, C.: Gardner, E.: Johnston, P.: Kelly, M.: McCaffrey, J.: Mullan, B.: Murphy, S.: Trinder, J.: Lavery, G.: McAuley, D. F.: Bradley, J. M.	2015	The REVIVE study: A randomised controlled trial of the effect of a programme of exercise on physical function in survivors of critical illness after discharge from the intensive care unit
22	D. B. McWilliams, S.: Atkinson, D.	2013	Outpatient based physical rehabilitation for survivors of prolonged critical illness-a randomised controlled trial
23	J. K. Paratz, J.: Comans, T.: Coyer, F.: Thomas, P.: Boots, R.	2016	A follow up clinic for sepsis survivors-preliminary results and feasibility
24	B. K. G. Patel, J. A.: Umunna, B. P.: Doman, E.: Pohlman, A. S.: Hall, J. B.: Kress, J. P.	2014	Quality of life and neuromuscular weakness at 1-year follow-up in patients enrolled in a randomized controlled trial of early mobilization
25	L. M. Salisbury, J.: Walsh, T.	2011	A pilot study to investigate the feasibility of a generic rehabilitation assistant to deliver enhanced ward-based rehabilitation after critical illness
26	S. W. Schaller, K: Edrich, T: Walz, Jm: Blobner, M: Eikermann, M	2016	Goal directed early mobilization reduces ICU length of stay and improves functional mobility: an international multi center, randomized, controlled trial
27	K. W. Schmidt, S.: Brunkhorst, F. M.: Davydow, D. S.: Ehlert, U.: Engel, C.: Kausche, S.: Pausch, C.: Reinhart, K.: Schmuecker, K.: Wensing, M.: Von Korff, M.: Gensichen, J.	2015	Sepsis survivors monitoring and coordination in outpatient health care (smooth)-a randomized controlled trial
28	K. W. Schmidt, S.: Brunkhorst, F. M.: Freytag, A.: Reinhart, K.: Scherag, A.: Schneider, N.: Gensichen, J.	2017	Long term effect of a sepsis aftercare intervention

Nr	Authors	Year	Title
29	S. F. Till, N: Norgaard, C: Gerkin, R: Bosak, A: Paulson, M: OwenReece, H	2015	Does debriefing ICU survivors before hospital discharge improve health-related quality of life?
30	A. C. W. Verceles, C.: Sorkin, J.: Terrin, M. L.: Beans, J.: Jenkins, T.: Goldberg, A.	2015	Improved weaning success and discharge home with a multimodal rehabilitation program in older patients with post ICU syndrome
31	M. B. Vitacca, L: Vanoglio, F: Luisa, A: Giordano, A: Bertella, E: Paneroni, M	2014	Home rehabilitation to improve respiratory muscles in patients recovering from a prolonged ICU stay and in-hospital rehabilitation
32	D. S. D. Wheelwright, N.: Griffiths, S.: Gordon, E.: Bederson, J.: Kellner, C.: O'Phelan, K.: Mayer, S.	2017	Does Intra-ICU initiation of guided mindfulness meditation decrease anxiety and depression in SAH?: A unique methodology for the neurocritical care setting
33	K. W. Wolfe, Bn: Patel, Sb: Patel, Bk: Greenberg, Ja: Pohlman, As: Hall, Jb: Kress, Jp	2013	Long-term survival and health care utilization of mechanically ventilated patients in a randomized controlled trial of early mobilization
34	S. T. Wright, K.: Baker, C.: Mansfield, L.: Stafford, V.: Wade, C.: Watson, G.: Bryant, A.: Chadwick, T.: Shen, J.: Wilkinson, J.: Furneval, J.: Henderson, A.: Hugill, K.: Howard, P.: Roy, A.: Bonner, S.: Baudouin, S.	2016	The extra physiotherapy in critical care (EPICC) multi-centre randomised controlled trial

Update search (19.09.2017 till 19.07.2018)

Characteristics of excluded studies (N= 11)

Nr	Authors	Year	Title study	Reason for exclusion
1	C. E. H. Cox, C. L.: Carson, S. S.: White, D. B.: Kahn, J. M.: Olsen, M. K.: Jones, D. M.: Somers, T. J.: Kelleher, S. A.: Porter, L. S.	2018	Effects of a Telephone- and Web-based Coping Skills Training Program Compared with an Education Program for Survivors of Critical Illness and Their Family Members. A Randomized Clinical Trial	Already included in original search
2	A. M. S. Dall' Acqua, Amanda: Santos, Laura J.: Lemos, Fernando A.: Bianchi, Tanara: Naue, Wagner S.: Dias, Alexandre S.: Sbruzzi, Graciele: Vieira, Silvia R. R.	2017	Use of neuromuscular electrical stimulation to preserve the thickness of abdominal and chest muscles of critically ill patients: a randomized clinical trial	No correct outcome: not measured after hospital discharge
3	M. F. Garrouste-Orgeas, C.: Fasse, L.: Ruckly, S.: Amdjar-Badidi, N.: Argaud, L.: Badie, J.: Bazire, A.: Bige, N.: Boulet, E.: Bouadma, L.: Bretonniere, C.: Floccard, B.: Gaffinel, A.: de Forceville, X.: Grand, H.: Halidfar, R.: Hamzaoui, O.: Jourdain, M.: Jost, P. H.: Kipnis, E.: Large, A.: Lautrette, A.: Lesieur, O.: Maxime, V.: Mercier, E.: Mira, J. P.: Monseau, Y.: Parmentier-Decrucq, E.: Rigaud, J. P.: Rouget, A.: Santoli, F.: Simon, G.: Tamion, F.: Thieulot-Rolin, N.: Thirion, M.: Valade, S.: Vinatier, I.: Vioulac, C.: Bailly, S.: Timsit, J. F.	2017	The ICU-Diary study: prospective, multicenter comparative study of the impact of an ICU diary on the wellbeing of patients and families in French ICUs	No correct design: study protocol
4	M. M. Gilmartin, Fidelma: Segurado, Ricardo: O'Neill, Brenda	2018	Intensive care discharge facilitation using the REhabilitation after Critical illness Assisted discharge Pack (RECAP) model: A pilot randomized controlled trial	No correct outcome: not measured after hospital discharge

Nr	Authors	Year	Title study	Reason for exclusion
5	W. P. Gruther, K.: Steiner, I.: Hein, C.: Hiesmayr, J. M.: Paternostro-Sluga, T.	2017	Can Early Rehabilitation on the General Ward After an Intensive Care Unit Stay Reduce Hospital Length of Stay in Survivors of Critical Illness?: A Randomized Controlled Trial	Already included in original search
6	B. L. Guidet, G.: Simon, T.: Woimant, M.: Quenot, J. P.: Ganansia, O.: Maignan, M.: Yordanov, Y.: Delerme, S.: Doumenc, B.: Fartoukh, M.: Charestan, P.: Trognon, P.: Galichon, B.: Javaud, N.: Patzak, A.: Garrouste-Orgeas, M.: Thomas, C.: Azerad, S.: Pateron, D.: Boumendil, A.	2017	Effect of Systematic Intensive Care Unit Triage on Long-term Mortality Among Critically Ill Elderly Patients in France: A Randomized Clinical Trial	No correct outcome: not measured after hospital discharge
7	R. J. J. Jonasdottir, H.: Gudmundsdottir, B.: Sigurdsson, G. H.	2018	Psychological recovery after intensive care: Outcomes of a long-term quasi-experimental study of structured nurse-led follow-up	Already included in original search
8	E. S. Karadag, Sevgin: Ozden, Dilek: Bakir, Ercan	2017	Effects of aromatherapy on sleep quality and anxiety of patients	Already included in original search
9	T. C. Mailhot, Sylvie: Côté, José: Bourbonnais, Anne: Côté, Marie-Claude: Lamarche, Yoan: Denault, André	2017	A post cardiac surgery intervention to manage delirium involving families: a randomized pilot study	Already included in original search
10	C. C. Medrinal, Y: Prieur, G: Robledo, Quesada A: Bonnevie, T: Gravier, Fe: Dupuis, Lozeron E: Frenoy, E: Contal, O: Lamia, B	2018	Comparison of exercise intensity during four early rehabilitation techniques in sedated and ventilated patients in ICU: a randomised cross-over trial	No correct outcome: not measured after hospital discharge
11	E. D. E. H. Papathanassoglou, M.: Miltiadous, P.: Lambrinou, E.: Papastavrou, E.: Paikousis, L.: Kyprianou, T.	2018	Effects of an Integrative Nursing Intervention on Pain in Critically Ill Patients: A Pilot Clinical Trial	No correct outcome: not measured after hospital discharge

Update search (19.09.2017 till 19.07.2018)

Characteristics of conference abstracts (N=13)

Nr	Authors	Year	Title
Nr	Author	Year	Title
1	F. M. Al-Janabi, N.: Islam, S.: Watson, N.: Mion, M.: Davies, J.: Karamasis, G.: Potter, M.: Keeble, T.	2017	Care after resuscitation-an early psychological support service for out of hospital cardiac arrest survivors
2	C. E. C. Cox, S. S.: Hough, C. L.: Kahn, J.: White, D. B.: Olsen, M. K.: Somers, T.: Kelleher, S.: Porter, L. S.	2017	Coping skills training to improve psychological distress among critical illness survivors: A randomized clinical trial
3	C. E. H. Cox, C.: Jones, D.: Ungar, A.: Reagan, W.: Key, M. D.: Gremore, T.: Olsen, M. K.: Sanders, L.: Greeson, J. M.: Poter, L. S.	2018	Effect of a self-directed mobile app mindfulness program for ICU survivors: A pilot RCT
4	S. L. Gandotra, J.: Case, D.: Bakhru, R. N.: Gibbs, K.: Berry, M.: Files, D. C.: Morris, P. E.	2017	Recovery trajectories of critically ill patients in a randomized controlled trial of early rehabilitation
5	R. N. Gawlytta, H.: Bottche, M.: Scherag, A.: Knaevelsrud, C.: Rosendahl, J.	2017	Internet-based cognitive-behavioural writing therapy for reducing post-traumatic stress after intensive care for sepsis in patients and their spouses (REPAIR): Results of two pilot cases
6	J. W. Grunow, T: Carbon, Nm: Kny, M: Giesecke, M: Birchmeier, C: Fielitz, J: Weber-Carstens, S	2017	Effect of protocol-based physiotherapy and muscle activating measures on muscle synthesis and degradation balance in intensive care unit acquired weakness
7	M. M. Kho, Aj: Clarke, F: Karachi, T: Fox-Robichaud, Ae: Lo, V: Mathur, S: Herridge, Ms: Seely, Aj: Burns, Ke: Ball, Im: Pellizzari, Jr: Rochwerg, B: Tarride, J-E: Koo, Kk: Rudkowski, J: Piraino, T: Mourtzakis, M: McCaughan, M: Reid, J: Costigan, Fa: Niven, L: Heels-Ansdell, D: Cook, Dj	2017	Cycle pilot RCT: a multicenter feasibility study of early in-bed cycling versus routine physiotherapy in medical-surgical ventilated patients

Nr	Authors	Year	Title
8	M. M. Kho, A. J.: Clarke, F. J.: Cook, D. J.: Rudkowski, J. C.: Obrovac, K.: McCaughan, M.: Millen, T.: Karachi, T. A.: Rochwerg, B.: Farley, C.: McDonald, E.: Fox-Robichaud, A.: Loreto, E.: Reid, J. C.: Matte, A.: Herridge, M. S.: Mathur, S.: Lo, V.: Smith, O. M.: Burns, K. E.: Feltracco, D.: Porteous, R.: Seely, A. J.: Lamontagne, J.: Campbell, E.: Ball, I.: Abercrombie, K.: Heels-Ansdell, D. M.: Tarride, J.: Pellizzari, J. R.: Costigan, A.: McCaskell, D.: Koo, K. K.	2018	Outcomes from a multicentre pilot randomized clinical trial of early in-bed cycling with mechanically ventilated patients: Cycle pilot rct
9	D. J. McWilliams, C: Atkins, G: Reeves, E: Snelson, C	2017	A comparison of early and enhanced rehabilitation of mechanically ventilated patients in critical care compared to standard care (REHAB): a single site feasibility randomized controlled trial
10	J. M. Messika, Y.: Maquigneau, N.: Henry-Lagarrigue, M.: Puechberty, C.: Stoclin, A.: Martin-Lefevre, L.: Blot, F.: Dreyfuss, D.: Dechanet, A.: Hajage, D.: Ricard, J.	2017	Effect of a musical intervention on tolerance and efficacy of non-invasive ventilation: The mus-ira randomized controlled trial
11	K. W. Schmidt, S.: Brunkhorst, F. M.: Freytag, A.: Reinhart, K.: Scherag, A.: Schneider, N.: Gensichen, J.	2017	Long term effect of a sepsis aftercare intervention
12	P. L. Silva, De Carvalho K: Araujo, Ae: Castro, Jd: Maldaner, V: Pereira, L: Nunes, L: Santos, M: Vieira, L: Melo, Pf: Babault, N: Cipriano, G: Quagliotti, Durigan Jl	2017	Efficacy of neuromuscular electrical stimulation for decreasing neuromuscular electrophysiological disorders in critical ill patients
13	S. A. Wappel, O: Serra, M: Wells, Cl: Davis, D: Alon, G: Goldberg, Ap: Parker, E: Sorkin, Jd: Terrin, Ml: Verceles, Ac	2017	The effect of an exercise, nutrition and neuromuscular electrical stimulation intervention on acute muscle wasting in critically ill patients receiving mechanical ventilation

Supplementary file 5. Data extraction form

Reviewers	
a) Name reviewer	
b) Date	
c) Cross-checked	

Study	
a) Title	
b) Authors (>2 et al.,)	
c) Year	

Objective and methods	
a) Objective or aim	
b) Study design	☐ Randomized controlled trial (RCT) (incl. cluster rct) ☐ Non-randomised controlled trial (nrct) / controlled clinical trial (CCT) ☐ Controlled before after study (CBA) ☐ Interrupted time serie (ITS) and repeated measure study
c) Pilot/ feasibility study	Yes/no
d) Study duration (inclusion/ recruitment)	

Participants and setting	
a) Setting	Hospital(s): Type of ICU: Level of ICU: Number of ICUs: Single/ multicenter:
b) Country	
c) Target population/ participants (inclusion criteria)	
d) Age (mean, sd/ median, IQR)	
e) Sex (n, %)	
f) Admission diagnosis (surgical, medical, trauma other) (n, %)	
g) Mechanical ventilation (n, %)	
h) Severity of illness (APACHE/ SOFA/ (mean +/- SD or median)	
i) Length of stay ICU (days)	
j) Length of stay in hospital (days)	
k) Co-morbidity	

Number of patients	
a) Total number of patients enrolled (inclusion +% = eligible and inclusion)	
b) Total number of patients at final analysis (ITT and PP)	
c) Loss to follow up (+ reasons)	

Intervention	
a) Description of intervention	
b) Total number of intervention groups	
c) Description of control group	
d) Single/ group based intervention	
e) Method (online, telephone etc).	
f) Provider (healthcare professional etc).	
g) Duration intervention	
h) Setting of intervention (pre/during/ post ICU	

Outcomes and results	
a) Outcome measure 1	Definition: Instrument/ scale: Scale range/ interpretation: Time points collected: Primary/ secondary outcome: Sample size: Missing participants: Summary data (means, SD etc): Control group Intervention group p- value :
b) Outcome measure 2	Definition: Instrument/ scale: Scale range/ interpretation: Time points collected: Primary/ secondary outcome: Sample size: Missing participants: Summary data (means, SD etc): Control group Intervention group p- value :

Outcomes and results	
c) Outcome measure 3	Definition: Instrument/ scale: Scale range/ interpretation: Time points collected: Primary/ secondary outcome: Sample size: Missing participants: Summary data (means, SD etc): Control group Intervention group p- value :
d) Outcome measure 4	Definition: Instrument/ scale: Scale range/ interpretation: Time points collected: Primary/ secondary outcome: Sample size: Missing participants: Summary data (means, SD etc): Control group Intervention group p- value :
e) Outcome measure 5	Definition: Instrument/ scale: Scale range/ interpretation: Time points collected: Primary/ secondary outcome: Sample size: Missing participants: Summary data (means, SD etc): Control group Intervention group p- value :

Miscellaneous	
a) Key conclusions of study authors	
b) Miscellaneous comments from the reviewers	

Supplementary file 6. Risk of bias form

Reviewers
a) Name reviewer
b) Date
c) Cross-checked

Study
a) Title
b) Authors (>2 et al.,)
c) Year

Quality rating	**Risk of bias**	**Support for judgement**
Random sequence generation (selection bias)		
Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups (randomisation)	Low risk High risk Unclear risk	
Allocation concealment (selection bias)		
Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Low risk High risk Unclear risk	
Blinding of participants and personnel (performance bias) (for each outcome)		
Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Low risk High risk Unclear risk	

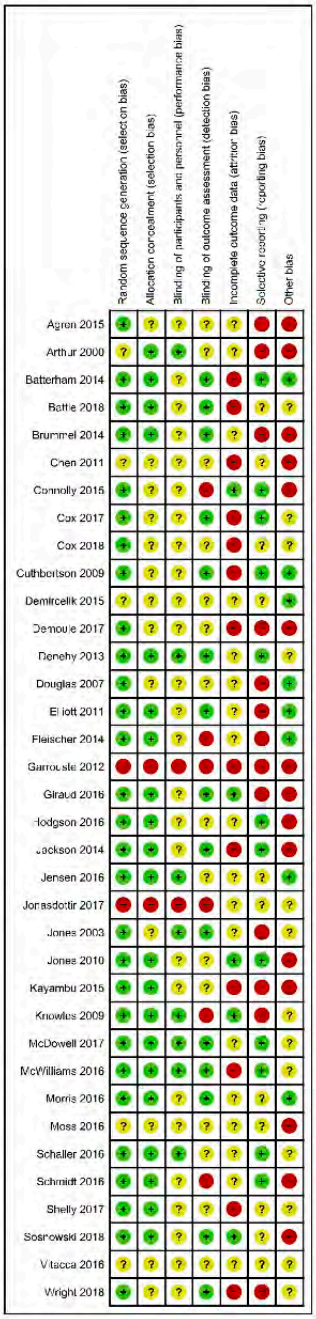
Quality rating	Risk of bias	Support for judgement
Blinding of outcome assessment (detection bias) (patient reported outcomes) (for each outcome)		
Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Low risk High risk Unclear risk	
Incomplete outcome data addressed (attrition bias) (for each outcome)		
Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Low risk High risk Unclear risk	
Selective reporting		
State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Low risk High risk Unclear risk	
Other sources of bias		
State any important concerns about bias not addressed in the other domains in the tool. If particular questions/ entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Low risk High risk Unclear risk	

Sources of bias

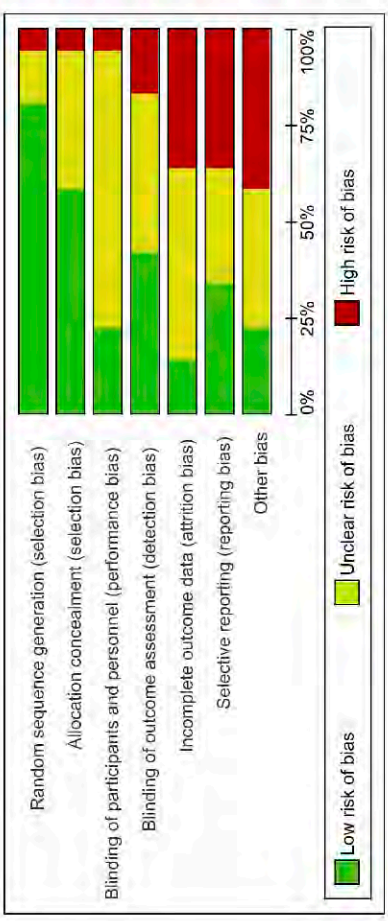
Item	Low Risk	High risk	Unclear risk
Random sequence generation (selection bias)	• Random number table • Computer random number generator • Stratified/ block randomisation • Minimisation • Low tech- coin toss, shuffling card, envelopes, throwing dice, drawing lots	• Quasi random, date of birth, day of visit, ID or record number, alternate allocation • Non random, choice of clinician or participants, test results, availability	• Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	• Central allocation (phone, web, pharmacy randomisation) • Sequentially numbered, sealed, opaque envelopes • Sequentially numbered, identical drug containers	• Random sequence known to staff in advance • Envelopes or packaging without all safeguards • Non random, predictable sequence, date of birth, case record number	• Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed
Blinding of participants and personnel (performance bias)	• Blinding, and unlikely that the blinding could have been broken • No blinding or incomplete blinding, but outcome unlikely to be influenced	• No blinding, incomplete or broken blinding, and outcome likely to be influenced	• Insufficient information to permit judgement of 'low risk' or 'high risk' • The study did not address this outcome
Blinding of outcome assessment (detection bias)	• Blinding, and unlikely that the blinding could have been broken • No blinding, but measurement unlikely to be influenced	• No blinding or broken blinding, and measurement likely to be influenced	• Insufficient information to permit judgement of 'low risk' or 'high risk' • The study did not address this outcome

Item	Low Risk	High risk	Unclear risk
Incomplete outcome data addressed (attrition bias)	• No missing data • Reasons for missing data not related to outcome • Missing data balanced across groups, and reasons similar • Proportion missing or plausible effect size not enough to have a clinically relevant effect	• Reasons related to outcome, and imbalance in number or reasons • Proportion missing or plausible effect size enough to have a clinically relevant effect • 'As treated' analysis with substantial departure from allocation • Inappropriate use of imputation	• Insufficient reporting of attrition/ exclusion to permit judgement of 'low risk' or 'high risk' (e.g. number randomised not stated, no reasons for missing data provided) • The study did not address this outcome
Selective reporting (reporting bias)	• Protocol is available and all pre-specified outcome of interest to the review reported in the pre-specified way • Protocol not available but it is clear that all pre-specified and expected outcomes of interest are reported	• Outcomes not reported as pre-specified or expected (e.g. missing, added, subsets, unexpected measurements or methods) • Outcomes reported incompletely so they cannot be entered in a meta-analysis.	• Most studies will be judged in this category
Other sources of bias	• Study appears to be free of other sources of risk	• Carry over in cross over trials • Recruitment bias in cluster RT • Non randomised studies • Baseline imbalance • Blocked randomisation in unblended trials • Differential diagnostic activity • Sponsoring • Other bias	• Insufficient information to assess whether an important risk of bias exist • Insufficient rationale or evidence that an identified problem will introduce bias

Supplementary file 7. Risk of bias summary



Supplementary file 8. Risk of bias graph



Study, year	Intervention, time delivered	Components of intervention	Duration and frequency	Provider	Control group
Exercise pre-hospital					
Arthur et al., 2000	Exercise training, education, social support	Individualized supervised (group) exercise training: warming up, stretching, aerobic interval training, cool down Education/reinforcement: cardiac risk factors, surgery, hospitalization events Phone calls: answering questions, providing reassurance	8 weeks, 2 x p/w (90 min) Study entry, 1 wk < surgery Phone calls: monthly	Kinesiologist, exercise specialist Nurse clinicians	Usual care: followed by PCP, cardiologist or surgeon
Exercise during ICU					
Wright et al., 2018	Intensive physical rehabilitation therapy	Intensive physical rehabilitation therapy	90 min p/d (mon-fri) (split between at least 2 sessions)	Physiotherapist	Usual care (30 min p/d)
Morris et al., 2016	Standardized rehabilitation therapy	Passive range of motion, physical therapy (e.g. transfers, balance training) and progressive resistance exercise (e.g. dorsiflexion)	3 sessions p/d	Physiotherapist, ICU nurse, nursing assistant	Usual physical therapy care, not in weekend
Hodgson et al., 2016	EGDM	Active functional activities (e.g. walking, standing, sitting). Goal is to maximise safe physical activity	Depending on patient level: 30 to 60 min p/d	Physiotherapist, health assistant, nurse	Usual care, no restrictions on physical therapy
Schaller et al., 2016	EGDM	Defining mobilization goal per day and implement it across shifts (e.g. addressing barriers and procedures to reach goals)	Daily during the ICU	Physical therapist, nurse or medical doctor	Usual care

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Supplementary file 9. Continued

Study, year	Intervention, time delivered	Components of intervention	Duration and frequency	Provider	Control group
Kayambu et al., 2015	Early physical rehabilitation + NMES	Passive + active range of motion (e.g. sitting out of bed, transfers) NMES (e.g. vastus medialis, vastus lateralis) 40-45 Hz at 20-25mA, pulse duration at 400µs of 12 sec on and 6 sec off	1 or 2 x daily (30 min) until ICU discharge	ICU research physiotherapist	Standard ICU physiotherapy care
Moss et al., 2015	Intensive physical therapy program	Breathing techniques, progressive range of motions, muscle strengthening, core mobility and strength, functional mobility and transfers	Up to 28 days: 30-60 min p/d (7d/w) or at home (3 d/w)	Physiotherapist	Standard physical therapy program
Denehy et al., 2013	Exercise rehabilitation program	Exercise: marching in place, moving from sitting to standing, cardiovascular progressive resistance strength training, functional exercise	Start day 5 > ICU admission (<15 min/ day). 7 d/w on ward (2× 30 min), 2x p/w for 8 weeks in outpatient setting (60 min)	Physiotherapists	Usual care, may included active bed exercises, sitting out of bed/ marching/walking
Chen et al,. 2011	Physical training	Diaphragmatic breathing control facilitation, strengthening exercises, active transfer chair, functional activity training Training of caregivers to assist patients using the same regime of exercise program	6 weeks, 5 d/w. After 6 weeks, weekly supervision	Physiotherapist	Weaning trial (daily spontaneous breathing test, nutritional support, postural drainage, mobility)
Exercise post ICU					

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Supplementary file 9. Continued

Study, year	Intervention, time delivered	Components of intervention	Duration and frequency	Provider	Control group
Vitacca et al., 2016	Home treatment program	Individually tailored pulmonary rehabilitation program	6 mo in total 2 p/d, 7d/w	Physiotherapist	Standard home care
		Rehabilitation session (e.g. bronchial hygiene) and physical activity	60-90 min: 3 sessions p/wk)		
		Home visit: observe session, monitor compliance, educational reinforcement	After first mo		
Brummel et al., 2014	Group 1: Physical + occupational therapy	Physical therapy and occupational therapy: from passive range of motions to independent ambulation	1 x p/d inpatient physical therapy	Physical and occupational therapists	Usual care: physical and occupational therapy (1-2 p/w)
	Group 2: Physical + occupational therapy + cognitive therapy	Cognitive therapy: orientation, memory, attention, problem solving. Optional is in-home therapy using Goal Management Training.	2x p/d inpatient cognitive therapy (20 min) + 1x p/d physical therapy + (optional) outpatient cognitive therapy: 12 weeks, 6 sessions	Physician, nurse, neuropsychologist	

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Supplementary file 9. Continued

Study, year	Intervention, time delivered	Components of intervention	Duration and frequency	Provider	Control group
Jones et al., 2003	Self help rehabilitation manual	Manual with text, diagrams and supporting illustrations Self-directed exercise program Diary to measure use of rehabilitation package Reinforcing telephone calls to use the manual	6 weeks 3 weekly calls	Not reported	Usual care (3 x phone calls after hospital discharge, visit follow-up clinic 2 and 6 mo)
Exercise post hospital					
Battle et al., 2018	Exercise rehabilitation	Individualised, supervised exercise programme: cardiopulmonary, strengthening and balance exercises. Advise on completing additional home exercise program	6 week program, 2 sessions up to 1 h, 2x p/wk	Therapist (physiotherapy technicians)	Usual care
Shelly et al.,2017	Home based exercise program	Respiratory exercises (e.g. deep breathing exercises) and mobility exercises (e.g sport marching). Exercise information sheet before discharge	4 week home based Training: 5 x p/w 15-20 min	Physiotherapist	Usual care, no formal exercise prescription
McDowell et al., 2016	Exercise program	Whole body conditioning and strengthening exercises, aerobic exercises + manual with standardised descriptions and pictures of the exercise	6 week program (session max 60 min): 2 x p/w supervised sessions (hospital) 1 x p/w unsupervised session (home)	Physiotherapist	Usual care (no additional support after hospital discharge)

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Supplementary file 9. Continued

Study, year	Intervention, time delivered	Components of intervention	Duration and frequency	Provider	Control group
McWilliams et al., 2016	Physical rehabilitation	Exercise training: circuit of 10 stations with 2× 1 min exercise at each station. Combination of cardiovascular exercises.	7 week program 3 ×20 min p/w (1 x supervised, 2 x self directed)	Physiotherapist	Usual care (physiotherapy, exercises and education until hospital discharge)
		Education session: benefits exercise, relaxation techniques, smoking cessation, anxiety management, group discussion forum	6 × 60 min		
Connolly et al., 2015	Exercise based rehabilitation	Supervised individually tailored exercises: combination of cardiovascular, upper/lower limb strength, balance, functional exercises	3 mo:16 sessions 40 min: 2 x p/w (outpatient)	Members of research team	Weekly telephone call from research team to monitor recovery progress
		Unsupervised exercise program using manual	1 x p/w		
Batterham et al., 2014	Exercise program (post	Supervised physiotherapy exercise sessions: warming up, cycle ergo-meter, cooling down	8 weeks; 3 x p/w: 2 × 40 min supervised sessions	Hospital physiotherapist	Usual care: no formal rehabilitation programme
		Unsupervised: e.g. walk at moderate space	1 × 30 min		

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Supplementary file 9. Continued

Study, year	Intervention, time delivered	Components of intervention	Duration and frequency	Provider	Control group
Jackson et al., 2012	Physical, functional and cognitive rehabilitation	Tailored exercises: targeting lower extremity function and endurance (using easily home performing exercises)	12 weekly post discharge: 60-75 min Exercise: 6 televideo visits + 6 phone calls	Exercise trainer, occupational therapist, social worker, psychology technician	Usual care (may include physical + occupational therapy and nursing care). No cognitive therapy or speech therapy
		Education: helping patient understand relation person, environment and activity + action plan	4 televideo visits + 4-6 calls		
		Cognitive rehabilitation (GMT based), improving executive function by increasing goal directed behaviour	6 in-persons visits		
Elliott et al., 2011	Physical rehabilitation program	Improving endurance (walking) + muscle strength (lower/ upper limb muscle groups; core stabilisation; flexibility and stretches)	8 week home based Program (goal = 5xp/w 20-30 min)	Physiotherapist, exercise physiologist, nurse with additional training	Usual community based care after hospital discharge
		Home visits by professional, providing instructions on exercise program	3 home visits (each		
		Telephone sessions to monitor progress	60- 90 min		
Follow-up services					

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Supplementary file 9. Continued

Study, year	Intervention, time delivered	Components of intervention	Duration and frequency	Provider	Control group
Jonasdottir et al., 2017	Nurse-led follow-up care (post ICU-post hospital)	Ward visit: focus on patient clinical condition, nightmares, delirium, depression, anxiety	Ward visit: < 24 h ICU discharge to ward	ICU clinical nurse specialist	Usual care (unstructured ward visits form ICU nurse)
		Telephone consultation: info about recovery after critical illness/ patient concerns in current recovery, mobilization, sleep, nutrition	1st week after hospital discharge: phone		
		Follow up appointment: ICU experience, current and future recovery	After 3 mo (60 min) + ward visit		
Jensen et al., 2016	Recovery program (post ICU-post hospital)	Illness narrative + photographs taken by ICU nurse during ICU recovery (session 1)	Session 1: clinic after 1-3 mo post ICU	Study nurse	Usual care, without follow up and diaries
		Patients prepare reflecting sheets about issues of importance (session 2 and 3)	Session 2+3: call after 5 + 10 mo post ICU		
Schmidt et al., 2016	Primary care intervention: case management (post ICU-post hospital)	Pro-active patient symptom monitoring (+ self management behaviours) using validated screening tools	Phone call: monthly (for first 6 mo), every 3 mo for final 6 mo	Case manager (ICU nurses), consulting physician	Usual care from PCP. No additional information or monitoring
		Clinical decision support for PCP			
		Evidence based sepsis aftercare training for patients and their PCPs	1 × 60 min training (8 days > ICU discharge)		

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Supplementary file 9. Continued

Study, year	Intervention, time delivered	Components of intervention	Duration and frequency	Provider	Control group
Cuthbertson et al., 2009	Nurse-led follow-up programme + physical rehabilitation program (post ICU-post hospital)	Manual based self directed physical rehabilitation program Clinical appointment: reviewing progress rehabilitation program, structured case review, ICU experiences, formal assessment of requirement for specialist medical referral, screening for psychological morbidity	 Meetings at nurse-led clinic at 3 and 9 mo after discharge	Program developed by physiotherapist, introduced by nurses	No IC follow-up; follow-up by GP + primary hospital specialty
Douglas et al., 2007	Disease management program (post ICU-post hospital)	Coordinate follow-up service, facilitate communication between patients' families +healthcare providers, provide supportive services for family members	Several meetings (>8 in 8 weeks)	Advance practice nurse	Usual care
Psychosocial programs					
Cox et al., 2018	Mindfulness training program (post hospital)	Intervention 1: Telephone mindfulness training (TMT): 1) discussion about stressors, 2) didactic elements (awareness and breathing, body systems, emotions, sound); 3) practice and review; 4 discussion of mindfulness skills Intervention 2: Mobile mindfulness training (MMT): 4 sessions series of videos, audio files and interactive text figures	Each week for 1 mo: 30 min phone call Phone call (week 1). Weekly session: background video (4-5 min), guide meditation (6-8 min), interactive suggestions (10 min)	Psychologist	Education program about critical illness + 2 phone calls

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Supplementary file 9. Continued

Study, year	Intervention, time delivered	Components of intervention	Duration and frequency	Provider	Control group
Cox et al., 2017	Telephone based coping skill training (post hospital)	Phone sessions: 1) relaxation exercise; 2) progressive muscle relaxation; 3) pleasant activities, activity-rest circle; 4) communication; 5) cognitive restructuring, pleasant imagery; 6) review and planning for sustainability Web content for applying skills	Six weekly phone sessions, each 30 min	Clinical psychologists	Education program addressing poor comprehension of critical illness: 6 videos + webbased content + 2 x 30 min phone call
Agren et al., 2015	Psychosocial support and education (post hospital)	Providing patients opportunity to process experiences regarding cardiac surgery, rehabilitation, concerns and questions, goals Information and advice to help patient handle rehabilitation phase	Sessions of 30-60 min in 24 weeks: 4-6 weeks (meeting team) 10-12 weeks (telephone) 22-24 weeks after discharge (phone)	Multidisciplinary team (physician, nurse, physiotherapist)	Usual care: hospital routines in cardiac surgery care. No follow-up visits
Diaries					
Garrouste et al., 2012	Diary (during ICU)	Chart of ICU staff, photo of ICU, explanation of monitoring systems, medical history < ICU admission. Family photos, written accounts by relatives. Receive diary at hospital discharge	Start at 4th calendar day > ICU admission	Senior and junior physician or nurse	Group 1: pre-diary group 2: post-diary Diaries were not opened in period
Jones et al., 2010	Diary (during ICU	Written by healthcare staff, family members + photos. Daily record of ICU stay. Receive diary as soon as they wanted (> 1 mo post ICU)	Few min p/d(except for starting diary)	Research nurse or physician	Diary (received diary after 3 mo)

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Supplementary file 9. Continued

Study, year	Intervention, time delivered	Components of intervention	Duration and frequency	Provider	Control group
Knowles et al., 2009	Diary (during ICU-post hospital)	Written by healthcare staff: patient condition, events on ward, treatment, names of visitors. Receive diary at meeting with ICU consultant	Meeting 1 month > ICU discharge (60 min)	ICU nurse consultant	Receive diary after 2 mo
Information & education programs					
Demircelik et al., 2016	Multimedia informational education program (during ICU)	NA	NA	ICU nurses	Usual care
Fleisher et al., 2014	Structured information program (during ICU)	Standardized part: information ICU (e.g. staff, monitoring, schedules, communication) + individualised part of common fears (complications, suffocating, pain, death, being helpless, lonely or confined)	NA	NA	Semi structured, non specific conversation with the study nurse
Other interventions					
Sosnowski et al., 2018	ABCDE bundle (during ICU)	ABCDE bundle with computer alert when bundle components were due for action: Awakening, breathing coordination + assessment of pain, sedation and delirium + early exercise and mobility	Pain every 2 h, alertness every 4 h, delirium every 12 h	Nursing, medical and allied health staff	Usual standard care (with routine pain, sedation and delirium assessment)
Demoule et al., 2017	Earplugs and eye mask (during ICU)	Early plugs and eye mask	10.00 pm - 8.00 a.m. ICU discharge	Trained nurses	Routine care during night
Giraud et al., 2016	Structured mirrors (during ICU)	Two mirrors to support mental status and attention, multisensory feedback, physical mobilization	When patient was awake after surgery	Nurse, physiotherapy	Usual care, no prescription around use of mirrors

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Supplementary file 10. Overview outcomes per study

Domain: Physical health

		Exercise and physical rehabilitation programs																				Follow-up service					Psy-cho-program			Diaries			Info		Other		
Outcome	**Instrument**	**Arthur, 2000**	**Wright, 2018**	**Morris, 2016**	**Hodgson, 2016**	**Schaller, 2016**	**Kayambu, 2015**	**Moss, 2015**	**Denehy, 2013**	**Chen, 2011**	**Vitacca, 2016**	**Brummel, 2014**	**Jones, 2003**	**Battle, 2018**	**Shelly, 2017**	**McDowell, 2016**	**McWilliams, 2016**	**Connolly, 2015**	**Batterham, 2014**	**Jackson, 2014**	**Elliott, 2011**	**Jonasdottir, 2017**	**Jensen, 2016**	**Schmidt, 2016**	**Cuthbertson, 2009**	**Douglas, 2007**	**Cox, 2018**	**Cox, 2017**	**Agren, 2015**	**Garrouste, 2012**	**Jones, 2010**	**Knowles, 2009**	**Demircelik, 2016**	**Fleisher, 2014**	**Sosnowski, 2018**	**Demoule, 2017**	**Giraud, 2016**
Exercise capacity	ISWT															1		1																			
Exercise capacity	6MWT		1						1					1				1			1																
Physical function	RMI															1																					
Muscle strength	QMVC																	1																			
Muscle strength	Dynamometer			1												1																					
Muscle strength	Handgrip		1	1										1				1																			
Muscle strength	MRC										1																										
Muscle strength	9 hole peg															1																					
Muscle size	RFCSA																	1																			
Muscle strength	FPI			1																																	
Physical function	CSPFP							1																													
Functional mobility	TUG/TUAG							1	1			1						1		1																	
Functional mobility	SPPB			1																																	
Physical mobility	XSMFA																							1													
Physical mobility	ABC																			1																	
Functional mobility	STS-5																	1																			
Balance	BBS							1						1																							
Balance	FTSTS							1																													
Fat free mass	Fat free mass																	1																			
Peak oxygen	Peak oxygen	1															1		1																		
AT	AT																1		1																		

		Exercise and physical rehabilitation programs		Follow-up service	Psy-cho-pro-gram	Diaries	Info	Other
PA02/ PAC02	PA02/ PAC02	1						
Pulmonary exp. vol	FVC/FEV	1						
Respiratory rate	Respiratory rate	1						
Ins/expiratory pres.	MIP/MEP	1						
Pain	GCPS			1				
Insomnia	RIS			1				
Sleep quality	PSQI							1
Malnutrition	MUST			1				
Neuropathy	NSS			1				
Dyspnoea	MRC dyspnoea scale		1					
Dyspnoea	Borg	1						

Domain: Mental health

		Exercise and physical rehabilitation programs																				Follow-up service					Psy-cho-pro-gram			Diaries			Info		Other		
Outcome	**Instrument**	**Arthur, 2000**	**Wright, 2018**	**Morris, 2016**	**Hodgson, 2016**	**Schaller, 2016**	**Kayambu, 2015**	**Moss, 2015**	**Denehy, 2013**	**Chen, 2011**	**Vitacca, 2016**	**Brummel, 2014**	**Jones, 2003**	**Battle, 2018**	**Shelly, 2017**	**McDowell, 2016**	**McWilliams, 2016**	**Connolly, 2015**	**Batterham, 2014**	**Jackson, 2014**	**Elliott, 2011**	**Jonasdottir, 2017**	**Jensen, 2016**	**Schmidt, 2016**	**Cuthbertson, 2009**	**Douglas, 2007**	**Cox, 2018**	**Cox, 2017**	**Agren, 2015**	**Garrouste, 2012**	**Jones, 2010**	**Knowles, 2009**	**Demircelik, 2016**	**Fleisher, 2014**	**Sosnowski, 2018**	**Demoule, 2017**	**Giraud, 2016**
Depression	BDI																												1								
Depression	HADS-D				1								1	1		1		1	1			1	1		1			1		1		1	1			1	
Depression	MDI																							1													
Depression	PHQ-9																										1										
Anxiety	HADS-A				1								1	1		1		1	1			1	1		1			1		1		1	1			1	
Anxiety	GAD-7																										1										
PTSD	Davidson																								1												
PTSD	IES-R												1									1						1		1						1	
PTSD	PDEQ																													1							
PTSD	HTQ-IV																						1														
PTSD	PTSS																							1			1				1						
PTSD	PDS																														1						
PTSD	New onset																														1						
Coping	BCOPE																										1	1									
Distress	PHQ-15																										1										
Mindfulness skills	CAMS-R																										1										

Domain: Cognitive health

		Exercise and physical rehabilitation programs																				Follow-up service					Psy-cho-pro-gram			Diaries			Info		Other		
Outcome	**Instrument**	**Arthur, 2000**	**Wright, 2018**	**Morris, 2016**	**Hodgson, 2016**	**Schaller, 2016**	**Kayambu, 2015**	**Moss, 2015**	**Denehy, 2013**	**Chen, 2011**	**Vitacca, 2016**	**Brummel, 2014**	**Jones, 2003**	**Battle, 2018**	**Shelly, 2017**	**McDowell, 2016**	**McWilliams, 2016**	**Connolly, 2015**	**Batterham, 2014**	**Jackson, 2014**	**Elliott, 2011**	**Jonasdottir, 2017**	**Jensen, 2016**	**Schmidt, 2016**	**Cuthbertson, 2009**	**Douglas, 2007**	**Cox, 2018**	**Cox, 2017**	**Agren, 2015**	**Garrouste, 2012**	**Jones, 2010**	**Knowles, 2009**	**Demircelik, 2016**	**Fleisher, 2014**	**Sosnowski, 2018**	**Demoule, 2017**	**Giraud, 2016**
Global recognition	MMSE			1								1								1																	
Cognitive function	Tower											1								1																	
Cognitive function	DEX											1								1																	
Cognitive status	TICS_M																							1													

Domain: Quality of life

Outcome	Instrument	Exercise and physical rehabilitation programs																			
		Arthur, 2000	Wright, 2018	Morris, 2016	Hodgson, 2016	Schaller, 2016	Kayambu, 2015	Moss, 2015	Denehy, 2013	Chen, 2011	Vitacca, 2016	Brummel, 2014	Jones, 2003	Battle, 2018	Shelly, 2017	McDowell, 2016	McWilliams, 2016	Connolly, 2015	Batterham, 2014	Jackson, 2014	Elliott, 2011
Quality of life	SF-36	1	1	1		1	1	1	1						1	1	1	1	1		1
Quality of life	SF-8																				
Quality of life	SF-12																				
Quality of life	EQ-5D		1		1						1	1				1			1		
Quality of life	AQOL								1												
Quality of life	SEIQoL																				

Outcome	Instrument	Follow-up service					Psy-cho-pro-gram			Diaries			Info		Other		
		Jonasdottir, 2017	Jensen, 2016	Schmidt, 2016	Cuthbertson, 2009	Douglas, 2007	Cox, 2018	Cox, 2017	Agren, 2015	Garrouste, 2012	Jones, 2010	Knowles, 2009	Demircelik, 2016	Fleisher, 2014	Sosnowski, 2018	Demoule, 2017	Giraud, 2016
Quality of life	SF-36		1	1	1				1						1		
Quality of life	SF-8					1											
Quality of life	SF-12													1			
Quality of life	EQ-5D				1		1	1									1
Quality of life	AQOL																
Quality of life	SEIQoL													1			

Domain: Other outcomes

		Exercise and physical rehabilitation programs																																					Follow-up service						Psy-cho-pro-gram			Diaries			Info		Other		
Outcome	**Instrument**	**Arthur, 2000**	**Wright, 2018**	**Morris, 2016**	**Hodgson, 2016**	**Schaller, 2016**	**Kayambu, 2015**	**Moss, 2015**	**Denehy, 2013**	**Chen, 2011**	**Vitacca, 2016**	**Brummel, 2014**	**Jones, 2003**	**Battle, 2018**	**Shelly, 2017**	**McDowell, 2016**	**McWilliams, 2016**	**Connolly, 2015**	**Batterham, 2014**	**Jackson, 2014**	**Elliott, 2011**	**Jonasdottir, 2017**	**Jensen, 2016**	**Schmidt, 2016**	**Cuthbertson, 2009**	**Douglas, 2007**	**Cox, 2018**	**Cox, 2017**	**Agren, 2015**	**Garrouste, 2012**	**Jones, 2010**	**Knowles, 2009**	**Demircelik, 2016**	**Fleisher, 2014**	**Sosnowski, 2018**	**Demoule, 2017**	**Giraud, 2016**
Perception of control	CAS																												1																				
Social support	ISEL	1																																														
Social support	NSSQ												1																																			
Activities daily living	KATZ										1	1								1																												
Activities daily living	OASIS																									1																						
Activities daily living	FAQ											1								1																												
Activities daily living	IADL				1																																										
Activities daily living	ADL																						1																								
Functional status	Barthel																	1																													
Functional status	FIM		1							1																																					
Patient reported outc.	PROMIS																												1																		
Self-efficacy	Lorig																												1																		
Self-efficacy	CDSES																1																														
Orientation life	SOC																					1																									

Study, year	Measurement time	Outcome and instrument	Intervention group	Control group	P value
Exercise pre-ICU					
Arthur et al., 2000 (Canada)	Baseline; 1 wk before surgery; 6 wk after surgery; 6 mo after surgery	Physical *Peak oxygen consumption:* Baseline: mean ml/min (sd) 1 wk <surgery 6 weeks: 6 mo: Quality of life *SF-36 PCS* Baseline 1 wk < surgery 6 weeks 6 mo *SF-36 MCS* Baseline 1 wk < surgery 6 weeks 6 mo Other *Social support: ISEL* Baseline 1 wk < surgery 6 weeks 6 mo	 1327.6 (320) N.A. N.A. N.A. 34.7 N.A. N.A. N.A. 49.1 N.A. N.A. N.A. 33.1 N.A. N.A. N.A.	 1201.2 (288) N.A. N.A. N.A. 34.2 N.A. N.A. N.A. 46.5 N.A. N.A. N.A. 33.6 N.A. N.A. N.A.	
Exercise during ICU					
Wright et al., 2018 (UK)	ICU discharge (ICU-D); hospital discharge (HD); 3 mo; 6 mo	Physical *Exercise capacity: 6MWT* HD: median (IQR) 3 mo: median (IQR) 6 mo: median (IQR) HD: adj. difference in means (95%CI) 3 mo: adj. difference in means (95%CI) 6 mo: adj. difference in means (95%CI) *Grip strength* ICU-D: mean (sd) HD: mean (sd) 3 mo: mean (sd) 6 mo: mean (sd) ICU-D: adj. difference in means (95%CI) HD: adj. difference in means (95%CI)	 195 (120–260) 293 (124–444) 374 (203–435) −27.9 (−86.1 to 31.8) −6.3 (−125.8 to 107.3) 61.7 (−47.2 to 157.0) 14 (9) 19 (10) 25 (16) 29 (19) −0.6 (−3.3 to 2.1) −3.5 (−8.1 to 1.2)	 173 (123–274) 255 (120–337) 321 (197–400) 15 (9) 22 (14) 24 (14) 24 (16)	

3 mo: adj. difference in means (95%CI)		1.8 (−6.7 to 10.3)			
6 mo: adj. difference in means (95%CI)		−0.5 (−11.3 to 10.3)			
Quality of life					
SF-36 PCS					
HD: mean (sd)		34 (8.0)		34 (9.0)	
3 mo: mean (sd)		35 (10.8)		34 (9.0)	
6 mo: mean (sd)		37 (12.2)		37 (11.3)	
HD: adj. difference in means (95%CI)		−1.0 (−4.2 to 2.2)			
3 mo: adj. difference in means (95%CI)		−1.4 (−5.9 to 3.0)			
6 mo: adj. difference in means (95%CI)		−1.1 (−7.1 to 5.0)			
SF-36 MCS					
HD: mean (sd)		40 (13.2)		39 (11.4)	
3 mo: mean (sd)		47 (11.8)		45 (12.3)	
6 mo: mean (sd)		47 (15.0)		48 (11.5)	
HD: adj. difference in means (95%CI)		1.3 (−3.4 to 6.0)			
3 mo: adj. difference in means (95%CI)		4.2 (−1.2 to 9.5)			
6 mo: adj. difference in means (95%CI)		−0.4 (−6.5 to 5.7)			
EQ-5D					
HD: mean (sd)		0·075		0·075	
3 mo: mean (sd)		0·512 (0·353)		0·446 (0·324)	
6 mo: mean (sd)		0·565 (0·390)		0·502 (0·347)	
HD: adj. difference in means (95%CI)		NA			
3 mo: mean (sd)		0·065 (-0·062–0·193)			
6 mo: mean (sd)		0·064 (-0·075–0·202)			
Other					
Functional independence: FIM					
ICU-D: mean (sd)		70 (27)		64 (25)	
HD: mean (sd)		113 (17)		108 (20)	
3 mo: mean (sd)		116 (19)		111 (23)	
6 mo: mean (sd)		118 (17)		117 (16)	
ICU-D: adj. difference in means (95%CI)		−0.6 (−7.1 to 8.3)			
HD: adj. difference in means (95%CI)		1.2 (−5.2 to 7.7)			
3 mo: adj. difference in means (95%CI)		9.7 (0.9 to 18.5)			
6 mo: adj. difference in means (95%CI)		3.7 (−5.4 to 12.7)			
Survival					
Day 0: number at risk		150		158	
Day 50: number at risk		119		117	
Day 100: number at risk		115		107	

		Day 150: number at risk Day 200: number at risk	108 107	103 102	
ris et al., 6 (USA)	ICU discharge (ICU-D); Hospital discharge (HD); 2 mo; 4 mo; 6 mo	Physical *Physical function: SPPB* ICU-D: least square mean (95%CI) HD: least square mean (95%CI) 2 mo: least square mean (95%CI) 4 mo: least square mean (95%CI) 6 mo: least square mean (95%CI) ICU-D: difference least square mean (95%CI) HD: difference least square mean (95%CI) 2 mo: difference least square mean (95%CI) 4 mo: difference least square mean (95%CI) 6 mo: difference least square mean (95%CI) *Muscular strength: dynamometer strength* ICU-D: least square mean (95%CI) HD: least square mean lb (95%CI) 2 mo: least square mean lb (95%CI) 4 mo: least square mean lb (95%CI) 6 mo: least square mean lb (95%CI) ICU-D: difference least square mean (95%CI) HD: difference least square mean(95%CI) 2 mo: difference least square mean (95%CI) 4 mo: difference least square mean (95%CI) 6 mo: difference least square mean(95%CI) *Handgrip strength* ICU-D: least square mean kg (95%CI) HD: least square mean kg (95%CI) 2 mo: least square mean kg (95%CI) 4 mo: least square mean kg (95%CI) 6 mo: least square mean kg (95%CI) ICU-D: difference least square mean (95%CI) HD: difference least square mean (95%CI) 2 mo: difference least square mean (95%CI) 4 mo: difference least square mean (95%CI) 6 mo: difference least square mean (95%CI) *Functional performance: FPI* 2 mo: least square mean (95%CI) 4 mo: least square mean (95%CI) 6 mo: least square mean (95%CI)	 1.6 (1.0 to 2.2) 4.7 (4.0 to 5.4) 8.7 (8.1 to 9.4) 8.9 (8.2 to 9.6) 9.0 (8.3 to 9.7) −0.3 (−1.1 to 0.5) −0.01 (−1.0 to 0.9) 0.9 (−0.01 to 1.9) 1.0 (−0.03 to 1.9) 1.1 (0.04 to 2.1) 20.3 (17.9 to 22.8) 23.7 (21.6 to 25.8) 28.5 (26.3 to 30.8) 28.8 (26.5 to 31.0) 31.1 (28.8 to 33.4) −2.4 (−5.8 to 1.0) −0.2 (−3.3 to 2.9) 0.5 (−2.8 to 3.8) −0.8 (−4.1 to 2.5) 0.4 (−2.9 to 3.7) 20.0 (17.8 to 22.3) 22.6 (20.6 to 24.6) 27.2 (25.1 to 29.2) 29.0 (26.8 to 31.2) 29.3 (26.9 to 31.6) −0.8 (−4.0 to 2.3) −1.7 (−4.6 to 1.2) 1.2 (−1.8 to 4.2) 1.8 (−1.3 to 5.0) 2.0 (−1.3 to 5.4) 2.0 (1.9 to 2.1) 2.2 (2.1 to 2.3) 2.2 (2.1 to 2.4)	 1.9 (1.3 to 2.4) 4.7 (4.0 to 5.4) 7.8 (7.1 to 8.5) 8.0 (7.2 to 8.7) 8.0 (7.2 to 8.7) 22.8 (20.4 to 25.1) 23.9 (21.7 to 26.2) 28.0 (25.6 to 30.4) 29.6 (27.2 to 31.9) 30.8 (28.4 to 33.1) 20.9 (18.7 to 23.1) 24.3 (22.2 to 26.4) 26.0 (23.8 to 28.1) 27.2 (24.9 to 29.4) 27.2 (24.8 to 29.6) 2.0 (1.9 to 2.1) 2.1 (1.9 to 2.2) 2.0 (1.9 to 2.2)	 0.46 0.97 0.05 0.06 0.04 0.16 0.90 0.76 0.63 0.82 0.60 0.25 0.43 0.25 0.23

		2 mo: difference least square mean (95%CI) 4 mo: difference least square mean (95%CI) 6 mo: difference least square mean (95%CI) Cognitive *MMSE* HD: least square mean (95%CI) 2 mo: least square mean (95%CI) 4 mo: least square mean (95%CI) 6 mo: least square mean (95%CI) HD: difference least square mean (95%CI) 2 mo: difference least square mean (95%CI) 4 mo: difference least square mean (95%CI) 6 mo: difference least square mean (95%CI) Quality of life *SF-36 PCS* HD: least square mean (95%CI) 2 mo: least square mean (95%CI) 4 mo: least square mean (95%CI) 6 mo: least square mean (95%CI) HD: difference least square mean (95%CI) 2 mo: difference least square mean (95%CI) 4 mo: difference least square mean (95%CI) 6 mo: difference least square mean (95%CI) *SF-36 MCS* HD: least square mean (95%CI) 2 mo: least square mean (95%CI) 4 mo: least square mean (95%CI) 6 mo: least square mean (95%CI) HD: difference least square mean (95%CI) 2 mo: difference least square mean (95%CI) 4 mo: difference least square mean (95%CI) 6 mo: difference least square mean (95%CI)	−0.03 (−0.2 to 0.1) 0.1 (−0.03 to 0.3) 0.2 (0.04 to 0.4) 25.4 (24.7 to 26.1) 26.7 (25.9 to 27.5) 27.6 (27.0 to 28.2) 27.6 (27.0 to 28.2) 0.3 (−0.7 to 1.3) −0.1 (−1.3 to 1.1) 0.4 (−0.5 to 1.3) 0.6 (−0.2 to 1.4) 30.2 (28.4 to 32.1) 33.4 (31.4 to 35.5) 36.0 (33.8 to 38.2) 36.9 (34.6 to 39.3) −0.1 (−2.8 to 2.7) 1.2 (−1.8 to 4.3) 2.3 (−0.9 to 5.5) 3.4 (−0.02 to 7.0) 43.6 (41.5 to 45.7) 46.3 (43.8 to 48.8) 47.8 (45.5 to 50.2) 48.8 (46.3 to 51.3) 0.3 (−2.7 to 3.3) 0.1 (−3.5 to 3.7) 0.2 (−3.2 to 3.6) 2.4 (−1.2 to 6.0)	 25.1 (24.3 to 25.8) 26.8 (26.0 to 27.7) 27.2 (26.5 to 27.8) 27.0 (26.4 to 27.6) 30.3 (28.4 to 32.2) 32.2 (31.0 to 34.4) 33.7 (31.4 to 36.0) 33.5 (31.1 to 36.0) 43.3 (41.2 to 45.5) 46.2 (43.6 to 48.8) 47.7 (45.2 to 50.1) 46.4 (43.8 to 49.0)	0.74 0.11 0.02 0.55 0.86 0.37 0.17 0.96 0.43 0.16 0.05 0.86 0.96 0.91 0.19
Hodgson et al., 2016 (Australia & New Zealand)	6 mo	Mental <u>*Anxiety and depression*</u>*: HADS-total* 6 mo: mean (sd) <u>Quality of life</u> *EQ-5D VAS* 6 mo: mean (sd)	 11.6 (9.1) 61 (19)	 11.3 (7.1) 68 (19)	 0.91 0.25

		EQ-5D Utility 6 mo: mean (sd) Other *Activities of daily living: IADL* 6 mo: mean (sd)	0.63 (0.27) 6.5 (1.9)	0.63 (0.33) 7 (1.3)	0.98 0.81
Schaller et al., 2016 (Germany, Austria, USA)	3 mo after hospital discharge	Quality of life *SF-36* 3 mo: mean (sd) 3 mo: group difference mean (95%CI)	 61.3 (18.4) -1.7 (-10.1 to 6.7)	 63.0 (19.9)	 0.69
Kayambu et al., 2015 (Australia)	6 mo post discharge	Quality of life *SF-36* 6 mo: mean (sd)	 *PCS +MCS not presented. Only subscales*		
Moss et al., 2015 (USA)	1 mo; 3 mo; 6 mo after study enrolment	Physical *Physical functioning: Total CS-PFP-10* 1 mo: mean ± SEM 3 mo: mean ± SEM 6 mo: mean ± SEM *CS-PFP-10: upper body strength* 1 mo: mean ± SEM 3 mo: mean ± SEM 6 mo: mean ± SEM *CS-PFP-10: upper body flexibility* 1 mo: mean ± SEM 3 mo: mean ± SEM 6 mo: mean ± SEM *CS-PFP-10: lower body strength*: 1 mo: mean ± SEM 3 mo: mean ± SEM 6 mo: mean ± SEM *CS-PFP-10: balance & coordination*: 1 mo: mean ± SEM 3 mo: mean ± SEM 6 mo: mean ± SEM *CS-PFP-10: endurance:* 1 mo: mean ± SEM 3 mo: mean ± SEM	 19 ± 3.7 30.7 ± 3.8 39.5 ± 3.9 19.5 ± 4.0 30.1 ± 4.2 40.3 ± 4.5 31.8 ± 5.6 50.4 ± 5.3 61.1 ± 4.3 14.5 ± 3.1 23.9 ± 3.4 30.4 ± 3.9 20.7 ± 4.2 30.9 ± 3.8 40.0 ± 3.9 19.0 ± 3.7 30.8 ± 3.8	 20.9 ± 4.1 36.8 ± 4.3 44.0 ± 4.0 22.6 ± 4.6 38.5 ± 4.8 47.2 ± 4.6 30.6 ± 5.5 50.1 ± 5.2 63.6 ± 4.7 17.6 ± 3.6 31.0 ± 4.0 36.6 ± 3.8 20.7 ± 4.0 37.2 ± 4.4 43.8 ± 4.1 20.8 ± 4.1 37.1 ± 4.4	 0.73 0.29 0.43 0.61 0.19 0.29 0.87 0.97 0.69 0.52 0.18 0.26 0.77 0.28 0.51 0.74 0.28

		6 mo: mean ± SEM	39.9 ± 3.9	43.9 ± 4.1	0.49
		Mobility: TUG:			
		1 mo: mean (sd)	15.6 (13.2)	15.2 (13.8)	0.9
		3 mo: mean (sd)	13.3 (8.1)	13.3 (12.4)	1.0
		6 mo: mean (sd)	14.2 (9.6)	11.1 (7.6)	0.15
		Balance: BBS			
		1 mo: mean (sd)	40.7 (24.4)	47.3 (13.7)	0.21
		3 mo: mean (sd)	45.6 (13.6)	51.3 (7.9)	0.06
		6 mo: mean (sd)	51.1 (6.9)	51.1 (6.9)	0.98
		FTSTS			
		1 mo: mean (sd)	11.9 (8.6)	15.8 (13.8)	0.19
		3 mo: mean (sd)	11.9 (8.3)	13.2 (8.2)	0.54
		6 mo: mean (sd)	11.9 (6.4)	11.3 (7.0)	0.72
		Quality of life			
		SF-36			
		1 mo: mean (sd)	*PCS +MCS not presented. Only subscales*		
		3 mo: mean (sd)			
		6 mo: mean (sd)			
Denehy et al., 2013 (Australia)	Baseline; ICU discharge (ICU-D); hospital discharge (HD) to home; 3 mo; 6 mo; 12 mo	Physical			
		Physical function: 6MWT			
		ICU-D: mean meters (sd)	146.4 (79.4)	187.9 (126.1)	
		HD: mean meters (sd)	244.2 (124.0)	266.7 (136.8)	
		3 mo: mean meters (sd)	384.5 (147.9)	382.1 (139.4)	
		6 mo: mean meters (sd)	394.2 (156.2)	402.4 (166.6)	
		12 mo: mean meters (sd)	433.8 (150.7)	409.6 (158.5)	
		ICU-D: model estimates: mean meters (SE)	145.1 (13.3)	189.8 (13.6)	
		HD: model estimates: mean meters (SE)	241.9 (16.6)	263.4 (16.9)	
		3 mo: model estimates: mean meters (SE)	382.2 (19.9)	366.7 (19.7)	
		6 mo: model estimates: mean meters (SE)	389.9 (22.6)	394.7 (22.4)	
		12 mo: model estimates: mean meters (SE)	409.6 (22.9)	404.9 (23.0)	
		ICU-D: mean difference from usual care (95% CI)	−44.7 (−82.3 to −7.1)		0.020
		HD: mean difference from usual care (95% CI)	−21.5 (−68.4 to 25.4)		0.365
		3 mo: mean difference from usual care (95% CI)	15.4 (−40.1 to 71)		0.583
		6 mo: mean difference from usual care (95% CI)	−4.9 (−68.0 to 58.3)		0.879
		12 mo: mean difference from usual care (95% CI)	4.7 (−59.7 to 69.2)		0.884
		TUG			

		ICU-D: mean seconds (sd) HD: mean seconds (sd) 3 mo: mean seconds (sd) 6 mo: mean seconds (sd) 12 mo: mean seconds (sd) Quality of life *AQoL* Baseline: mean (sd) utility 3 mo: mean (sd) utility 6 mo: mean (sd) utility 12 mo: mean (sd) utility *SF-36 PCS* Baseline: mean (sd) 3 mo: mean (sd) 6 mo: mean (sd) 12 mo: mean (sd) *SF-36 MCS* Baseline: mean (sd) 3 mo: mean (sd) 6 mo: mean (sd) 12 mo: mean (sd)	41.1 (43.2) 18.8 (24.5) 12.2 (10.0) 9.8 (5.1) 10.3 (6.2) 0.6 (0.3) 0.5 (0.4) 0.5 (0.4) 0.5 (0.4) 39.3 (12.9) 41.0 (11.4) 41.6 (13.2) 44.7 (10.9) 41.8 (13.3) 46.0 (13.9) 45.8 (12.9) 47.9 (12.3)	36.1 (42.9) 12.9 (6.6) 11.6 (11.2) 12.9 (17.9) 14.2 (24.7) 0.6 (0.3) 0.5 (0.4) 0.6 (0.4) 0.5 (0.4) 41.7 (11.5) 42.1 (9.6) 44.4 (10.7) 46.2 (9.4) 44.3 (12.8) 46.3 (12.0) 46.2 (12.9) 44.7 (15.7)	
Chen et al., 2011 (Taiwan)	Baseline; after 6 week of training; after 6 weeks of unsupervised maintenance; 6 mo and 12 mo after enrolment	Other <u>*Functional status*</u>*: FIM: motor domain score* Baseline: median (IQR) Post training: median (IQR) After 6 weeks: median (IQR) After 6 mo: median (IQR) After 12 mo: median (IQR) <u>Functional status</u>: *FIM: cognitive domain score* Baseline: median (IQR) Post training: median (IQR) After 6 weeks: median (IQR) After 6 mo: median (IQR) After 12 mo: median (IQR) <u>Functional status</u>*: FIM: total score* Baseline: median (IQR) Post training: median (IQR) After 6 weeks: median (IQR)	 14.5 (13-18.3)* 26.5 (22-40.3)* 36 (27-49)* 47 (34-74.5)* 47 (34-91)* 19.5 (16.5-20.3) 24.5 (20.8-27.3)* 29 (23-34)* 33.5 (28-34.8)* 33 (28-35) 34 (30.3-38.3) 49 (45-66.3) 65 (54-82)*	 13 (13-14.8)* 13 (13-16.8)* 13 (13-20)* 13.5 (13-16.8)* 13.5 (13-28.3)* 18 (11-22.5)* 12.5(6-20)* 13 (5.8-22.3)* 13.5 (7.3-22.8)* 17.5 (7.8-22)* 31.5 (24-37) 26 (19-35.5)* 29 (21-45)*	

		After 6 mo: median (IQR) After 12 mo: median (IQR)	78 (60-109.3)* 78 (62-126)	28 (20.3-39)* 31 (21-50)	
1c. Exercise post ICU					
Vitacca et al., 2016 (Italy)	Hospital discharge (HD); 6 mo	Physical Maximal inspiratory pressure (MIP) HD: mean cmH_2O (95% CI) 6 mo: difference in mean cmH_2O (95% CI) Maximal expiratory pressure (MEP) HD: mean cmH_2O (95% CI) 6 mo: difference in mean cmH_2O (95% CI) Forced expiratory volume (FEV_1) in 1 second HD: % of predicted normal 6 mo: difference in % of predicted normal Forced vital capacity (FVC) HD: % predicted forced volume capacity 6 mo: difference in % predicted forced volume capacity Arterial blood gas values (PaO_2/ FiO_2) HD: mean (95% CI) 6 mo: difference in mean (95% CI) Carbon dioxide arterial tension ($PaCO_2$) HD: mean mmHg (95% CI) 6 mo: difference in mean mmHg (95% CI) Respiratory rate HD: mean a/min (95%CI) 6 mo: difference in mean a/min (95%CI) Dyspnoea: *Borg scale* HD: mean score (95%CI) 6 mo: difference in mean score (95%CI) Physical function: *MRC-SS Quadriceps* HD: mean (95%CI) 6 mo: difference in mean (95%CI) *MRC SS_biceps* HD: mean (95%CI) 6 mo: difference in mean (95%CI)	 38.16 (0 to 89) 13.76 (5.8 to 21.6) 48.85 (0 to 115) 27 (14.39) 54.15 (22.5 to 105) 9.85 (-8.5.39) 62.2 (34.5 to 112.5) 10.24 (-13.58) 319 (181 to 466) 16.19 (-85.138) 45.13 (29 to 70) -0.09 (-3.8 to 3.6) 17 (12 to 22) -1.8 (2.9 to -0.5) 2.26 (0 to 8) -1.1 (-5.4) 3.70 (2.75 to 5) 0.48 (0 to 0.88) 3.96 (2.75 to 5)	 39.95 (19 to 70) -0.2 (7.8 to 7.4) 46.30 (0 to 97) 6.4 (-5.18) 53.09 (10 to 97) -3.87 (65.22) 65.47 (33 to108) -2.47 (-90.20) 314 (125 to 442) 11.96 (-83.114) 44.83 (34 to 69) -0.33 (-5.6 to 4.9) 16 (14 to 23) -0.46 (-1.9.1) 2.82 (0 to 6) -0.3 (-10.3) 3.46 (0 to 5) 0.30 (-0.88 to 1) 3.66 (0 to 5)	 0.8433 0.007 0.7966 0.009 0.9110 0.03 0.6989 0.10 0.8502 0.86 0.9288 0.46 0.789 0.91 0.4739 0.46 0.4528 0.53 0.4720

		Quality of life *EQ-5D* HD: mean (95%CI) 6 mo: difference in mean (95%CI) Other Basic activities of daily living: *Katz ADL* HD: mean (95%CI) 6 mo: difference in mean (95%CI)	0.46 (0.4) 0.44 (0.4 to 0.84) 0.23 (-0.29 to 0.73) 2.5 (0 to 6) 0.71 (0.4)		- 0.07 (-1 to 1.13) 0.38 (0.03 to 1) 0.032 (0.29 to 0.24) 3.46 (0 to 6) 0.93 (0.4)	0.07 0.1261 0.04 0.1461 0.63
Brummel et al., 2014 (USA)	Hospital discharge (HD); 3 mo after HD	Physical Functional mobility: *TUG* HD: median (IQR) 3 mo: median (IQR) Cognitive Executive function: *Tower Test* HD: median (IQR) 3 mo: median (IQR) *DEX* HD: median (IQR) 3 mo: median (IQR) Global cognition: *MMSE* HD: median (IQR) 3 mo: median (IQR) Quality of life *EQ-5D VAS* 3 mo: median (IQR) Other Activities of daily living: *Katz ADL* HD: median (IQR) 3 mo: median (IQR) Instrument activities of daily living: *FAQ* HD: median (IQR) 3 mo: median (IQR)	I1 16.0 (12.0-22.0) 10.0 (8.0-13.0) 8.0 (3.5-9.0) 11.0 (11.0-12.0) 6.5 (3.8-10.2) 10.0 (5.0-17.0) 25.6 (23.2-27.8) 29.0 (27.0-30.0) 80 (62-89) 0.5 (0.0-4.5) 0 (0-1) 7.0 (2.8-19.5) 2.0 (0.0-4.8)	I2 17 (11.0-27.0) 11.0 (9.0-13.0) I 8.5 (5.8-10.2) 10.0 (8.0-11.0) 5.0 (3.0-9.0) 9.0 (2.0-17.5) 28.0 (25.8-29.0) 29.0 (27.9-29.8) 75 (54-80) 3.0 (1.0-6.0) 0 (0-2) 15.0 (4.5-20.0) 1.0 (0.0-3.8)	C 33.0 (18.5-68.5) 8.0 (7.5-13.5) 8.0 (4.5-11.5) 10.0 (8.8-12.2) 7.0 (3.0-11.5) 17.5 (8.5-28.8) 25.0 (24.0-28.0) 28.0 (26.8-29.0) 75 (61-86) 1.0 (0.0-2.8) 0 (0-0) 7.5 (3.5-11.8) 2.5 (0.8-5.5)	0.20 0.79 0.51 0.20 0.93 0.08 0.09 0.64 0.44 0.25 0.69 0.28 0.67
Jones et al., 2003 (UK)	Baseline (recruitment), 2 mo, 6 mo	Mental Anxiety: *HADS-Anxiety*				

		Baseline: mean (sd) 2 mo: mean (sd) 6 mo: mean (sd) <u>Depression:</u> *HADS-Depression* Baseline: mean (sd) 2 mo: mean (sd) 6 mo: mean (sd) <u>PTSD:</u> *IES-R* 2 mo: mean (sd) 6 mo: mean (sd) Other <u>Perceived social support:</u> *NSSQ* Baseline: mean (sd)	7.6 (5)* 6.5 (4.7)* 6.8 (4.7)* 6.8 (4)* 5.1 (3.3)* 5 (3.7)* 18.7 (15.4)* 24.9 (18.3)* 226.1 (137)*	7.7 4)* 5.8 (3.8)* 5.8 (4)* 6.8 (4.5)* 5.8 (4.7)* 5.1 (3.7)* 21 (17)* 26 (17.3)* 215.4 (143)*	 0.38 0.94
1d. Exercise post hospital					
Battle et al., 2018 (UK)	Baseline (1 week after recruitment), week 7, 6 mo, 12 mo	Physical <u>Physical function:</u> *6MWT* Baseline: mean (sd) 7 week: mean (sd) 6 mo: mean (sd) 12 mo: mean (sd) <u>Balance:</u> *BBS* Baseline: mean (sd) 7 week: mean (sd) 6 mo: mean (sd) 12 mo: mean (sd) <u>Grip strength left</u> Baseline: mean (sd) 7 week: mean (sd) 6 mo: mean (sd) 12 mo: mean (sd) <u>Grip strength right</u> Baseline: mean (sd) 7 week: mean (sd) 6 mo: mean (sd) 12 mo: mean (sd) Mental	 283.5 (203.2) 379.3 (207.3) 381.6 (207.9) 363.6 (239.9) 52.4 (4.8) 53.4 (6.2) 55.1 (1.9) 54.1 (4.4) 16.6 (9.7) 20.7 (11.4) 22.5 (15.6) 20.1 (12.4) 20.4 (11.6) 22.4 (10.3) 27.7 (15.9) 20.1 (12.4)	 269.7 (196.5) 283.6 (229.3) 304.8 (213.7) 294.7 (250.5) 50.7 (7.0) 50.5 (7.6) 49.7 (7.9) 47.2 (11.4) 19.1 (11.9) 19.5 (12.5) 20.5 (14.2) 24.9 (16.2) 20.1 (13.7) 22.1 (14.1) 22.7 (14.2) 24.9 (16.2)	 0.491 0.990 0.283 0.807

		Anxiety: *HADS-Anxiety*			
		Baseline: mean (sd)	5.4 (4.9)	10.3 (4.9)	0.495
		7 week: mean (sd)	3.9 (4.0)	9.3 (3.9)	
		6 mo: mean (sd)	4.9 (4.0)	8.6 (4.5)	
		12 mo: mean (sd)	3.7 (3.0)	8.6 (4.1)	
		Depression: *HADS-Depression*			
		Baseline: mean (sd)	4.9 (2.8)	8.3 (4.4)	0.761
		7 week: mean (sd)	3.7 (3.0)	7.8 (4.3)	
		6 mo: mean (sd)	4.4 (3.7)	7.3 (3.3)	
		12 mo: mean (sd)	4.0 (3.8)	7.6 (4.7)	
Shelly et al.,2017 (India)	ICU discharge (ICU-D), HD, 4 weeks	Quality of life			
		SF-36 PCS			
		ICU-D: mean (sd)	30.1 (4.6)	29.9 (3.6)	0.48
		4 wk: difference HD - 4 weeks: median (IQR)	10.3 (8.5-14.9)	7.4 (3.7-8.5)	0.003
		SF-36 MCS			
		ICU-D: mean (sd)	30.2 (6.1)	30.2 (4.8)	0.40
		difference HD - 4 weeks: median (IQR)	21.8 (15.7-24.1)	14.1 (10.8-19.5)	0.006
McDowell et al., 2016 (Northern Ireland, UK)	Baseline, 6 weeks, 6 mo	Physical			
		Physical function: *RMI*			
		Baseline: mean (sd)	10.9 (3.5)	11.8 (2.7)	
		6 wk: mean change (sd)	1.3 (2.1)	1.1 (1.8)	0.82
		Difference mean change scores (95%CI)	0.13 (-0.98 to 1.2)		
		Breathlessness: *MRC Dyspnoea scale*			
		Baseline: median (IQR)	3.0 (2.0-3.3)	2.0 (1.5-3.0)	
		6 wk: mean change (sd)	-0.14 (0.94)	0.00 (1.00)	0.63
		Difference mean change scores (95%CI)	-0.14 (-0.7 to 0.4)		
		Hand function:			
		Handheld dynamometry: Dominant hand			
		Baseline: number (% predicted score)	60.4 (31.2)	66.9 (20.1)	
		6 wk: mean change (sd)	6.1 (28.1)	12.5 (22.8)	
		Difference mean change scores (95%CI)	-6.4 (-21.2 to 8.4)		0.39
		Handheld dynamometry: Non-dominant hand			
		Baseline: number (% predicted score)	58.5 (34.7)	67.4 (21.9)	
		6 wk: mean change (sd)	9.1 (28.2)	14.0 (28.7)	
		Difference mean change scores (95%CI)	-4.9 (-21.5 to 11.7)		0.56
		NHPT: Dominant hand			
		Baseline: number (% predicted score)	75.9 (16.1)	79.0 (13.4)	

		6 wk: mean change (sd) Difference mean change scores (95%CI) *NHPT: Dominant hand* Baseline: number (% predicted score) 6 wk: mean change (sd) Difference mean change scores (95%CI) <u>Exercise capacity:</u> *ISWT* Baseline: mean (sd) 6 wk: mean change (sd) Difference mean change scores (95%CI) Mental <u>Anxiety:</u> *HADS-Anxiety* Baseline: mean (sd) 6 wk: mean change (sd) Difference mean change scores (95%CI) <u>Depression:</u> *HADS-Depression* Baseline: mean (sd) 6 wk: mean change (sd) Difference mean change scores (95%CI) Quality of life *SF-36 PCS* Baseline: mean (sd) 6 wk: mean change (sd) Difference mean change scores (95%CI) *SF-36 MCS* Baseline: mean (sd) 6 wk: mean change (sd) Difference mean change scores (95%CI) *EQ-5D VAS* Baseline: mean (sd) 6 wk: mean change (sd) Difference mean change scores (95%CI) *EQ-5D index* Baseline: mean (sd) 6 wk: mean change (sd)	9.4 (15.3) 4.1 (-3.4 to 11.7) 77.2 (14.3) 8.9 (13.7) 3.6 (-5.2 to 12.4) 166.1 (134.0) 135.5 (119.8) 83.1 (8.3 to 157.9) 10.5 (5.4) -0.59 (3.6) -0.77 (-2.7 to 1.2) 7.6 (4.9) -1.2 (4.4) -1.6 (-3.7 to 0.6) 33.0 (8.0) 7.0 (7.8) 3.8 (-0.2 to 7.8) 38.0 (14.1) 5.8 (13.6) 4.6 (-2.7 to 11.9) 61.6 (18.8) 7.4 (20.4) 0.97 (-9.9 to 11.9) 0.5 (0.3) 0.02 (0.20)	5.3 (10.7) 77.6 (15.0) 5.3 (16.1) 258.6 (171.7) 52.4 (126.7) 6.7 (4.2) 0.18 (3.3) 5.1 (3.3) 0.36 (3.1) 34.0 (8.0) 3.2 (6.7) 45.0 (12.8) 1.1 (13.1) 60.3 (18.3) 6.4 (17.9) 0.6 (0.2) 0.02 (0.17)	0.28 0.41 0.03 0.43 0.15 0.06 0.21 0.86

		Difference mean change scores (95%CI)	0.00 (-0.1 to 0.1)		0.998
		Other			
		Exercise self efficacy: *CDSES*			
		Baseline: mean (sd)	5.3 (2.5)	6.3 (2.2)	
		6 wk: mean change (sd)	1.6 (3.0)	-0.57 (2.1)	
		Difference mean change scores (95%CI)	2.2 (0.8 to 3.7)		0.01
		Functioning: *FLP Physical dimension*			
		Baseline: mean (sd)	28.0 (16.7)	21.2 (15.8)	
		6 wk: mean change (sd)	-10.0 (9.7)	-5.3 (7.5)	
		Difference mean change scores (95%CI)	-4.7 (-9.5 to 0.2)		0.06
		FLP: Psychosocial dimension			
		Baseline: mean (sd)	29.6 (21.2)	19.5 (14.8)	
		6 wk: mean change (sd)	-7.4 (12.3)	-2.4 (9.2)	
		Difference mean change scores (95%CI)	-5.0 (-11.1 to 1.1)		0.11
		FLP: overall score			
		Baseline: mean (sd)	26.8 (15.3)	19.7 (12.3)	
		6 wk: mean change (sd)	-7.8 (7.4)	-3.0 (6.3)	
		Difference mean change scores (95%CI)	-4.8 (-8.7 to -0.9)		0.02
McWilliams et al., 2016 (UK)	Baseline (6wks following hospital discharge); 8-10 weeks later	Physical			
		Anaerobic threshold			
		Baseline: mean ml O_2 KG^{-1} min^{-1} (sd)	10.3 (2.5)	10.3 (3.4)	
		Follow up: mean ml O_2 KG^{-1} min^{-1} (sd)	11.8 (3.4)	11.5 (3.7)	
		Change mean ml O_2 KG^{-1} min^{-1} (95%CI)	1.4 (0.5 to 2.3)	1.4 (0.4 to 2.3)	
		% change mean (95%CI)	14.6 (4.6 to 23.2)	11.7 (6.1 to 26.4)	
		Peak $V0_2$			
		Baseline: mean ml$O_2$$KG^{-1}$ min^{-1}% predicted (sd)	13.8 (3.7)	13.6 (3.9)	
		Follow up: mean ml$O_2$$KG^{-1}$$min^{-1}$% predicted (sd)	16.4 (4.9)	15.5 (5.4)	
		Change mean ml$O_2$$KG^{-1}$$min^{-1}$% predicted (95%CI)	2.3 (1.3 to 3.4)	2.1 (1.0 to 3.1)	
		% change mean predicted (95% CI)	18.8 (9.8 to 25.5)	14.0 (7.6 to 23)	
		Baseline: mean % peak predicted (sd)	52.3 (13.0)	56.3 (15.6)	
		Follow up: mean % peak predicted (sd)	62.4 (18.4)	62.5 (16.3)	
		Change mean ml$O_2$$KG^{-1}$$min^{-1}$% predicted (95%CI)	10.1 (4.8 to 13.5)	6.2 (2.9 to 11.2)	
		Quality of life			
		SF-36 PCS			
		Baseline: mean (sd)	31.0 (8.5)	32.6 (7.8)	

		Follow up: mean (sd) Change: adj. mean (95%CI) *SF-36 MCS* Baseline: mean (sd) Follow up: mean (sd) Change: adj. mean (95%CI)	39.6 (9.1) 8.6 (5.4 to 10.6) 38.4 (11.8) 48.6 (11.2) 10.2 (6.9 to 14.4)	36.1 (9.2) 3.5 (1.6 to 6.7) 37.0 (11.2) 41.3 (10.6) 4.3 (0.5 to 7.6)	
Connolly et al., 2015 (UK)	Hospital discharge (HD); 3 mo	Physical <u>Exercise capacity:</u> *ISWT* HD: median m (IQR) 3 mo: median m (IQR) median change (IQR) *6MWT* HD: median m (IQR) 3 mo: median m (IQR) median change (IQR) <u>Peripheral skeletal muscle strength:</u> *QMVC* HD: median kg (IQR) 3 mo: median kg (IQR) Median change (IQR) *Handgrip* HD: median kg (IQR) 3 mo: median kg (IQR) Median change (IQR) <u>Skeletal muscle size:</u> RF_{CSA} HD: median (mm^2) (IQR) 3 mo: median (mm^2) (IQR) Median change (IQR) <u>Physical function:</u> *TUG* HD: median s (IQR) 3 mo: median s (IQR) Median change (IQR) *STS-5* HD: median s (IQR) 3 mo: median s (IQR) Median change (IQR)	 55.0 (7.8-120.0) 200 (132.5-340.0) 115 (-2.5-237.5) 180.0 (125.0-221.5) 328.5 (230.0-393.8) 140.0 (35.8-210.3) 10.0 (6.6-24.6) 14.0 (8.2-26.3) 2.1 (0.8-4.5) 22.0 (9.0-22.0) 24.0 (18.0-30.0) 8.0 (4.0-9.0) 241.3 (238.3-296.3) 487.3 (344.0-519.0) 222.7 (102.7-249.0) 18.0 (13.5-125.0) 10.0 (7.3-41.5) -7.0 (-86.3- -4.0) 17.5 (14.9-27.3) 13.0 (9.3-26.5) -2.3 (-17.3-8.6)	 20.0 (10.0-60.0) 190.0 (70.0-355.0) 170 (40.0-315.0) 150 (100.5-207.0) 335.0 (177.5-455.0) 185.0 (40.0-285.0) 17.7 (16.2-20.7) 23.7 (17.8-36.7) 6.0 (1.6-16.0) 17.0 (14.0-22.0) 22.0 (17.5-28.5) 3.5 (2.0-11.3) 395.0 (343.0-487.1) 497.5 (410.6-673.6) 61.7 (36.5-261.5) 25.0 (17.3-34.0) 12.5 (8.0-19.0) -11.5 (-25.5-0.8) 23.0 (19.8-30.5) 17.3 (14.3-20.0) -3.8 (-16.3- -0.8)	

		Fat free mass			
		HD: median kg (IQR)	45.1 (38.4-55.1)	51.8 (34.6-59.9)	
		3 mo: median kg (IQR)	49.7 (42.3-51.3)	43.6 (34.4-62.9)	
		Median change (IQR)	0.6 (-3.5-5.1)	2.3 (-2.3-4.7)	
		Fat free mass index (FFMI)			
		HD: median kg/m^2 (IQR)	17.4 (13.4-19.9)	18.3 (13.0-19.7)	
		3 mo: median kg/m^2 (IQR)	16.7 (16.0-19.6)	15.5 (14.1-20.7)	
		Median change (IQR)	0.3 (-1.3-1.6)	0.7 (-0.8-1.6)	
		Mental			
		Anxiety: *HADS anxiety*			
		HD: median (IQR)	7.0 (4.5-9.3)	6.0 (1.5-11.5)	
		3 mo: median (IQR)	4.0 (1.8-5.5)	4.0 (0.8-6.0)	
		Median change (IQR)	-3.5 (−5.0- -1.3)	0.0 (-7.0- 0.0)	
		Depression: *HADS depression*			
		HD: median (IQR)	5.5 (2.8-11.0)	8.5 (7.3-10.0)	
		3 mo: median (IQR)	4.5 (1.0-7.3)	2.5 (2.0-8.0)	
		Median change (IQR)	-1.5 (-3.3-2.0)	-4.5 (-6.3- -1.8)	
		HADS total			
		HD: median (IQR)	13.0 (7.0-19.0)	14.0 (9.0-20.0)	
		3 mo: median (IQR)	9.0 (3.5-10.3)	6.5 (5.5-10.3)	
		Median change (IQR)	-6 (-9.3- -2.8)	-4.5 (-13.3- -2.5)	
		Quality of life			
		SF-36 PCS			
		HD: median (IQR)	29.8 (24.1-33.2)	20.6 (19.4-33.3)	
		3 mo: median (IQR)	33.2 (23.8-45.4)	42.3 (27.9-47.6)	
		Median change (IQR)	1.8 (-6.8-15.9)	11.0 (4.3- 28.3)	
		SF-36 MCS			
		HD: median (IQR)	31.6 (28.6-49.1)	50.9 (35.6-57.8)	
		3 mo: median (IQR)	53.4 (39.5-58.8)	45.6 (34.3-54.7)	
		Median change (IQR)	14.3 (-3.2–26.7)	-11.4 (-19.0–19.1)	
		Other			
		Barthel scale:			
		HD: median (IQR)	87.5 (65.0-96.3)	82.5 (75.0-95.0)	
		3 mo: median (IQR)	100.0 (82.5-100.0)	100.0 (88.8-100.0)	
		Median change (IQR)	7.5 (0.0-21.3)	10.0 (2.5-25.0)	

Batterham et al., 2014 (UK)	Baseline; 9 wk; 26 wk	Physical Oxygen consumption: *AT* Baseline: mean ml O_2 KG^{-1} min^{-1}(sd) 9 wk: mean ml O_2 KG^{-1} min^{-1}(sd) 26 wk: mean ml O_2 KG^{-1} min^{-1}(sd) 9 wk: difference ml O_2 KG^{-1} min^{-1}(95%CI) 26 wk: difference ml O_2 KG^{-1} min^{-1}(95%CI) Peak oxygen uptake Baseline: mean ml O_2 KG^{-1} min^{-1}(sd) 9 wk: mean ml O_2 KG^{-1} min^{-1}(sd) 26 wk: mean ml O_2 KG^{-1} min^{-1}(sd) 9 wk: difference mean ml O_2 KG^{-1} min^{-1}(95%CI) 26 wk: difference mean ml O_2 KG^{-1} min^{-1}(95%CI) Mental Anxiety: *HADS-Anxiety* Baseline: median (IQR) 9 wk: adj. mean 26 wk: adj. mean 9 wk: adj. mean difference (95%CI) 26 wk: adj. mean difference (95%CI) Depression: *HADS depression* Baseline: median (IQR) 9 wk: adj. mean 26 wk: adj. mean 9 wk: adj. mean difference (95%CI) 26 wk: adj. mean difference (95%CI) Quality of life *EQ-5D index* Baseline: median (IQR) 9 wk: adj. mean 26 wk: adj. mean 9 wk: adj. mean difference (95%CI) 26 wk: adj. mean difference (95%CI) *EQ-5D VAS* Baseline: median (IQR) 9 wk: adj. mean 26 wk: adj. mean 9 wk: adj. mean difference (95%CI)	 10.4 (3.5) 12.5 (13) 12.7 (18) 1.8 (0.4 to 3.2) 0.6 (-1.6 to 2.8) 17.7 (6.9) 21.1 (18) 22.0 (21) 0.6 (-1.8 to 3.0) 1.6 (-1.0 to 4.2) 7.0 (4.0-12.0) 6.7 (18) 6.3 (21) 0.1 (-1.6 to 1.8) -0.7 (-2.9 to 1.5) 5.0 (2.0-8.5) 4.1(18) 4.0 (21) -0.8 (-2.1 to 0.5) -0.8 (-2.6 to 1.0) 0.689 (0.258-0.822) 0.700 (18) 0.669 (21) 0.016 (-0.104 to 0.137) -0.043 (-0.174 to 0.088) 61 (26) 70.1 (18) 70.0 (20) -0.2 (-8.7 to 8.3)	 10.4 (2.8) 10.7 (17) 12.1 (20) 17.8 (7.7) 20.5 (21) 20.4 (23) 7.0 (2.5-11.0) 6.6 (23) 7.0 (25) 3.0 (1.0-7.5) 4.9 (23) 4.8 (25) 0.725 (0.516-0.814) 0.684 (23) 0.712 (25) 64 (23) 70.3 (22) 74.1 (24)	

		26 wk: adj. mean difference (95%CI)	-4.1 (-14.9 to 6.7)		
Jackson et al., 2012 (USA)	Hospital discharge (HD); 3 mo	Physical Physical function: *TUG* HD: median (IQR) 3 mo: median (IQR) *ABC* HD: median (IQR) (%) 3 mo: median (IQR) (%) Cognitive Cognitive function: *TOWER* Baseline: median (IQR) 3 mo: median (IQR) *MMSE* HD: median (IQR) 3 mo: median (IQR) *DEX* HD: median (IQR) 3 mo: median (IQR) Other Daily functioning: *FAQ* HD: median (IQR) 3 mo: median (IQR) *KATZ ADL* HD: little to no dependency (%) 3 mo: little to no dependency(%) HD: moderate to severe dependency(%) 3 mo: moderate to severe dependency(%)	 18 (15-20) 9.0 (8.5-11.8) 68 (36-81) 82 (78-89) 8.0 (6.5-10.0) 13.0 (11.5-14.0) 28.0 (25-29) 30.0 (29.0-30.0) 13.0 (8.0-15.0) 8.0 (6.0-13.5) 0.0 (0.0-4.0) 1.0 (0.0-2.5) 71 100 29 0	 15 (12-20) 10.2 (9.2-11.7) 54 (28-75) 83 (38-91) 7.5 (4.5-9.0) 7.5 (4.0-8.5) 27 (22.5-28.2) 26.5 (24.8-28.5) 27.0 (13.5-31.0) 16.0 (7.8-19.2) 7.0 (1.5-14.2) 8.0 (6.0-11.8) 75 75 25 25	 0.47 0.51 0.58 0.35 0.37 <0.01 0.54 0.25 0.12 0.74 0.14 0.04
Elliott et al., 2011 (Australia)	Within 1 week of hospital discharge (HD); 8 weeks, 26 weeks post discharge	Physical Functional exercise capacity: *6MWT* Baseline: mean meters (sd) 8 week: mean change (95%CI) 26 week: mean change (95%CI) 8 week: effect size (mean change baseline) 26 week: effect size (mean change baseline) 8 week: difference (95%CI) 26 week: difference (95%CI)	 291 (129) 88.7 (62.6 to 114.8) 125.8 (98.7 to 152.9) 0.69 0.98 8.4 (-29.6 to 46.4) 9.6 (-31.4 to 50.5)	 324 (143) 80.3 (52.3 to 108.3) 116.2 (85.6 to 146.8) 0.55 0.80	

		8 week: effect size (I - C mean change/pooled sd) 26 week: effect size(I - C mean change/pooled sd) Quality of life *SF-36 PCS* Baseline: mean (sd) 8 week: mean change, effect size 26 week: mean change, effect size 8 week: effect size (mean change baseline) 26 week: effect size (mean change baseline) 8 week: difference (95%CI) 26 week: difference (95%CI) 8 week: effect size(I-C mean change/pooled sd) 26 week: effect size(I-C mean change/pooled sd) *SF-36 MCS* Baseline: mean (sd) 8 week: mean change, effect size 26 week: mean change, effect size 8 week: effect size (mean change baseline) 26 week: effect size (mean change) 8 week: difference (95% CI) 26 week: difference (95% CI) 8 week: effect size (I-C mean change/pooled sd) 26 week: effect size (I-C mean change/pooled sd)	0.07 0.08 31.7 (10.0) 8.6 (6.6 to 10.5) 10.9 (8.2 to 13.6) 0.87 1.11 -1.3 (-4.3 to 1.7) 0.3 (-3.2 to 3.7) -0.14 0.03 36.7 (15.1) 9.7 (6.4 to 12.9) 9.6 (6.1 to 13.1) 0.66 0.65 1.8 (-2.6 to 6.2) 1.5 (-3.1 to 6.2) 0.13 0.10	 32.7 (8.6) 9.9 (7.6 to 12.2) 10.6, (8.4 to 12.8) 1.10 1.18 39.8 (13.5) 7.8 (4.8 to 10.9) 8.1 (5.0 to 11.2) 0.59 0.61	
2.Follow-up services					
Jonasdottir et al., 2017 (Iceland)	Ward discharge; 3 mo; 6 mo; 12 mo after ICU discharge	Mental <u>PTSD:</u> *IES-R* 3 mo: mean (sd) 6 mo: mean (sd) 12 mo: mean (sd) *IES-R ≥28-88* 3 mo: mean (sd) 6 mo: mean (sd) 12 mo: mean (sd) <u>Anxiety: *HADS anxiety*</u> Ward discharge: mean (sd) 3 mo: mean (sd)	 11 (16) 18 (18) 20 (17) 36 (13) 39 (14) 37 (14) 4.0 (4.1) 4.4 (4.2)	 12 (14) 13 (16) 14 (15) 33 (11) 50 (9) 39 (11) 2.7 (3.8) 2.8 (3.1)	 0.157 0.097 0.066 0.422 0.039 0.613 0.064 0.011

		6 mo: mean (sd) 12 mo: mean (sd) <u>Depression:</u> *HADS depression*: Ward discharge: mean (sd) 3 mo: mean (sd) 6 mo: mean (sd) 12 mo: mean (sd)	3.7 (3.6) 4.0 (3.2) 4.3 (3.4) 3.7 (3.4) 4.7 (3.9) 3.8 (2.9)	2.4 (2.8) 2.5 (2.8) 4.0 (3.4) 3.5 (3.0) 3.4 (3.2) 3.7 (3.6)	0.030 0.005 0.539 0.745 0.053 0.895
Jensen et al., 2016 (Denmark)	3 mo after ICU discharge, 12 mo after ICU discharge	Mental <u>Anxiety:</u> *HADS- Anxiety* 3 mo (ITT): absolute difference C vs I (95%CI) 12 mo (ITT): absolute difference C vs I (95%CI) 3-12 mo (ITT):absolute difference C vs I (95%CI) 3 mo (PP): absolute difference C vs I (95%CI) 12 mo (PP): absolute difference C vs I (95%CI) 3-12 mo (PP): absolute difference C vs I (95%CI) <u>Depression:</u> *HADS- Depression* 3 mo (ITT): absolute difference C vs I (95%CI) 12 mo (ITT): absolute difference C vs I (95%CI) 3-12 mo (ITT):absolute difference C vs I (95%CI) 3 mo (PP): absolute difference C vs I (95%CI) 12 mo (PP): absolute difference C vs I (95%CI) 3-12 mo (PP): absolute difference C vs I (95%CI) <u>PTSD severity:</u> *HTQ-IV* 3 mo (ITT): absolute difference C vs I (95%CI) 12 mo (ITT): absolute difference C vs I (95%CI) 3-12 mo (ITT):absolute difference C vs I (95%CI) 3 mo (PP): absolute difference C vs I (95%CI) 12 mo (PP): absolute difference C vs I (95%CI) 3-12 mo (PP): absolute difference C vs I (95%CI) Quality of life *SF-36 PCS* 3 mo (ITT): absolute difference C vs I (95%CI) 12 mo (ITT): absolute difference C vs I (95%CI) 3-12 mo (ITT):absolute difference C vs I (95%CI) 3 mo (PP): absolute difference C vs I (95%CI) 12 mo (PP): absolute difference C vs I (95%CI) 3-12 mo (PP): absolute difference C vs I (95%CI) *SF-36 MCS*	 -0.16 (-1.15 to 0.82) -0.21 (-1.22 to 0.80) -0.05 (-0.99 to 0.89) -0.26 (-1.29 to 0.77) -0.37 (-1.46 to 0.71) -0.22 (-1.23 to 0.76) 0.10 (-0.84 to 1.03) -0.20 (-1.12 to 0.72) -0.31 (-1.19 to 0.57) 0.24 (-0.77 to 1.25) -0.07 (-1.08 to 0.93) -0.59 (-1.50 to 0.31) 0.24 (-2.07 to 2.55) -1.42 (-3.94 to 1.11) -0.89 (-3.13 to 1.35) 0.06 (-2.40 to 2.51) -1.58 (-4.27 to 1.10) -1.23 (-3.62 to 1.17) 1.87 (-0.93 to 4.67) 1.41 (-1.53 to 4.35) 0.24 (-2.15 to 2.62) 0.60 (-2.38 to 3.57) 0.67 (-2.60 to 3.94) 0.72 (-1.74 to 3.17) 	 0.75 0.68 0.92 0.62 0.51 0.66 0.84 0.67 0.48 0.64 0.89 0.20 0.84 0.27 0.43 0.96 0.25 0.31 0.19 0.35 0.85 0.69 0.69 0.56

		3 mo (ITT): absolute difference C vs I (95%CI) 12 mo (ITT): absolute difference C vs I (95%CI) 3-12 mo (ITT):absolute difference C vs I (95%CI) 3 mo (PP): absolute difference C vs I (95%CI) 12 mo (PP): absolute difference C vs I (95%CI) 3-12 mo (PP): absolute difference C vs I (95%CI) Other <u>Orientation to life:</u> *SOC* 3 mo (ITT): absolute difference C vs I (95%CI) 12 mo (ITT): absolute difference C vs I (95%CI) 3-12 mo (ITT):absolute difference C vs I (95%CI) 3 mo (PP): absolute difference C vs I (95%CI) 12 mo (PP): absolute difference C vs I (95%CI) 3-12 mo (PP): absolute difference C vs I (95%CI)	-0.41 (-3.20 to 2.39) 1.92 (-1.06 to 4.90) 1.63 (-1.38 to 4.63) -0.17 (-3.19 to 2.84) 1.32 (-1.87 to 4.51) 1.84 (-1.39 to 5.07) 2.02 (-1.35 to 5.38) -0.93 (-4.72 to 2.85) -2.44 (-6.07 to 1.19) 2.90 (-0.60 to 6.40) -0.34 (-4.38 to 3.71) -1.64 (-5.46 to 2.19)		0.78 0.21 0.29 0.91 0.42 0.26 0.24 0.63 0.19 0.11 0.87 0.40
Schmidt et al., 2016 (Germany)	6 mo; 12 mo post ICU	Physical <u>Physical function:</u> *XSMFA-F* 6 mo: median (IQR) 12 mo: median (IQR) 6 mo: estimated treatment effect (95%CI) 12 mo: estimated treatment effect (95%CI) <u>Disability:</u> *XSMFA-B* 6 mo: median (IQR) 12 mo: median (IQR) 6 mo: estimated treatment effect (95%CI) 12 mo: estimated treatment effect (95%CI) <u>Disability:</u> GCPS-DS Baseline: mean difference (sd) 6 mo: mean difference (sd) 12 mo: mean difference (sd) 6 mo: estimated treatment effect (95%CI) 12 mo: estimated treatment effect (95%CI) <u>Pain:</u> *GCPS-PI* Baseline: mean difference (sd) 6 mo: mean difference (sd) 12 mo: mean difference (sd) 6 mo: estimated treatment effect (95%CI) 12 mo: estimated treatment effect (95%CI) <u>Malnutrition:</u> *MUST*	 31 (12-58) 17 (6-54) -8.9 (-17.0 to -0.7) -6.8 (-15.0 to 1.5) 38 (12-69) 25 (6-50) -9.9 (-18,5 to -1.2) -8.6 (-17.2 to 0.1) 36.0 (34.5) -8.0 (36.9) -14.8 (34.0) -2.4 (-12.9 to 8.1) -7.2 (-17.3 to 2.8) 43.7 (25.6) -6.8 (23.7) -11.7 (22.1) 1.0 (-6.0 to 7.9) -2.1 (-9.4 to 5.2)	 46 (17-76) 36 (9-61) 56 (25-81) 38 (11-69) 36.4 (34.8) -5.6 (40.5) -7.6 (37.1) 43.9 (23.1) -7.7 (27.9) -9.6 (28.9)	 0.04 0.15 0.03 0.06 0.65 0.16 0.78 0.57

		Baseline: > low risk, n (%)	12 (8.3)	11 (8.3)	
		6 mo: > low risk, n (%)	8 (7.3)	9 (8.8)	
		12 mo: > low risk, n (%)	5 (4.7)	6 (6.4)	
		6 mo: estimated treatment effect (95%CI)	0.8 (0.3 to 2.5)		0.80
		12 mo: estimated treatment effect (95%CI)	0.7 (0.2 to 3.0)		0.76
		Neuropathy: *NSS*			
		Baseline: mean difference (sd)	3.6 (3.3)	3.7 (3.1)	
		6 mo: mean difference (sd)	0.6 (3.3)	0.6 (3.4)	
		12 mo: mean difference (sd)	0.9 (3.5)	0.7 (3.5)	
		6 mo: estimated treatment effect (95%CI)	0.0 (-0.9 to 0.9)		0.98
		12 mo: estimated treatment effect (95%CI)	0.1 (-0.8 to 1.1)		0.77
		Insomnia: *RIS*			
		6 mo: median (IQR)	10 (7-14)	11 (7-18)	
		12 mo: median (IQR)	9 (6-13)	12 (7-15)	
		6 mo: estimated treatment effect (95%CI)	-1.9 (-3.7 to -0.1)		0.14
		12 mo: estimated treatment effect (95%CI)	-1.8 (-3.5 to -0.1)		0.03
		Mental			
		Depression: *MDI*			
		Baseline: mean (sd)	18.4 (9.8)	17.8 (10.1)	
		6 mo: difference mean (sd)	-6.9 (10.3)	-6.9 (10.7)	
		12 mo: difference mean (sd)	-8.8 (10.4)	-7.4 (11.7)	
		6 mo: estimated treatment effect (95%CI)	-0.0 (-2.8 to 2.8)		0.99
		12 mo: estimated treatment effect (95%CI)	-1.4 (-4.5 to 1.7)		0.36
		PTSS: *PTSS-10*			
		Baseline: mean (sd)	24.0 (11.0)	23.2 (9.7)	
		6 mo: difference mean (sd)	-2.0 (11.0)	-0.2 (11.2)	
		12 mo: difference mean (sd)	-2.1 (12.9)	0.2 (10.9)	
		6 mo: estimated treatment effect (95%CI)	-1.8 (-4.8 to 1.2)		0.24
		12 mo: estimated treatment effect (95%CI)	-2.3 (-5.6 to 1.0)		0.17
		Cognitive			
		Cognitive status: *TICS-M*			
		Baseline: mean (sd)	33.7 (3.4)	33.1 (3.9)	
		6 mo: difference mean (sd)	0.4 (3.9)	0.7 (4.0)	
		12 mo: difference mean (sd)	0.8 (4.1)	1.3 (4.5)	
		6 mo: estimated treatment effect (95%CI)	-0.3 (-1.3 to 0.8)		0.63
		12 mo: estimated treatment effect (95%CI)	-0.5 (-1.7 to 0.7)		0.39
		Quality of life			

		SF-36 PCS			
		Baseline: mean (sd)	25.9 (9.4)	24.7 (8.0)	
		6 mo: difference mean (sd)	5.6 (13.1)	6.2 (12.3)	
		12 mo: difference mean (sd)	9.5 (12.3)	8.4 (13.5)	
		6 mo: estimated treatment effect (95%CI)	-0.6 (-4.1 to 3.0)		0.75
		12 mo: estimated treatment effect (95%CI)	1.1 (-2.7 to 4.9)		0.56
		SF-36 MCS			
		Baseline: mean (sd)	48.8 (12.5)	49.2 (12.6)	
		12 mo: difference: mean (sd)	3.7 (13.4)	2.3 (12.6)	
		12 mo: estimated treatment effect (95%CI)	-1.4 (-2.4 to 5.2)		0.47
		Other			
		Functional outcome: *ADL*			
		6 mo: median (IQR)	10 (7-11)	8 (6-11)	
		12 mo: median (IQR)	10 (8-11)	10 (6-11)	
		6 mo: estimated treatment effect (95%CI)	(0.2 to 1.8)		0.03
		12 mo: estimated treatment effect (95%CI)	0.9 (0.0 to 1.7)		0.05
Cuthbertson et al., 2009 (UK)	6 mo, 12 mo	Mental			
		PTSD/ Trauma: *Davidson incidence*			
		6 mo: mean (sd)	16.1 (15.7)	19.5 (16.7)	
		12 mo: mean (sd)	13.7 (14.5)	17.1 (14.7)	
		6 mo: effect size (95%CI)	-3.6 (-7.6 to 0.4)		0.07
		12 mo: effect size (95%CI)	-3.7 (-7.4 to 0.0)		0.05
		Davidson severity			
		6 mo: mean (sd)	12.3 (14.1)	15.1 (15.8)	
		12 mo: mean (sd)	10.3 (13.9)	11.9 (13.3)	
		6 mo: effect size (95%CI)	-3.1 (-6.7 to 0.6)		0.10
		12 mo: effect size (95%CI)	-1.6 (-5.0 to 1.9)		0.37
		Anxiety: *HADS anxiety*			
		Baseline: median (IQR)	7.0 (3-10)	7.0 (4-10)	
		6 mo: mean (sd) (ITT)	6.0 (4.5)	7.0 (4.6)	
		12 mo: mean (sd) (ITT)	5.5 (4.6)	6.4 (4.4)	
		6 mo: effect size (95%CI)	-0.9 (-2.0 to 0.1)		0.09
		12 mo: effect size (95%CI)	-0.8 (-1.9 to 0.4)		0.18
		Depression: *HADS depression*			
		Baseline: median (IQR)	6 (3-9)	5 (3-9)	
		6 mo: mean (sd) (ITT)	5.3 (4.3)	5.3 (4.0)	
		12 mo: mean (sd) (ITT)	NR	N.R.	
		6 mo: effect size (95%CI)	-0.0 (-1.0 to 1.0)		0.99

		12 mo: effect size (95%CI)	-0.1 (-1.2 to 1.0)		0.86
		Quality of life			
		SF-36 PCS			
		Baseline: mean (sd)	33.4 (10.0)	32.6 (9.9)	
		6 mo: mean (sd) (ITT)	39.8 (9.5)	40.1 (11.7)	
		12 mo: mean (sd) (ITT)	42.0 (10.6)	40.8 (11.9)	
		12 mo: mean (sd) (PP)	42.3 (10.8)	40.8 (11.9)	
		12 mo: mean (sd) (TRA)	42.3 (10.8)	40.7 (11.7)	
		6 mo: effect size (95%CI)	-0.8 (-3.6 to 2.0)		0.59
		12 mo: ITT effect size (95%CI)	1.1 (-1.9 to 4.2)		0.46
		SF-36: PCS: 12 mo: PP effect size (95%CI)	1.6 (-1.6 to 4.8)		0.33
		SF-36: PCS: 12 mo: TRA effect size (95%CI)	1.7 (-1.4 to 4.8)		0.27
		SF-36: MCS			
		Baseline: mean (sd)	40.9 (15.2)	41.4 (14.2)	
		6 mo: mean (sd) (ITT)	44.7 (14.2)	45.2 (12.0)	
		12 mo: mean (sd) (ITT)	47.1 (12.7)	46.8 (12.4)	
		12 mo: mean (sd) (PP)	48.5 (11.8)	46.8 (12.4)	
		12 mo: mean (sd) (TRA)	48.5 (11.8)	45.8 (13.0)	
		6 mo: effect size (95%CI)	-0.6 (-3.9 to 2.8)		0.74
		12 mo: ITT effect size (95%CI)	0.4 (-3.0 to 3.7)		0.83
		12 mo: PP effect size (95%CI)	1.7 (-1.7 to 5.1)		0.33
		12 mo: TRA effect size (95%CI)	2.6 (-0.8 to 6.0)		0.14
		EQ-5D			
		Baseline: median (IQR)	0.52 (0.26-0.73)	0.49 (0.19-0.69)	
		6 mo: mean (sd) (ITT)	0.63 (0.31)	0.62 (0.3)	
		12 mo: mean (sd) (ITT)	0.58 (0.37)	0.60 (0.3)	
		6 mo: effect size (95%CI)	0.0 (-0.1 to 0.1)		0.83
		12 mo: effect size (95%CI)	-0.0 (-0.1 to 0.1)		0.57
Douglas et al., 2007 (USA)	ICU stay; discharge; 2 mo	Quality of life Baseline: mean (sd) Discharge: mean (sd) 2 mo: mean (sd) Other <u>Daily living activities/ instrumental activities:</u> *OASIS* Baseline: mean (sd) Discharge: mean (sd) 2 mo: mean (sd)	*PCS and MCS not presented. Only subscales* NA 24.5 (11.6) NA	 NA 22.5 (13.5) NA	 0.33
3.Psychosocial program					

Cox et al., 2018 *(USA)*	Baseline, 1 mo, 3 mo	Mental Depression: *PHQ-9* Baseline: model estimated mean (SE) 1 mo: model estimated mean (SE) 3 mo: model estimated mean (SE) 1 mo: mean change from baseline (95%CI) 3 mo: mean change from baseline (95%CI) Anxiety: *GAD-7* Baseline: model estimated mean (SE) 1 mo: model estimated mean (SE) 3 mo: model estimated mean (SE) 1 mo: mean change from baseline (95%CI) 3 mo: mean change from baseline (95%CI) PTSD symptoms: *PTSS* Baseline: model estimated mean (SE) 1 mo: model estimated mean (SE) 3 mo: model estimated mean (SE) 1 mo: mean change from baseline (95%CI) 3 mo: mean change from baseline (95%CI) Distress associated with physical symptoms: *PHQ-15* Baseline: model estimated mean (SE) 1 mo: model estimated mean (SE) 3 mo: model estimated mean (SE) 1 mo: mean change from baseline (95%CI) 3 mo: mean change from baseline (95%CI) Mindfulness skills: *CAMS-R* Baseline: model estimated mean (SE) 1 mo: model estimated mean (SE) 3 mo: model estimated mean (SE) 1 mo: mean change from baseline (95%CI) 3 mo: mean change from baseline (95%CI) Coping skills: *BCOPE* Baseline: model estimated mean (SE) 1 mo: model estimated mean (SE) 3 mo: model estimated mean (SE) 1 mo: mean change from baseline (95%CI) 3 mo: mean change from baseline (95%CI)	I1 8.2 (0.8) 4.4 (0.9) 3.4 (0.9) −3.8 (−5.6 to −1.9) −4.8 (−6.6 to −2.9) 4.8 (0.7) 3.4 (0.8) 2.8 (0.8) −1.4 (−3.0 to 0.1) −2.1 (−3.7 to −0.5) 22.1 (1.9) 20.5 (2.0) 19.6 (2.1) −1.7 (−5.3 to 2.0) −2.6 (−6.3 to 1.2) 10.1 (0.7) 6.9 (0.8) 4.7 (0.8) −3.1 (−4.8 to −1.5) −5.3 (−7.0 to −3.7) 31.9 (1.1) 31.0 (1.2) 32.6 (1.3) −0.9 (−3.2 to 1.3) 0.7 (−1.7 to 3.0) 14.5 (0.7) 14.6 (0.8) 14.1 (0.8) 0.05 (−1.4 to 1.5) −0.5 (−1.9 to 1.0)	I2 7.6 (0.8) 4.6 (1.4) 3.1 (1.4) −2.4 (−4.2 to −0.7) −3.9 (−5.6 to −2.2) 5.1 (0.7) 2.8 (1.2) 2.9 (1.2) −1.7 (−3.1 to −0.2) −1.6 (−3.0 to −0.1) 21.9 (1.9) 19.7 (3.0) 19.2 (3.0) −1.7 (−5.2 to 1.7) −2.2 (−5.6 to 1.2) 10.1 (0.7) 8.4 (1.2) 7.3 (1.2) −2.6 (−4.1 to −1.1) −3.7 (−5.2 to −2.2) 31.2 (1.1) 28.7 (1.8) 29.2 (1.8) −1.4 (−3.5 to 0.8) −0.9 (−3.1 to 1.3) 13.0 (0.7) 15.2 (1.2) 15.2 (1.2) 1.4 (0.04 to 2.7) 1.3 (−0.03 to 2.7)	 7.1 (1.1) 5.8 (1.1) 4.0 (1.1) −1.3 (−3.5 to 0.9) −3.0 (−5.3 to 0.8) 4.5 (1.0) 4.1 (1.0) 3.9 (1.0) −0.4 (−2.3 to 1.5) −0.6 (−2.5 to 1.3) 21.4 (2.4) 20.4 (2.5) 17.9 (2.5) −1.0 (−5.4 to 3.5) −3.5 (−8.0 to 1.0) 11.0 (0.9) 7.6 (0.9) 6.3 (1.0) −3.4 (−5.4 to 1.5) −4.8 (−6.8 to 2.7) 30.1 (1.5) 30.0 (1.5) 28.8 (1.5) −0.1 (−2.9 to 2.6) −1.3 (−4.1 to 1.5) 13.8 (1.0) 13.1 (1.0) 13.6 (1.0) −0.8 (−2.5 to 1.0) −0.2 (−2.0 to 1.6)

		Quality of life *EQ-5D VAS* Baseline: model estimated mean (SE) 1 mo: model estimated mean (SE) 3 mo: model estimated mean (SE) 1 mo: mean change from baseline (95%CI) 3 mo: mean change from baseline (95%CI)	 80.4 (3.3) 72.9 (3.7) 77.6 (3.8) −7.5 (−15.1 to 0.2) −2.7 (−10.6 to 5.1)		 74.3 (3.3) 72.6 (5.7) 75.0 (5.7) 0.8 (−6.4 to 8.0) 3.2 (−4.0 to 10.4)		 71.8 (4.3) 72.5 (4.4) 72.5 (4.5) 0.7 (−8.6 to 9.9) 0.7 (−8.9 to 10.1)	
Cox et al., 2017 (USA)	Baseline (pre randomization), 3 mo, 6 mo	Mental <u>Anxiety:</u> *HADS anxiety* Baseline: estimate mean difference (SE) 3 mo: estimate mean difference (SE) 6 mo: estimate mean difference (SE) 3 mo: mean difference change baseline (95%CI) 6 mo: mean difference change baseline (95%CI) <u>Depression:</u> *HADS depression* Baseline: estimate mean difference (SE) 3 mo: estimate mean difference (SE) 6 mo: estimate mean difference (SE) 3 mo: mean difference change baseline (95%CI) 6 mo: mean difference change baseline (95%CI) *HADS total* Baseline: estimate mean difference (SE) 3 mo: estimate mean difference (SE) 6 mo: estimate mean difference (SE) 3 mo: mean difference change baseline (95%CI) 6 mo: mean difference change baseline (95%CI) <u>PTSD:</u> *IES-R* Baseline: estimate mean difference (SE) 3 mo: estimate mean difference (SE) 6 mo: estimate mean difference (SE) 3 mo: mean difference change baseline (95%CI) 6 mo: mean difference change baseline (95%CI) <u>Coping:</u> BCOPE Baseline: estimate mean difference (SE) 3 mo: estimate mean difference (SE) 6 mo: estimate mean difference (SE) 3 mo: mean difference change baseline (95%CI) 6 mo: mean difference change baseline (95%CI)	 8.3 (0.4) 8.6 (0.6) 8.3 (0.6) 0.3 (-1.0 to 1.6) -0.2 (-1.6 to 1.2) 7.6 (0.4) 7.6 (0.5) 7.0 (0.6) 0.9 (-0.4 to 2.1) -0.2 (-1.6 to 1.2) 16.0 (0.6) 16.6 (0.9) 15.6 (1.0) 1.3 (-0.9 to 3.4) -0.3 (-2.7 to 2.0) 31.6 (2.1) 31.0 (2.6) 29.4 (2.9) 3.1 (-1.9 to 8.1) 3.6 (-2.7 to 10.0) 32.4 (0.8) 30.3 (1.0) 29.6 (1.1) -0.8 (-3.0 to 1.4) -0.4 (-2.9 to 2.1)		 8.3 (0.4) 8.3 (0.6) 8.5 (0.6) 7.6 (0.4) 6.7 (0.5) 7.2 (0.6) 16.0 (0.6) 15.3 (0.9) 15.9 (1.0) 31.6 (2.1) 27.9 (2.6) 25.8 (2.9) 32.4 (0.8) 31.1 (1.0) 30.0 (1.1)		 0.65 0.78 0.16 0.76 0.24 0.78 0.22 0.26 0.49 0.75

		Quality of life *EQ-5D VAS* Baseline: estimate mean difference (SE) 3 mo: estimate mean difference (SE) 6 mo: estimate mean difference (SE) 3 mo: mean difference change baseline (95%CI) 6 mo: mean difference change baseline (95%CI) Other <u>Global physical health:</u> *PROMIS* Baseline: estimate mean difference (SE) 3 mo: estimate mean difference (SE) 6 mo: estimate mean difference (SE) 3 mo: mean difference change baseline (95%CI) 6 mo: mean difference change baseline (95%CI) <u>Global physical health:</u> *PROMIS* Baseline: estimate mean difference (SE) 3 mo: estimate mean difference (SE) 6 mo: estimate mean difference (SE) 3 mo: mean difference change baseline (95%CI) 6 mo: mean difference change baseline (95%CI) <u>Self efficacy:</u> *Lorig* Baseline: estimate mean difference (SE) 3 mo: estimate mean difference (SE) 6 mo: estimate mean difference (SE) 3 mo: mean difference change baseline (95%CI) 6 mo: mean difference change baseline (95%CI)	 63.7 (2.7) 62.3 (3.3) 61.0 (3.2) -3.0 (-9.6 to 3.6) 0.3 (-5.9 to 6.6) 10.9 (0.3) 11.6 (0.4) 12.0 (0.4) -0.3 (-1.3 to 0.6) 0.4 (-0.5 to 1.4) 12.2 (0.4) 11.4 (0.5) 11.9 (0.5) -0.7 (-1.8 to 0.3) 0.08 (-0.9 to1.1) 5.8 (0.3) 5.8 (0.3) 6.2 (0.3) 0.3 (-0.3 to 1.0) 0.4 (-0.2 to 1.0)	 63.7 (2.7) 65.3 (3.3) 60.7 (3.1) 10.9 (0.3) 11.9 (0.4) 11.5 (0.4) 12.2 (0.4) 12.1 (0.5) 11.8 (0.5) 5.8 (0.3) 5.4 (0.3) 5.8 (0.3)	 0.37 0.92 0.53 0.36 0.16 0.88 0.31 0.23
Agren et al., 2015 (Sweden)	Hospital discharge (HD); 3 mo, 12 mo	Mental <u>Depression:</u> *BDI-II* Baseline: score 14-63: n (%) 3 mo: score 14-63: (n (%) 12 mo: score 14-63: (n (%) Quality of life *SF-36 PCS* Baseline: mean (sd) 3 mo: mean (sd) 12 mo: mean (sd) *SF-36 MCS*	 10.2 (7.4)* 5.1 (6.3)* 7.7 (5.5)* 33.6 (6.8)* 39.7 (11.2)* 13.8 (9.9)*	 8.5 (5.5)* 6.8 (7.2)* 13.6 (13.8)* 31.8 (8.8)* 36.7 (14.4)* 37.9 (13.1)*	

		Baseline: mean (sd) 3 mo: mean (sd) 12 mo: mean (sd) Other Perception of control: *CAS* Baseline: mean (sd) 3 mo: mean (sd) 12 mo: mean (sd)	40.2 (12.7)* 50.6 (12.7)* 48.9 (12.0)* *Numbers not reported*		43.4 (14.0)* 51.7 (11.1)* 45.7 (11.4)*	
4. Diary						
Garrouste et al., 2012 (France)	3 mo and 12 mo after ICU discharge	Mental Anxiety: *HADS-Anxiety* 3 mo: n (%) 3 mo: mean (sd) Depression: *HADS- Depression* 3 mo: n (%) 3 mo: mean (sd) Traumatic stress: *PDEQ* 3 mo: mean (sd) 3 mo: median (IQR) 3 mo: score: > 15, n (%) *IES-R*: 12 mo: total score: mean (sd) 12 mo: total score: median (IQR) 12 mo: total score: score > 22	 2 (10.5) 5.0 (3.7)* 3 (15.8) 3.7 (5.1)* 22.5 (10.1) 13 (22-28) 10 (66.7) 21 (12.2) 21 (11-30.5) 10 (50)	C1 6 (28.6) 6.2 (4.5)* 8 (38.1) 6.3 (6.9)* 27 (10.2) 20 (28-35) 16 (76.2) 34.6 (15.9) 35 (17-48) 11 (64.7)	C2 4 (33.3) 7.3 (2.8) 5 (41.7) 6.5 (4.7)* 27.9 (9.5) 20 (31-37) 9 (81.8) 29.8 (15.1) 26 (22-44) 14 (73.7)	 0.28 0.21 0.27 0.66 0.03 0.30
Jones et al., 2010 (UK, Denmark, Italy, Norway, Portugal, Sweden)	1 mo; 3 mo post ICU	Mental PTSS: *Total PTSS 14 score* 1 mo: median (range) 3 mo: median (range) *PDS ICU seen as traumatic* 3 mo: n (%) *New onset PTSD* 3 mo: n (%)	 22.5 (14-84) 24 (±12.2) 70 (43.2) 8 (5)		 25 (13-65) 24 (±11.6) 76 (47.5) 21 (13.1)	 NS NS 0.36 0.02
Knowles et al., 2009 (UK)	1 mo post ICU discharge, 3 weeks later	Mental Anxiety: *HADS anxiety* 1 mo: mean (sd) 2 mo: mean (sd) 1 mo: median	 6.61 (3.88) 4.72 (2.99) 7.00		 7.22 (4.60) 6.59 (4.50) 7.00	

		2 mo: median Mean change Median change Depression: *HADS depression*: 1 mo: mean (sd) 1 mo: mean (sd) 2 mo: mean (sd) 1 mo: median 2 mo: median Mean change Median change	4.50 -1.83 (3.03) -1.5 6.72 (4.64) 4.17 (2.98) 6.00 4.00 -2.56 (3.26) -2.00	6.00 -0.65 (2.64) -1.00 8.89 (5.12) 8.29 (5.13) 9.00 7.00 -0.18 (2.48) 0.00	
5. Information/ education program					
Demircelik et al., 2016 (Turkey)	During ICU stay; 1 week after HD	Mental Anxiety: *HADS anxiety* ICU stay: mean (sd) 1 week: mean (sd) Change: mean (sd) Depression: *HADS depression* ICU stay: mean (sd) 1 week: mean (sd) Change: mean (sd)	 6.1 (0.7) 1.9 (0.2) 4.2 (0.58) 5.4 (0.6) 1.9 (0.25) 3.5 (0.53)	 5.7 (0.6) 5.1 (0.6) 0.6 (0.42) 5.1 (0.5) 4.8 (0.5) 0.3 (0.46)	 <0.01 <0.01
Fleisher et al., 2014 (Germany)	3 mo after discharge	Quality of life *SF-12 PCS* 3 mo after discharge: mean (sd) *SF-12 MCS* 3 mo after discharge: mean (sd) *SEIQoL* 3 mo after discharge: mean (sd)	 40.6 (9.4) 46.9 (11.3) 74.9 (18.2)	 40.4 (10.0) 48.2 (11.2) 73.6 (20.1)	
6. Other interventions					
Sosnowski et al., 2018 (Australia)	ICU (baseline), day 90 post discharge	Quality of life *SF-36 PCS* Baseline: mean (sd) 90 day post discharge: mean (sd) *SF-36 MCS* Baseline: mean (sd) 90 day post discharge: mean (sd)	 32.7 (11.1) 43.8 (12.0) 45.0 (14.4) 47.4 (16.0)	 41.6 (11.4) 37.9 (10.7) 41.8 (14.1) 40.3 (15.9)	
Demoule et al., 2017 (France)	ICU discharge (ICU-D); day 90	Physical Sleep quality: *PSQI* Day 90: median (IQR)	 8 (5–11)	 5 (5–8)	 0.25

		Mental Depression: *HADS depression* ICU-D: median (IQR) Day 90: median (IQR) Anxiety: *HADS anxiety* ICU-D: median (IQR) Day 90: median (IQR) Post traumatic disorder related symptoms: *IES-R* Day 90: median (IQR)	 4.5 (2–9) 6 (3–12) 8 (6–10) 8 (4–11) 11 (5–18)	 8 (4–9) 6 (2–9) 9 (6–11) 6 (4–12) 16 (9–27)	 0.25 0.63 0.66 0.69 0.15
Giraud et al., 2016 (UK)	12 weeks after surgery	Quality of life *EQ-5D VAS* 12 weeks: mean (sd) 12 weeks: estimate (95%CI) *EQ-5D index* 12 weeks: mean (sd) 12 weeks: estimate (95%CI)	 73 (19) -0.04 (-0.09 to 0.01) 0.87 (0.13) -0.00 (-0.05 to 0.04)	 77 (15) 0.87 (0.13)	 0.127 0.950

**Data provided by authors after request*

General abbreviations

ADJ:	Adjusted	PP:	Per protocol
CI:	Confidence interval	RCT:	Randomized controlled trial
HD	Hospital discharge	SD:	Standard deviation
ICU-D:	Intensive care unit discharge	SE:	Standard error
IQR:	Inter quartile range	SEM:	Standard error of mean
ITT:	Intention to treat	TRA:	Treatment received analysis
NA:	Not applicable	WK:	Week
NS:	Not significant		

Instrument abbreviations

6MWT	Six minute walking test: increase in distance indicates improvement in basic mobility		
NHPT	Nine hole peg test	0-18	Higher scores indicate better functioning
ABC	Activities Balance and Confidence	0-100	Higher scores indicate greater confidence in balance
ADL	Activities of Daily living	0-11	Higher score indicate low impairment
AQoL utility	Assessment of Quality of Life	1.00-0.00	Full health to death equivalent health states
AT	Anaerobic threshold		
Barthel	Barthel index	0-100	Higher scores indicate more independence
BBS	Berg Balance Scale	0-56	Higher scores indicating lower fall risk
BDI-II	Beck Depression Inventory	0-63	Higher scores indicating more severe depressive symptoms.
Borg scale	Modified Borg Dyspnoe scale	0-10	Higher score indicate more difficulty with breathing
BCOPE	Brief Cope		Higher scores indicate more difficulty in coping
CAMS-R	Cognitive and Affective Mindfulness Scale-revised	12-48	Higher scores indicate more ability
CAS	Control Attitude Scale	8-40	Higher scores reflecting higher levels of perceived control
CDSES	Chronic disease self efficacy scale	1-10	Higher scores indicate more self-efficacy
CS-PFP	Continuous Scale Physical Functional Performance Test:	0-100	Higher scores indicting better functioning
DEX	Dysexecutive Questionnaire:	0-80	Lower scores indicating better functioning
EQ-5D	EuroQol	0-100	Higher scores indicate better quality of life
EQ-5D-VAS	Visual analogue scale	0-100	Higher score reflecting better imaginable health state
FAQ	Functional Activities Questionnaire	0-30	Lower scores indicating better functioning
FEV	Forced expiratory volume		
FFM	Fat free mass		
FFMI	Fat free mass index		
FIM	Functional Independence Measure	18-126	Higher score indicating more independence

FLP	Functional Limitation Profile	0-100	Lower scores indicating good health
FPI	Functional Performance Inventory	0-3	Higher scores indicating higher levels of functional activity
FTSTS	Five Times Sit to Stand		Higher time scores is associated with increased disability and morbidity
FVC	Forced vital capacity		
GAD-7	Generalized Anxiety Disorder 7-item scale	0-21	Higher score indicate more distress
GCPSDS/PI	Graded Chronic Pain Scale: Disability Score/ Pain Intensity 0-100		High scores indicate high impairment
HADS	Hospital Anxiety and Depression Scale:	0-21	Higher scores indicate higher impairment
Handgrip			Higher scores indicate better handgrip
HTQ	Harvard Trauma Questionnaire	16-64	Cut of point ≥2.5 indicate probable PTSD
IADL	Instrumental Activities of Daily Living	0-21	Higher score indicate dependence
IES-R	Impact of Event Scale-Revised	0-88	Higher scores indicate probable PTSD
ISEL	Interpersonal Support Evaluation List	0-40	Higher scores reflect greater perceived availability of support resources
ISWT	Incremental Shuttle Walk Test		Higher scores indicates better functional capacity
KATZ ADL		0-12	Lower scores indicating better functioning
Lorig:	Self efficacy for managing chronic disease		Higher scores indicates higher self efficacy
MDI	Major Depression Inventory	0-50	Higher scores indicating high impairment
MIP	Maximal Inspiratory Pressure		
MEP	Maximal Expiratory Pressure		
MMSE	Mini Mental State Exam	0-30	Lower scores indicating worse functioning
MRC-SS	Medical Research Counsil Muscle Sum Score	0-60	Higher scores indicate normal muscle strength
MUST	Malnutrition Universal Screening Tool	0-6	Higher scores indicate higher risk of malnutrition
NSS	Neuropathy Symptom Score	0-9	higher scores indicate more symptoms
NSSQ	Norbeck Social Support Questionnaire		Higher scores indicate more social support
OASIS	Outcome and Assessment Information Set	0-66	Higher scores indicating increases dependency in performing specific activities
PaCO2	Partial pressure of carbon dioxide		
PaO2/ FiO2	Partial pressure of oxygen		
PDEQ	Peri-traumatic Dissociative Experiences Questionnaire		Higher scores indicate more dissociation
Peak VO2	Maximum rate of oxygen consumption		

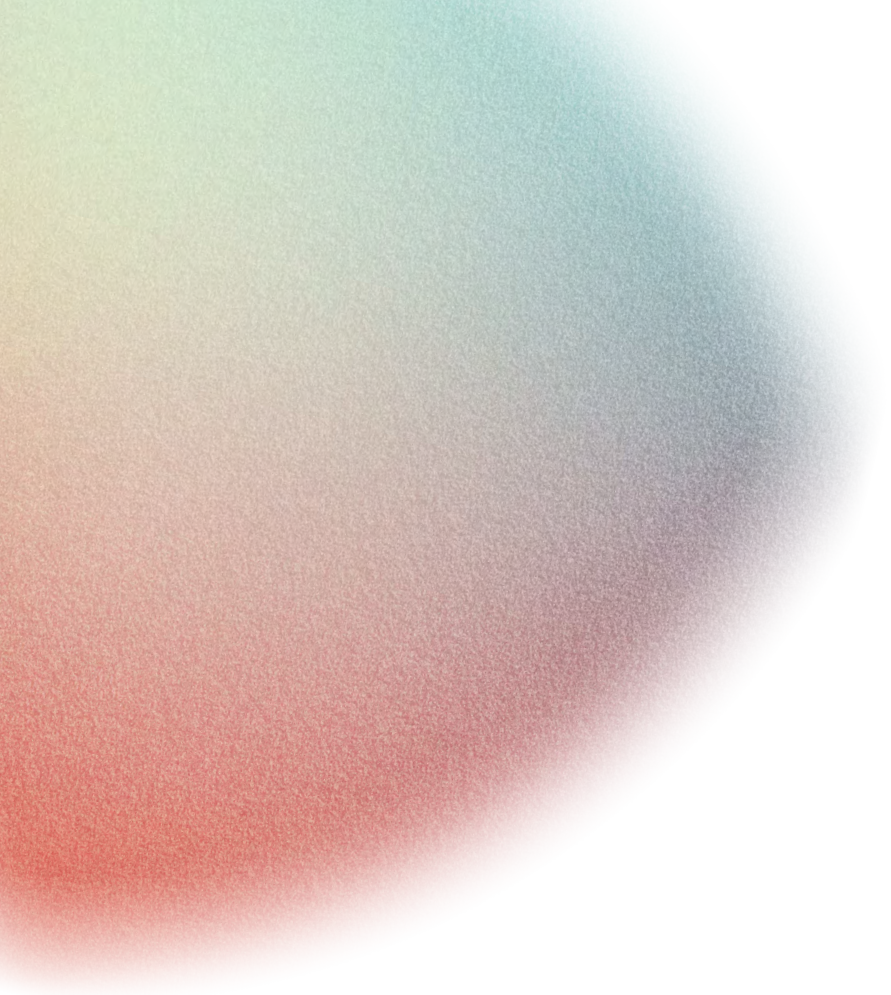
PHQ-9	Patient Health Questionnaire 9 item depression scale	0-27	Higher scores indicate more distress
PHQ-15	Patient Health Questionnaire 10 item physical symptom	0-30	Higher score indicate more problems
PROMIS	Patient Reported Outcomes Measurement Information system		Depends on domain
PTSS-10	Post Traumatic Symptom Scale	10-70	Higher scores indicates higher impairment
QMVC	Quadriceps maximum voluntary contraction		
RFcsa	Rectus femoris cross sectional area		
RIS	Regensburg Insomnia Scale	0-40	Higher scores are indicative of psycho physiological insomnia symptoms
RMI	Rivermead mobility index	0-15	Higher scores indicate better mobility performance
RR	Respiratory Rate		
SEIQoL	Schedule for Evaluation of Individual Quality of Life	0-100	Higher scores representing better quality of life
SF-8, 12, 36	Short Form	0-100	Higher scores indicating better health
SF36 PCS	Physical composite summary	0-100	Higher scores indicating better health
SF36 MCS	Mental composite summary	0-100	Higher scores indicating better health
SOC	Sense of coherence	13-91	Higher scores indicate greater levels of coherence
SPPB	Short Physical Performance Battery	0-12	Higher scores indicate better performance
STS-5	Sit-to-Stand		higher scores indicate better physical performance
TICS-M	Modified Telephone Interview for Cognitive Status	0-50	Higher scores indicate low impairment
TOWER/TT	Tower Test:	1-19	Higher scores indicating better performance
TUG/ TUAG	Timed Up and Go Test		Higher score indicate more disability
VAS	Visual Analogue Scale		
XSMFA-F	Short Musculosketal Function Assessment physical function	0-100	Higher scores indicate high impairment
XSMFA-B	Short Musculosketal Function Assessment disability	0-100	Higher scores indicate high impairment

Supplementary file 12. Summary of meta-analysis effect of interventions on patients' outcomes

Outcome	Instruments	Intervention	Studies (n)	N = I	N = C	Follow-up time	MD or SMD (95%CI)	P value
Physical health								
Walking distance	6MWT	Subgroup						
		Exercise	5	201	199	3 mo	MD, 5.84 (-37.75; 49.43)	.79
			4	168	176	6 mo	MD, 23.74 (-19.92; 67.39)	.29
			2	56	57	12 mo	MD, 31.01 (-34.45; 96.48)	.35
			5	181	180	L.E	MD, 31.99 (-9.76; 73.74)	.13
Muscle strength	Handheld, handgrip, QMVC, MRC quadriceps, MRC biceps	Subgroup						
		Exercise	3	233	179	3 mo	SMD, -0.11 (-0.69; 0.47)	.71
			3	243	230	6 mo	SMD, 0.13 (-0.06; 0.31)	.17
			4	253	236	L.E	SMD, 0.01 (-0.45; 0.46)	.97
Physical performance	SPPB, TUG	Subgroup						
		Exercise	3	165	158	3 mo	SMD, 0.11 (-0.15; 0.37)	.40
			3	153	156	6 mo	SMD, 0.11 (-0.28; 0.51)	.57
			3	153	156	L.E	SMD, 0.11 (-0.28; 0.51)	.57
Balance	BBS	Subgroup						
		Exercise	2	53	56	3 mo	MD, -1.10 (-9.15; 6.95)	.79
			2	47	45	6 mo	MD, 2.75 (-2.32; 7.81)	.29
			2	47	51	L.E	MD, 0.10 (-10.41; 10.61)	.99
Oxygen uptake efficiency	Anaerobic threshold	Subgroup						
		Exercise	2	66	66	3 mo	MD, 0.00 (-1.04; 1.04)	1.00
Mental health								
Depression	HADS-D, BDI, PHQ-9	Overall						
			12	542	517	3 mo	SMD, 0.82(-0.33; 1.96)	.16
			6	328	343	6mo	SMD, 0.04(-0.26; 0.34)	.79
			5	312	325	12 mo	SMD, 0.16 (-0.19; 0.50)	.37
			13	635	619	L.E	SMD, 0.75(-0.31; 1.81)	.17
		Subgroup						
		Exercise	4	117	104	3 mo	SMD, 0.35 (-0.17; 0.88)	.19
			3	99	90	6 mo	SMD, 0.25 (-0.25; 0.75)	.32
			4	117	104	L.E	SMD, 0.35 (-0.17; 0.88)	.19
		Follow-up service	2	204	211	3 mo	SMD, -0.01(-0.20; 0.19)	.96
			2	167	184	6 mo	SMD, -0.15 (-0.52; 0.21)	.41
			3	278	293	12 mo	SMD, -0.04 (-0.20; 0.12)	.64
			3	297	314	L.E	SMD, -0.11 (-0.34; 0.12)	.36
		Psychosocial program	3	134	101	3 mo	SMD, -0.01 (-0.31; 0.30)	.97
			3	134	100	L.E	SMD, 0.11 (-0.32; 0.53)	.62
		Diary	2	37	51	3 mo	SMD, 0.68 (0.14; 1.21)	.01*

Anxiety	HADS-A, GAD-7	Overall					
			11	523	505	3	SMD, 0.78(-0.46; 2.02)	.22
			6	328	343	6	SMD, 0.02 (-0.32; 0.36)	.90
			4	279	301	12	SMD, 0.19 (-0.52; 0.90)	.60
			12	603	596	L.E	SMD, 0.72(-0.42; 1.85)	.22
		Subgroup					
		Exercise	4	117	106	3 mo	SMD, 0.29 (-0.41; 1.00)	.41
			3	99	90	6 mo	SMD, 0.18 (-0.44; 0.80)	.57
			4	115	101	L.E	SMD, 0.28 (-0.43; 0.99)	.44
		Follow-up service	2	204	211	3 mo	SMD, -0.21 (-0.60; 0.18)	.29
			2	167	184	6 mo	SMD, -0.08 (-0.67; 0.50)	.79
			3	264	282	12 mo	SMD, -0.10 (-0.49; 0.29)	.61
			3	289	309	L.E	SMD, -0.08 (-0.44; 0.28)	.68
		Psychosocial program	2	115	87	3 mo	SMD, 0.03 (-0.29; 0.34)	.86
			2	112	85	L.E	SMD, -0.01 (-0.35; 0.34)	.97
		Diary	2	37	51	3 mo	SMD, 0.44 (0.01; 0.87)	.05*
Post traumatic stress	IES-R, HTQ-IV, PTSS, PDEQ	Overall					
			6	385	362	3 mo	SMD, -0.76 (-2.34; 0.82)	.35
			4	283	293	6 mo	SMD, -0.03 (-0.26; 0.20)	.78
			3	254	277	12 mo	SMD, -0.12 (-0.39; 0.16)	.40
			7	460	459	L.E	SMD, -0.72 (-2.04; 0.61)	.29
		Subgroup					
		Follow-up service	2	188	191	3 mo	SMD, 0.04 (-0.16, 0.24)	.71
			2	163	180	6 mo	SMD, -0.04 (-0.49; 0.41)	.86
			3	254	277	12 mo	SMD, -0.12 (-0.39; 0.16)	.40
			3	210	227	L.E	SMD, -0.09 (-0.41; 0.22)	.55
		Psychosocial program	2	115	87	3 mo	SMD, -0.03 (-0.32; 0.26)	.82
			2	112	85	L.E	SMD, -0.13 (-0.42; 0.17)	.40
Coping	BCOPE	Psychosocial program	2	115	87	3 mo	MD, 0.13 (-2.11; 2.37)	.91

Quality of life								
Quality of life	SF-36 PCS	Overall						
			11	580	576	3	MD, 0.19 (-1.60; 1.99)	.83
			5	369	375	6	MD, 0.18 (-1.71; 2.07)	.85
			4	267	267	12	MD, 0.22 (-2.88; 3.32)	.89
			12	661	670	L.E	MD, 0.56 (-1.37; 2.48)	.57
		Subgroup						
		Exercise	7	352	345	3 mo	MD, 0.14 (-2.08; 2.36)	.90
			4	267	265	6 mo	MD, 0.31 (-2.09; 2.71)	.80
			7	343	343	L.E	MD, 0,27 (-2.30; 2,83)	.84
		Follow-up service	2	206	216	12 mo	MD, -0.20 (-2.89; 2.48)	.88
			2	207	211	L.E	MD, -0.39 (-3.35; 2.56)	.79
	SF-36 MCS	Overall						
			11	584	579	3	MD, 1.05 (-0.69; 2.78)	.24
			5	369	375	6	MD, 0.76 (-0.86; 2.37)	.36
			4	267	267	12	MD, 0.14 (-2.62; 2.89)	.92
			12	662	676	L.E	MD, 1.57 (-0.11; 3.25)	.07
		Subgroup						
		Exercise	7	287	276	3 mo	MD, 1,53 (-0.56; 3.62)	.15
			4	267	265	6 mo	MD, 0.98 (-0.89; 2.86)	.30
			7	333	331	L.E	MD, 2.62 (0.92; 4.32)	<.01*
		Follow-up service	2	206	119	12 mo	MD, -0.97 (-3.55; 1.60)	.46
			2	218	229	L.E	MD, -1.32 (-3.64; 1.00)	.27
	EQ-5D VAS	Overall						
			4	230	202	3 mo	MD, -2.25 (-6.24; 1.75)	.27
			3	100	108	6 mo	MD, -2.93 (-8.81; 2.94)	.33
			5	253	220	L.E	MD, -3.33 (-7.37; 0.72)	.11
		Subgroup						
		Exercise	2	41	40	6 mo	MD, -5.32 (-13.34; 2.71)	.19
		Psychosocial program	2	113	84	3 mo	MD, -0.91 (-8.22; 6.40)	.81
	EQ-5D Index	Overall						
			3	172	175	3 mo	MD, 0.01 (-0.03; 0.05)	.67
			4	207	221	6 mo	MD, 0.01 (-0.05; 0.07)	.65
			5	306	317	L.E	MD, 0.00 (-0.04; 0.04)	.83
		Subgroup						
		Exercise	2	73	79	3 mo	MD, 0.04 (-0.05; 0.13)	.38
			3	97	100	6 mo	MD, 0.02 (-0.07; 0.10)	.72
			3	97	100	L.E	MD, 0.01 (-0.08; 0.10)	.83
Other								
Daily activities	IADL, BADL	Subgroup						
		Exercise	2	42	31	6 mo	SMD, -0.29 (-0.60; 0.45)	.78



CHAPTER 8

GENERAL DISCUSSION

This thesis focuses on ICU survivors' health outcomes and quality of life (QoL) before and one year after ICU admission, and interventions to prevent or mitigate the adverse long-term health outcomes. In this chapter, the main findings are provided, followed by a discussion of these findings within a broader context, and implications for clinical practice and future research.

MAIN FINDINGS

Health status before ICU admission

Based on the multicenter prospective MONITOR-IC cohort study, the results of this thesis indicate that a substantial part of the ICU survivors already experienced serious impairments in physical, mental, and cognitive functioning before their ICU admission. More than half of the patients suffered from symptoms of fatigue (65%), and a quarter from symptoms of anxiety and depression. A lower proportion was frail (13%) or cognitive impaired (6%). Substantial differences were seen between patient subgroups: patients with a poor pre-ICU health status were more often female, older, lower educated and suffering from a chronic condition. Unplanned ICU patients were significantly more frail and showed more often symptoms of depression, while planned patients suffered more often from fatigue.

Physical, mental, and cognitive health outcomes one year following ICU admission

One year after ICU admission, 58% of the medical, 64% of the urgent surgical, and 43% of the elective surgical ICU patients were suffering from *new* physical, mental, and/or cognitive health problems. Most patients experienced problems in a single health domain, with physical problems the most common, including fatigue, weakened condition, muscle weakness, and joint stiffness. Compared to their health status before ICU admission, urgent surgical patients experienced a significant deterioration, whereas elective surgical patients overall experienced a significant improvement in their physical and mental health one year after admission. Medical ICU patients did not experience a significant change in their physical and mental health status. A significant decline in cognitive functioning was seen in the medical, urgent surgical as well as in the elective surgical ICU patients.

Factors associated with physical, mental and cognitive health outcomes

The most important factor associated with new physical, mental, and cognitive

post-ICU problems is the health status before ICU admission. For example, patients who were suffering from symptoms of depression before ICU admission, more often had higher levels of frailly and symptoms of anxiety and fatigue one year after ICU admission. Other associated factors were length of hospital stay (associated with frailty and fatigue) and being older (associated with frailty). Factors associated with a lower likelihood of post-ICU health problems were male gender, higher level of education, and ICU admission after elective surgery. ICU length of stay, APACHE-IV score and having a chronic condition were not associated with the long-term outcomes studied in this manuscript.

Quality of life one year after ICU admission

In line with the changes in the physical and mental health status, a significant decline in QoL was seen in urgent surgical patients, whereas in the elective surgical patients a significant improvement was seen one year after ICU admission. Medical ICU patients did not experience a significant difference in their QoL one year after ICU admission. ICU survivors who reported a reduced QoL in the one-year questionnaire, explained in the interviews that their QoL was affected by physical, mental, and/or cognitive health problems they experience every day, impacting their daily life, and restricting what they wanted to do, including hobbies, work, and social activities. A new balance in their life, including in their relationship, had to be found. However, the reduction in QoL was not primarily due to the critical illness and related health problems; pre-existing comorbidities and other major life events also affected their QoL negatively. Some ICU survivors mentioned that their QoL has not been reduced despite impairments and daily problems, because they were grateful for being alive, and were able to set new life priorities and to accept life with its limitations.

Nonpharmacologic interventions to prevent or mitigate the long-term health problems

Rigorous analyses of all existing (non-) randomized controlled studies evaluating interventions aiming to prevent or mitigate adverse long-term physical, mental and cognitive outcomes, showed very thin evidence that diaries and exercise programs have a positive effect on the long-term mental health outcomes. Other commonly used nonpharmacologic interventions in daily ICU practice, such as follow-up services, psychosocial programs, and

information and education, were not supported by conclusive evidence despite outcomes favoring the intervention group. Due to considerable heterogeneity in interventions, outcomes, instruments, and follow-up time, comparing and analyzing data were difficult. Research in this field is in its early stages and more evaluation studies are necessary to generate effective interventions to achieve better health outcomes for ICU patients. Strongly recommended is the use of a core outcome set (COS), a consensus-based agreed minimum set of outcomes and instruments, to compare and combine the results in for example meta-analysis.

INTERPRETATION OF FINDINGS

In 2012, the term post-intensive care syndrome (PICS) was introduced at the Society of Critical Care Medicine (SCCM) conference, describing the *new or worsening impairments in physical, mental or cognitive health status arising after critical illness and persisting beyond acute care hospitalization* (1). Interestingly, three attendees of the conference wrote in the same year a letter, that they expected the definition of PICS might change as the body of research evaluating critical illness continues to grow (2). Although the amount of PICS studies has substantially increased recent years, improving the awareness of PICS and generating more knowledge regarding the epidemiology, pathophysiology, treatment and prognostication of the specific morbidities, the definition of PICS has never been changed. But maybe it should. Based on the results of this thesis it could be questioned whether the term and definition of PICS are still accurate.

Although suggestions have been made to even further extend the definition of PICS with social impairments (3, 4), the definition is possibly already too broad. *All* new or worsening physical, mental, or cognitive problems are covered. No distinction is made in the severity and number of symptoms, despite that the term 'syndrome' implies that patients must suffer from several symptoms: one survivor suffering from nightmares, and another one suffering from severe muscle weakness, depression, post-traumatic stress disorder (PTSD), and cognitive impairment, both suffer from PICS. It can be questioned if that is justifiable. Moreover, in chapter four of this manuscript, only the *new* experienced health problems were assessed, resulting in already 40% of the elective surgery patients, and 60% of the medical and urgent surgical patients suffering from PICS one year after their ICU admission. The *worsening* of

symptoms was not included, presumably leading to much higher PICS rates. The width of the definition might lead to a devaluation of PICS.

Furthermore, it should be discussed whether PICS is the right term and whether it is a unique syndrome. Recent years, a proliferation of 'post-'disease' syndromes is seen in subgroups of ICU patients, all representing phenotypes as distinct from PICS. For example the '*post-cardiac arrest syndrome*' (5): common long-term problems in cardiac arrest survivors are musculoskeletal impairments (including muscle weakness, physical fatigue and pain), mental health impairments (anxiety, depression and PTSD), and cognitive impairments (including problems in attention, memory, executive function) (6, 7). Problems similar to those reported in non-cardiac arrest ICU patients. In addition, common problems in sepsis survivors are fatigue, tiredness, sleep disturbances, anxiety, depression and memory loss, also summarized as '*post-sepsis syndrome*' (8, 9). Despite the overlap in symptoms between PICS and post-sepsis syndrome, the authors of one of the studies concluded they do not purport that the PICS and post-sepsis syndromes are 'one and the same' (9).
Are PICS, post-sepsis syndrome, and post-cardiac arrest syndrome indeed all different syndromes? Or are they actually the same? And are these long-term health problems only experienced in individuals who have been admitted to the ICU? There are absolutely unique health problems specific for ICU survivors, such as swallowing problems after intubation (10) and ICU acquired weakness (11). Furthermore, there are absolutely unique ICU risk factors, including the use of sedatives and mechanical ventilation (3). However, many long-term health problems in ICU survivors, are also seen in patients who have not been admitted to the ICU.
A recent example is long-COVID or '*post-COVID syndrome*'. Since the worldwide outbreak it becomes clear that many patients, including those who have not been admitted to the ICU, suffer from long-term problems, such as from fatigue, muscle weakness, depression, PTSD, and cognitive impairments (12-15). Also in cancer survivors are long-term problems frequently seen; they experience symptoms of depression and anxiety with pooled prevalence rates of 21% (16), corresponding with rates found in our study (17). Other frequently reported long-term problems are fatigue, pain, sexual dysfunction, and impairments in memory, executive functions, and processing speed (18-20). And also in stroke survivors are symptoms reported that are common in ICU survivors, such as fatigue, depression, anxiety and cognitive dysfunction (21).

A possible explanation for these common long-term health problems is that many risk factors are not specifically related to ICU admission. Social or demographic factors, including older age, female gender and low-economic status, play an important role, as well as pre-existing functional disability, frailty, mental health problems and cognitive impairment (3, 22, 23). Moreover, despite the patients' health status, a hospital admission in general may add an extra burden on the already psychologically or physically vulnerable patients (24), for example due to loss of privacy and autonomy, alarming and unpredictable sounds, pain and discomfort, and medications that can alter the cognition and physical function (25, 26). Besides, when patients suffer from one problem, it is likely they will also suffer from other related problems, as the physical, mental and cognitive health problems are strongly correlated (27): within domains (e.g. symptoms of depression are strongly correlated with anxiety and PTSD (28)), but also between domains (29) (e.g. physical problems are strongly correlated with mental health problems (30, 31)). A problem such as long-term fatigue illustrates the complexity of the underlying factors, as it is for example caused by pain, the need for extra energy to repair body tissue damaged by injury or treatment, sleep disturbances, underlying conditions (e.g. cardiac or pulmonary disfunction), anemia, nutritional imbalances, medication side effects, decreased functional status (including physical activity), social support, and emotional stress associated with the diagnosis, implications for daily life, and fear of dying (32, 33). Perhaps the post-intensive care syndrome is more a post-critical illness syndrome, including life-threatening illnesses that can result in significant morbidity or mortality, such as cancer, kidney failure, heart diseases or stroke. PCIS instead of PICS.

FUTURE DIRECTIONS FOR CLINICAL PRACTICE AND RESEARCH

To make and keep the definition of PICS useful in clinical practice and research, we recommend changing the definition and term. We don't have the solution yet, but an option might be to narrow the definition, for example by including a minimum amount of problems, or by including only specific health problems. Another solution might be the use of a severity classification system, such as the Lung Injury Score (34). More studies are needed to explore how the definition and term of PICS can be changed, to prevent the term becoming too broad to have a meaning.

Despite the discussion regarding the term and definition of PICS, the long-term physical, mental and cognitive health problems in ICU survivors should be prevented and mitigated as much as possible. Unfortunately, effective interventions are (still) lacking despite the increased awareness of PICS. As shown in the systematic review and meta-analysis in this thesis (Chapter 7, (35)), evaluation studies are lagging behind the rapid development of interventions, and research in this field is still in its early stages. This lack of compelling evidence emphasizes the importance to continue with the development, implementation, and evaluation of interventions. As critical care is defined by a whole episode of care, and not just the ICU stay (36), interventions before, during and after ICU should be performed.

For example, by identifying patients at high risk for adverse long-term outcomes at ICU admission using their pre-ICU health status (37, 38). Subsequently, it is possible to intervene early (39), for example by starting with psychological interventions in patients with pre-existing mental health problems (40). In addition, screening at ICU admission may help inform conversations about goals of care, treatment decisions and rehabilitation needs, and it is a baseline for evaluating changes in the health status that occur during the hospitalization.

During ICU admission, ICU related risk factors can be reduced or prevented, for example by early mobilization and physical therapy, family participation, ICU diaries, cognitive interventions, and by minimizing pain, delirium, sedation, agitation, and distress in the ICU (9, 41) using the ABCDEF bundle (41). Besides, early rehabilitation can improve physical, mental and cognitive functioning and prevent future problems (42). Moreover, discussing patients' values and preferences, and their presumed future health status, recovery, functional independence and QoL is necessary (43, 44). However, less than 20% of the ICU physicians discuss post-ICU challenges with patients and families (45). This is striking, because information about the occurrence of the post-ICU problems and recovery trajectory, can decrease patients' fear of the unknown and their feelings something else being terribly wrong with them (43).

At ICU discharge, the continuity of rehabilitation is of utterly importance, for example by the handover of an individualized structured rehabilitation program to the general ward team (42). Moreover, the identification of patients at risk could help to select patients who might benefit from attending post-ICU interventions or who are in need of referral to specialized clinicians and

services (23, 46-48). Patients at risk are, for example, patients with obvious significant physical or neurological injuries, patients with hallucinations or intrusive memories of traumatic events, and patient being unable to mobilize or to get in and out of bed independently (42).

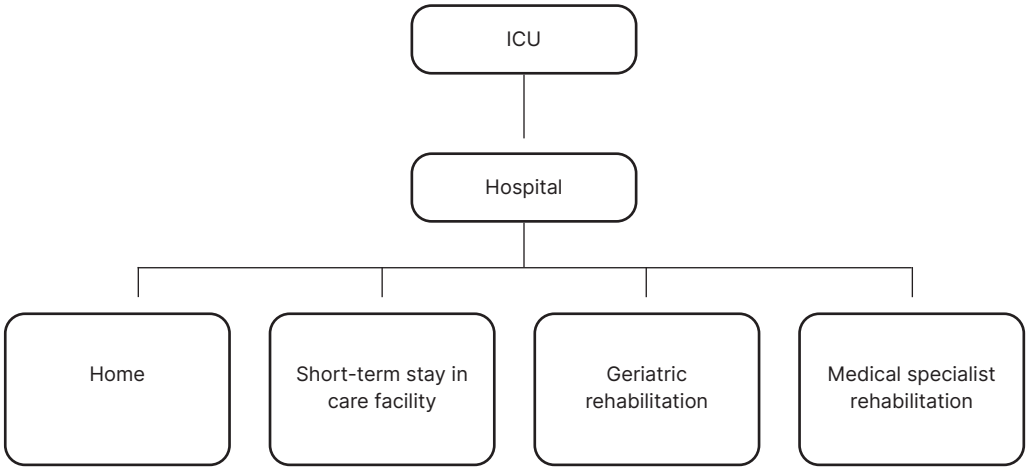
After ICU discharge, care is fragmented, and relatively little is known about how to structure healthcare systems to improve the outcomes of ICU survivors (49, 50). National guidelines for post-ICU follow-up care are scarce, as well as established rehabilitation pathways as are seen for oncology and heart failure patients (49). Rehabilitation for ICU survivors is now disease specific: cardiac patients may get streamed to cardiac rehabilitation pathways and those with chronic respiratory disease to pulmonary rehabilitation. However, these pathways are not designed to address specific long term ICU-related problems, such as ICU acquired weakness and symptoms of PTSD, and subsequently many former ICU patients receive sub-optimal post-ICU care (51).

Results from a survey study showed that the organization of post-ICU care in the Netherlands is diverse, without protocols or a structured approach (52). Although 99% of the Dutch ICUs mentioned they provided some form of post-ICU care, an outpatient post-ICU clinic was only available in 52% of the ICUs. Remarkably, most ICUs included patients for the post-ICU clinic based on their ICU length of stay and/or duration of mechanical ventilation, two factors presumably not associated with the adverse long-term outcomes. In line with the international literature (50, 53, 54), the Dutch study (52) also concluded that the critical care community is strongly divided over who is responsible for the post-ICU follow-up care: ICU clinicians, general practitioners (GPs), or other medical specialists. One third of the ICU professionals stated they were responsible, while more than halve stated that the GP should take the responsibility. Although the frequency of GP consultations indeed substantially increases in the year following ICU discharge (55), GPs are often unaware of the given ICU treatment and have limited knowledge of the long-term problems ICU survivors can experience (50, 56). Although most of the Dutch ICUs (91%) inform GPs about the ICU admission, only one third informs the GP about how to recognize and treat long-term ICU symptoms (52).

Due to the fragmented post-ICU care, patients may become “lost” in the healthcare system, with delays in accessing clinical care that recognizes and proactively addresses their unique limitations and needs, and consequently

a further deterioration of the post-ICU problems (49, 57). Effective longitudinal care models for ICU survivors are therefore urgently needed to facilitate the transition of patients from in-hospital to an outpatient setting, allowing for early recognition of post-ICU impairments, increased access to a range of healthcare providers and, ultimately, to improved QoL (49, 50, 58). Ideally, ICU patients are seen by a multidisciplinary team before being discharged from the hospital, to decide about the post-hospital trajectory. This team might consist of rehabilitation specialists, physiotherapists, occupational therapists, social workers, dieticians, speech language therapists, geriatricians, or psychologist, to enhance the wide diversity of physical, mental and cognitive recovery of ICU survivors (59-61). For Dutch ICU patients, several post-hospital trajectories are possible (Figure 1).

Figure 1. Rehabilitation trajectories for ICU patients after hospital discharge



Based on the Dutch guideline 'Aftercare for ICU patients with COVID-19 (62).

Patients with mild problems can be discharged home. The GP will coordinate the care, and optional support of homecare and professionals, such as physiotherapists and dieticians, is available. Patients who are temporarily unable to be discharged home, but for whom a longer hospital stay or an admission to a rehabilitation centre is not necessary, can stay for a short period of time in a care facility. They are expected to return home after their

stay. Frail elderly patients with complex multimorbidity, limitations in their daily functioning, and who need multidisciplinary care, can be discharge to a geriatric rehabilitation centre. ICU survivors with multiple physical, mental or cognitive problems, with high premorbid levels of functioning and participation ambition, and who require multidisciplinary care, can receive medical specialist rehabilitation. Patients can be treated in a rehabilitation centre of outpatient clinic.

Furthermore, it is recommended to plan a follow-up appointment by the medical specialist two or three months after hospital discharge, for example by the pulmonologist or cardiologist, depending on the medical condition. Despite the lack of scientific evidence yet, it is strongly recommended to invite patients at the post-ICU clinic as well, because intensivist along with nurses and allied healthcare professionals, understand the complexity of all the aspects of critical illness a patient may have encountered (57). In the post-ICU clinic, a brief summary of significant events during their ICU stay can be explained, their recovery discussed, and their physical, mental, cognitive and social problems identified. However, to define the most optimal aftercare, more research is needed (59, 63).

Above all, it is pivotal to raise awareness about the ICU survivor's long-term problems and ongoing care needs among policymakers and healthcare providers, including the non-critical care providers, such as the rehabilitation specialists and GPs (1, 36, 49). In the Dutch Family and Patient Centered Intensive care (FCIC) foundation (64), patients, ICU professionals and scientist have joined forces to share knowledge and to educate healthcare professionals. But most of all, patients need to know they are not alone (36). Patient organizations, such as the Dutch IC Connect which is part of the FCIC (65), have an important role in providing support, disseminating information and organizing and stimulating peer support for (former) ICU patients and their loved ones. Understanding of the critical illness experience and coping with the long-term problems and stress will enable patients to reclaim ownership of their lives (66).

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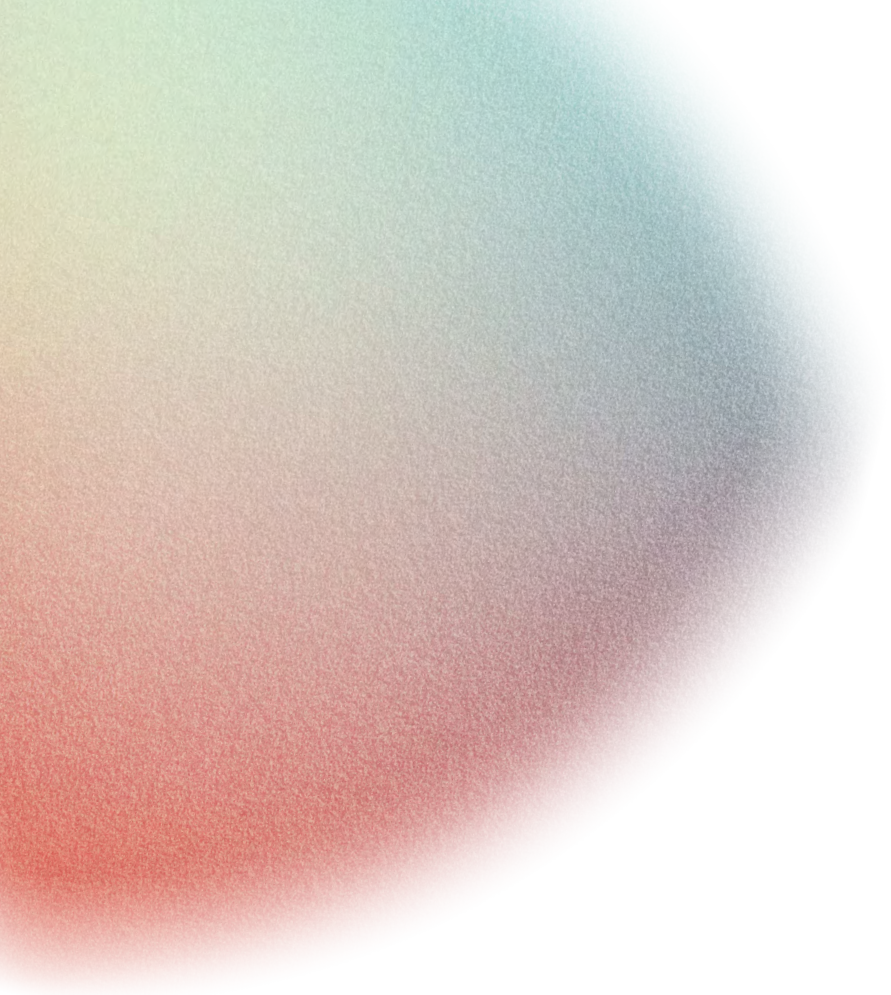


CHAPTER 9

SUMMARY

This thesis aims to gain insight into the health outcomes and quality of life (QoL) of ICU patients before and one year following ICU admission, and interventions to prevent or mitigate adverse outcomes. For that purpose the following items were investigated: 1) the health status of ICU survivors before ICU admission; 2) their physical, mental, and cognitive health outcomes, and quality of life after ICU admission; 3) factors associated with these one-year health outcomes; and 4) the effectiveness of interventions to prevent or mitigate long-term physical, mental, and cognitive health problems in ICU survivors.

This is the first thesis based on the MONITOR-IC study. In **Chapter 2** the study protocol of the MONITOR-IC study is described; a prospective multicenter cohort study, started in 2016, aiming to study the long-term outcomes of Dutch ICU survivors. In this chapter, the inclusion criteria, patient recruitment, time of follow-up, the outcomes measures and outcome instruments are described.

In **Chapter 3**, the health status of 2467 ICU survivors *before* their ICU admission is reported. A part of the ICU survivors already experienced serious impairments in their physical, mental, and/or cognitive functioning prior to their ICU admission: 13% were frail, 65% had symptoms of fatigue, 28% symptoms of anxiety, 26% symptoms of depression, and 6% were cognitive impaired. Substantial differences were found between patient subgroups: patients with pre-ICU health problems were more often likely to be female, lower educated and suffering from a chronic condition.

The health status one year *after* ICU admission in 2345 ICU survivors is described in **Chapter 4**. Patients were divided into three groups based on their ICU admission: urgent surgical admission (n=284), medical admission (n=649), or elective surgical admission (n=1412). New physical, mental, and/or cognitive problems were experienced by 43% of the elective surgical, 58% of the medical, and 64% of the urgent surgical patients. The majority of the patients reported problems in a single health domain with physical problems the most common. Significant differences were seen in urgent surgical patients compared to elective surgical patients in fatigue (45% vs 24%), depression (20% vs 10%), and cognitive impairment (13% vs 6%), respectively.
Compared to their pre-ICU health status, urgent surgical patients experienced a significant deterioration in their physical health, mental health and QoL, whereas elective surgical patients experienced a significant improvement. In

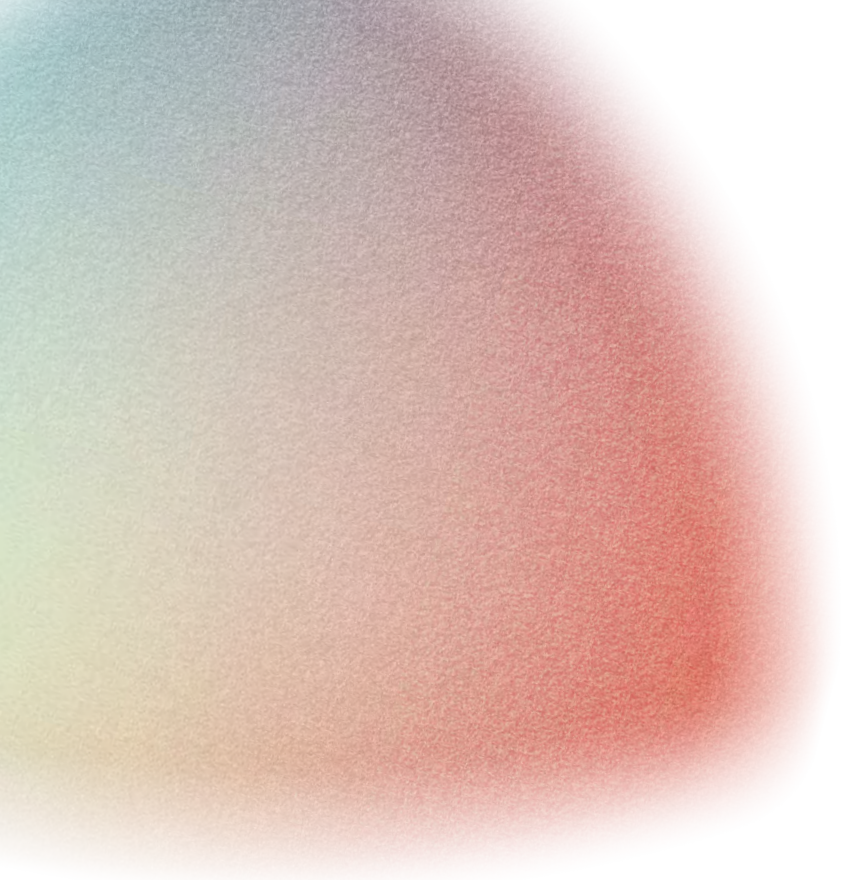
the medical ICU patients no significant differences were seen. A significant deterioration in cognitive functioning was reported in all three patient groups. Patients' pre-ICU health status was strongly associated with new post-ICU health problems. For example, patients with symptoms of anxiety before ICU admission, were more likely to have symptoms of depression and PTSD one year later. Furthermore, a lengthy hospital stay was associated with frailty and fatigue, and being older with frailty. Factors that were associated with a lower likelihood of one-year health problems were higher education, male gender, and being admitted for elective surgery.

Chapter 5 zooms in on frailty levels among 1300 ICU survivors before their ICU admission, at hospital discharge, and three and 12 months after ICU admission. In this chapter, patients were divided into two groups: patients with an unplanned and planned ICU admission. Compared to their pre-ICU frailty levels, 23% of the patient with an unplanned admission were less frail, 42% more frail and 35% experienced the same frailty levels one year after ICU admission. In patients with a planned admission, this was 32%, 27% and 41%, respectively. Factors that were associated with being more frail after one year were older age, a longer hospital stay, and discharge location. In patients with a planned ICU admission were male sex, higher education level and mechanical ventilation associated with being less frail.

In **Chapter 6** the story behind the number is described. Of a group of 173 ICU survivors, who reported a reduced QoL one year after ICU admission, 19 survivors were interviewed to get more insight into their daily functioning. In the interviews, the ICU survivors mentioned they were suffering from physical, mental, and cognitive health problems, impacting their daily life, and restricting what they wanted to do, including their hobbies, work and social activities. A new balance in life, including relationships, had to be found. Despite that only participants with a reduced QoL were invited for the interviews, some participants mentioned in the interviews they experienced no changes in QoL as they were grateful for being alive, were able to set new life priorities and accept their life with its limitations.

Recent years, a wide range of interventions has been developed to prevent or mitigate the adverse long-term physical, mental or cognitive impairments.

In **Chapter 7** the effectiveness of these interventions are described, based on the results of a comprehensive systematic review with multiple meta-analyses on these interventions. After screening more than 17.000 studies, 36 studies met the inclusion criteria. The interventions were subdivided into six categories: 1) exercise and physical rehabilitation programs; 2) follow-up services; 3) psychosocial programs; 4) ICU diaries; 5) information and education; and 6) other interventions. Although many outcomes favored the interventions, only the use of ICU diaries was associated with a significant reduction in depression and anxiety, and the use of exercise and physical rehabilitation programs with a significant improvement in the mental component score of the SF-36 QoL questionnaire. However, the results should be interpreted with caution: the effects for the diaries were based on only two studies, with one having substantial methodological limitations, and the improvement on the SF-36 mental component score for early exercise and physical rehabilitation programs was very small. Due to the considerable heterogeneity in interventions, outcomes, instruments, and follow-up time, comparing and analyzing data were difficult. The lack of compelling evidence emphasizes the importance to continue with the development, implementation, and evaluation of interventions to prevent or mitigate long-term adverse outcomes among ICU survivors.



CHAPTER 10

NEDERLANDSE SAMENVATTING

In Nederland worden per jaar ongeveer 80.000 patiënten per jaar opgenomen op de intensive care (IC), waarvan 85-90% de IC-opname overleeft. Echter, veel voormalig IC-patiënten kampen nog maanden tot jaren na hun opname met allerlei fysieke, mentale en cognitieve problemen, zoals vermoeidheid, pijn, angst, depressie en problemen in concentratie en geheugen. Alle nieuwe of verergerde fysieke, mentale en/of cognitieve klachten die ontstaan ten gevolge van kritieke ziekte en de intensive care behandeling worden het 'post-intensive care syndroom' (PICS) genoemd. De problemen kunnen een grote impact hebben op het dagelijks functioneren, zoals werk, hobby's en relaties.

Waarom sommige voormalig IC-patiënten met deze problemen kampen en anderen niet, is nog grotendeels onbekend. De problemen worden veroorzaakt door een combinatie van factoren, waarbij vooral de gezondheidsstatus voor de IC een belangrijke factor lijkt te zijn. Hoewel er de afgelopen jaren veel onderzoek is gedaan naar de fysieke, mentale en cognitieve problemen bij voormalig IC-patiënten, variëren de percentages van deze langetermijn problemen aanzienlijk in internationale studies. Dit komt door de grote verschillen in studiedesigns, geïncludeerde patiënten, gebruikte meetinstrumenten en meetmomenten. Daarbij zijn veel studies gebaseerd op kleine aantallen, richten ze zich op problemen binnen één gezondheidsdomein en is de gezondheidsstatus voor de IC niet meegenomen wat leidt tot een overschatting van de langetermijn problemen.

Daarom is in 2016 de MONITOR-IC studie opgezet, een grote Nederlandse prospectieve cohort studie, met als doel om de fysieke, mentale en cognitie gezondheidsstatus bij voormalig IC-patiënten voor en tot vijf jaar na IC-opname in kaart te brengen. Dit proefschrift is het eerste proefschrift dat gebaseerd is op de MONITOR-IC studie. In dit proefschrift is het volgende onderzocht: 1) de gezondheidsstatus van voormalig IC-patiënten voor IC-opname; 2) de fysieke, mentale en cognitieve gezondheidsstatus en de kwaliteit van leven één jaar na IC opname; 3) factoren die geassocieerd zijn met deze 1-jaars gezondheidsuitkomsten; en 4) de effectiviteit van interventies die als doel hebben om de fysieke, mentale en cognitie problemen bij voormalig IC-patiënten te voorkomen of te verminderen.

In **hoofdstuk 2** is het studieprotocol van de MONITOR-IC studie beschreven. In dit hoofdstuk worden de inclusiecriteria, patiënten rekrutering, meetmomenten, uitkomstenmaten en meetinstrumenten beschreven.

In **hoofdstuk 3** is de gezondheidsstatus *voor* de IC opname gerapporteerd van 2467 voormalig IC-patiënten. Een deel van deze patiënten ervaart voor IC-opname al ernstige beperkingen in hun fysiek, mentaal en/of cognitief functioneren: 13% was kwetsbaar (frail), 65% had symptomen van vermoeidheid, 28% symptomen van angst, 26% symptomen van depressie en 6% had cognitieve problemen. Substantiële verschillen werden gevonden tussen verschillende patiëntengroepen; vrouwen, lager opgeleiden en mensen met een chronische aandoening kampten vaak met gezondheidsproblemen voor de IC opname.

De gezondheidsstatus van 2345 voormalig IC-patiënten een jaar *na* IC-opname is beschreven in **hoofdstuk 4**. Patiënten werden op basis van hun opnametype onderverdeeld in drie groepen: spoed chirurgische opname (n=284), medische opname (n=649) of gepland chirurgische opname (n=1412). Nieuwe fysieke, mentale en/of cognitieve problemen werden door 43% van de gepland chirurgische patiënten, 58% van de medische patiënten en 64% van de spoed chirurgische patiënten ervaren. De meeste voormalig IC-patiënten rapporteerden problemen in één gezondheidsdomein, met fysieke problemen als meest voorkomend. Significante verschillen werden gezien tussen de spoed chirurgische en gepland chirurgische patiënten in respectievelijk vermoeidheid (45% vs 24%), depressie (20% vs 10%) en cognitieve beperkingen (13% vs 6%). Vergeleken met hun gezondheidsstatus voor de IC-opname, ervaren spoed chirurgische patiënten een significante verslechtering in hun fysieke en mentale gezondheid en hun kwaliteit van leven, terwijl de gepland chirurgische patiënten een significante verbetering ervaren een jaar na IC-opname. Bij de medische IC-patiënten werden geen significante verandering gezien in fysiek en mentaal functioneren. Een significante verslechtering in cognitief functionering werd in alle drie de patiëntengroepen gerapporteerd.
De gezondheidsstatus voor IC-opname was sterk geassocieerd met de nieuwe gezondheidsproblemen een jaar na IC-opname. Patiënten die bijvoorbeeld voor hun IC-opname symptomen van angst rapporteerden, hadden een jaar later een grotere kans op symptomen van depressie en PTSD. Daarnaast was een langere ziekenhuisopnameduur geassocieerd met meer kwetsbaarheid en vermoeidheid, en een hogere leeftijd met meer kwetsbaarheid. Factoren die geassocieerd waren met een lagere kans op gezondheidsproblemen een jaar na IC-opname waren een hoger opleidingsniveau, het mannelijk geslacht en een IC-opname na geplande chirurgie.

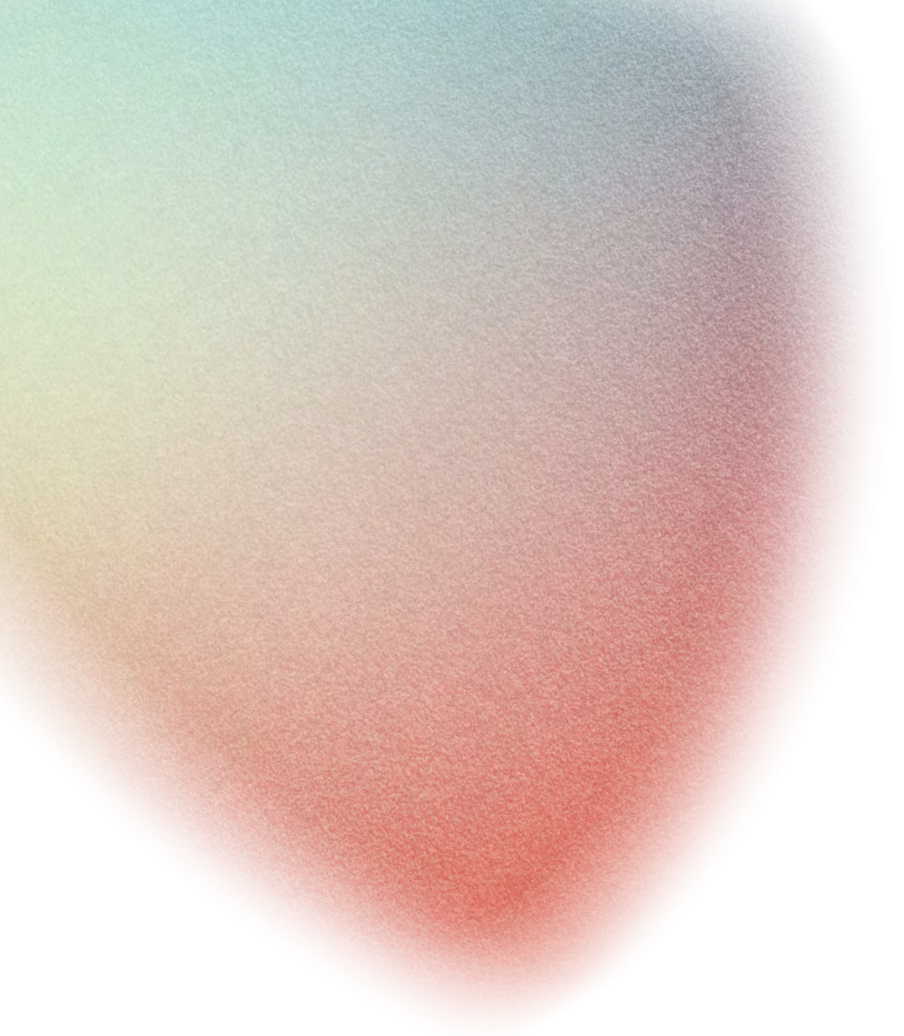
In **hoofdstuk 5** is verder ingezoomd op de mate van kwetsbaarheid van 1300 voormalig IC-patiënten voor hun IC-opname, bij ziekenhuisontslag en bij drie en twaalf maanden na IC-opname. In dit hoofdstuk zijn de patiënten onderverdeeld in twee groepen: patiënten met een ongeplande en geplande IC-opname. Van de patiënten met een ongeplande IC-opname waren na een jaar, 23% van de patiënten minder kwetsbaar, 42% meer kwetsbaar en 35% even kwetsbaar als voor hun IC-opname. In de patiënten met een geplande IC opname was dit respectievelijk 32%, 27% en 41%. Factoren die geassocieerd waren met meer kwetsbaarheid een jaar na IC-opname waren een hogere leeftijd, een langere ziekenhuisopnameduur en ontslaglocatie. Bij patiënten met een geplande IC-opname waren het mannelijk geslacht, een hoger opleidingsniveau en beademingsduur geassocieerd met minder kwetsbaarheid.

In **hoofdstuk 6** is het verhaal achter de cijfers beschreven. Uit een groep van 173 voormalig IC-patiënten, die een jaar na hun IC-opname een verminderde kwaliteit van leven rapporteerden, werden 19 patiënten geïnterviewd om meer inzicht te krijgen in hun dagelijks functioneren. In de interviews gaven patiënten aan dat zij veel fysieke, mentale en cognitieve problemen ervaren, die een grote impact hebben op hun dagelijks leven en hun beperken in wat ze willen doen, zoals hun hobby's, werk en sociale activiteiten. Een nieuwe balans in hun leven, inclusief in hun relaties, moest gevonden worden. Ondanks dat alleen patiënten met een verminderde kwaliteit van leven geselecteerd werden voor de interviews, gaven sommige deelnemers in de interviews aan dat hun kwaliteit van leven niet veranderd was; zij gaven aan dankbaar te zijn dat ze nog leefden, dat ze nieuwe prioriteiten hebben gekregen, en dat ze hun leven met beperkingen hebben kunnen accepteren.

Afgelopen jaren zijn er veel verschillende interventies ontwikkeld om de lichamelijke, mentale en cognitieve langetermijn problemen bij IC-patiënten te voorkomen of te verminderen. In **hoofdstuk 7** is de effectiviteit van deze interventies beoordeeld en beschreven, gebaseerd op de resultaten van een uitgebreide systematische literatuurstudie met meerdere meta-analyses. Na het screenen van ruim 17.000 artikelen, voldeden 36 studies aan de inclusiecriteria. De interventies werden onderverdeeld in zes categorieën: 1) beweeg- en fysieke revalidatieprogramma's; 2) nazorgprogramma's; 3) psychosociale programma's; 4) IC-dagboeken; 5) informatie en educatie; en 6) overige interventies. Hoewel veel uitkomsten in het voordeel leken van de

interventies, was alleen het gebruik van IC-dagboeken geassocieerd met een significante vermindering in depressie en angst, en het gebruik van beweeg- en fysiekerevalidatieprogramma met een significante verbetering in de mentale component score (MCS) van de SF-36 kwaliteit van leven vragenlijst. Echter, deze resultaten moeten met de nodige voorzichtigheid geïnterpreteerd worden: de effecten voor de dagboeken waren gebaseerd op slechts twee studies, waarvan er één aanzienlijke methodologische beperkingen had, en de verbetering in de SF-36 MCS voor de beweeg- en fysieke revalidatieprogramma's was erg klein. Door de aanzienlijke heterogeniteit in interventies, uitkomsten, meetinstrumenten en follow-up tijd was het vergelijken en het analyseren van de gegevens ingewikkeld. Het gebrek aan overtuigend bewijs benadrukt het belang om door te gaan met de ontwikkeling, implementatie en evaluatie van interventies om de langetermijn problemen bij IC-patiënten te voorkomen of te verminderen.

In **hoofdstuk 8** zijn de hoofdbevindingen uit dit proefschrift beschreven in de praktische en wetenschappelijke context, inclusief de implicaties voor de klinische praktijk en vervolgonderzoek.



APPENDICES

DATAMANAGEMENT

This thesis is based on the results of human studies, which were conducted in accordance with the principles of the Declaration of Helsinki. The medical and ethical review board Committee on Research Involving Human Subjects Region Arnhem Nijmegen, Nijmegen, the Netherlands has given approval to conduct these studies. All participants gave their informed consent to participate.

All data presented in this project is stored on the Radboudumc, department server: \\Umcfs080\icdata$\ in the folder 'Monitor-IC'. All paper data were stored in the department archive (Radboudumc, room M340 -1.124). All paper data were entered into the computer by use of Teleform. Data management and monitoring were also performed within Teleform, and data where converged from Teleform to SPSS (SPSS Inc., Chicago, Illinois, USA). For the qualitative study, audio-taped data were used. Transcripts were stored and analyzed in ATLAS.ti, licenced under Radboudumc.

The privacy of the participants in this thesis is warranted by use of an encrypted and unique individual subject code. This code correspondents with the code on the questionnaires. The code was stored separately from the study data. The data will be saved for 15 years after termination of the study. The datasets analyzed during these studies are available from the corresponding author on reasonable request.

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Alone we can do so little, together we can do so much - Helen Keller

Dit proefschrift had nooit tot stand kunnen komen zonder de hulp, steun en vertrouwen van velen. Mijn speciale dank gaat uit naar:

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CURRICULUM VITAE

Wytske Geense werd geboren op 31 mei 1986 te Apeldoorn. Na het behalen van haar HAVO diploma aan De Heemgaard in Apeldoorn, heeft zij HBO-Verpleegkundige gestudeerd aan de Hogeschool Windesheim in Zwolle. Na afronding van haar studie in 2008 heeft zij een jaar als verpleegkundige gewerkt op verschillende afdelingen in het Diaconessenhuis in Meppel en het Canisius Wilhelmina Ziekenhuis in Nijmegen.

In 2009 is zij gestart met de premaster gezondheidswetenschappen aan de Vrije Universiteit in Amsterdam, waarna zij in 2011 haar master Prevention and Public Health cum laude behaalde. Van 2011 tot 2016 heeft zij als onderzoeksmedewerker en junior onderzoeker gewerkt aan verschillende projecten bij IQ healthcare, een wetenschappelijk afdeling binnen het Radboudumc.

In 2017 is zij begonnen aan haar promotieonderzoek dat leidde tot dit proefschrift, onder begeleiding van prof. dr. Hans van der Hoeven, prof. dr. Hester Vermeulen, dr. Marieke Zegers en dr. Mark van den Boogaard. De bevindingen uit het onderzoek heeft zij gepresenteerd op diverse congressen in binnen-en buitenland, en in 2020 is zij genomineerd voor de Anne Reijnvaan Wetenschapsprijs.

Sinds 2021 is zij als postdoc onderzoeker verbonden aan het programma Beter Gezond binnen de afdeling Health Evidence (HEV) van het Radboudumc. Dit programma geeft leefstijl een plek in de spreekkamer en in het behandelplan van de oncologische patiënt.

LIST OF PUBLICATIONS

This thesis

Geense W, de Graaf M, Vermeulen H, van der Hoeven J, Zegers M, van den Boogaard M.
Reduced quality of life in ICU survivors 1-year after admission: the story behind the numbers. An interview study. *Journal of Critical Care, 2021*

Geense WW, Zegers M, Peters MAA, Ewalds E, Simons KS, Vermeulen H, van der Hoeven, JG, van den Boogaard M. New physical, mental, and cognitive problems 1 year after ICU admission: a prospective multicenter study. *American Journal of Respiratory and Critical Care Medicine, 2021*

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Geense W, Zegers M, Dieperink P, Vermeulen H, Van der Hoeven J, Van den Boogaard M. Changes in frailty among ICU survivors and associated factors: results of a one-year prospective cohort study using the Dutch Clinical Frailty Sca*le. Journal of Critical Care, 2020*

Geense WW, van den Boogaard M, van der Hoeven J, Vermeulen H, Hannink G, Zegers M. Nonpharmacologic interventions to prevent or mitigate adverse long-term outcomes among ICU survivors: a systematic review and meta-analysis. *Critical Care Medicine, 2019*

Geense W, Zegers M, Vermeulen H, van den Boogaard M, van der Hoeven J. MONITOR-IC study, a mixed methods prospective multicentre controlled cohort study assessing 5-year outcomes of ICU survivors and related healthcare costs: a study protocol.
British Medical Journal Open, 2017

Other publications

Geense WW, van den Boogaard M. Response letter. *American Journal of Respiratory and Critical Care Medicine, 2021 (submitted)*

Geense W, Siebel M, Brackel M, Zegers M, van den Boogaard M, van der Laar F. Zorg voor patiënten na een ic-opname. *Huisarts en Wetenschap, 2020*

Van Sleeuwen D, van de Laar F, **Geense W**, van den Boogaard M, Zegers M. Health problems among family caregivers of former intensive care unit (ICU) patients: an interview study. *British Journal of General Practice Open, 2020*

Geense W, Zegers M, van den Boogaard M, Hannink G. The authors reply. *Critical Care Medicine, 2020*

Verschuur EML, **Geense WW**, Adriaansen MJM. Support needs among patients with Huntington disease in the Netherlands: results of a focusgroup study. *Nursing & Primary Care, 2020*

Van den Wijngaart LS, **Geense WW**, Boehmer AL, Brouwer ML, Hugen CA, van Ewijk BE, Koenen-Jacobs MJ, Landstra AM, Niers LE, van Onzenoort-Bokken L, Ottink MD, Rikkers-Mutsaerts ER, Groothuis I, Vaessen-Verberne AA, Roukema J, Merkus PJ. Barriers and facilitators when implementing web-based disease monitoring and management as a substitution for regular outpatient care in paediatric asthma: qualitative survey study. *Journal of Medical Internet Research, 2018*

Geense WW, van Gaal BG, Knoll JL, Maas NM, Kok G, Cornelissen EA, Nijhuis-van der Sander MW. Effect and process evaluation of e-Powered Parents, a web-based support program for parents of children with a chronic kidney disease: feasibility randomized controlled trial. *Journal of Medical Internet Research, 2018*

Hesselink G, Batalden P, Carlson M, **Geense W**, Groenewoud S, Jones S, Roy B, Sansone C, Wolf JRLM, Bart B, Wollersheim H. Reframing healthcare services through the lens of co-production (Rhelaunch): a study protocol for a mixed methods evaluation of mechanisms by which healthcare and social services impact the health and well-being of COPD and CHF patients in the USA and the Netherlands. *British Medical Journal Open, 2017*

Geense WW, van Gaal BGI, Knoll J, Cornelissen EAM, van Achterberg T. The support needs of parents having a child with a chronic kidney disease: a focus group study. *Child: Care, Health and Development. 2017*

Zegers M, Hesselink G, **Geense W**, Vincent C, Wollersheim H. Evidence-based interventions to reduce adverse events in hospitals: a systematic review of systematic review. *British Medical Journal Open, 2016*

Van de Glind IM, Heinen MM, **Geense WW**, Mester I, Wensing M, van Achterberg T. Exploring the range of lifestyle interventions used in Dutch health care practice: a qualitative description. *Health Promotion Practice, 2016*

Geense WW, van Gaal BGI, Knoll JK, Cornelissen EAM, Schoonhoven L, Kok G. Online support program for parents of children with a chronic kidney disease using intervention mapping: a development and evaluation protocol. *Journal of Medical Internet research Research Protocols, 2016*

Van Achterberg, T, van Gaal BG, **Geense WW**, Verbeke G, van der Vleuten C, Schoonhoven L. Completeness of assisted bathing in nursing homes related to dementia and bathing method: results from a secondary analysis of cluster-randomized trial data. *International Journal of Older Person Nursing, 2016*

Zegers M, Hesselink G, Roes K, Geense W, Wollersheim H. Een proactieve benadering van risico's. *Nederlands Tijdschrift voor Geneeskunde, 2015*

Van de Glind I, Heinen M, **Geense W**, Mesters I, Wensing M, van Achterberg T. Making the connection-factors influencing implementation of evidence supported and non-evaluated lifestyle interventions in healthcare: a multiple case study. *Health Education Research, 2015*

Geense WW, van de Glind IM, Visscher TL, van Achterberg T. Barriers, facilitators and attitudes influencing health promotion activities in general practice: an explorative pilot study. *British Medical Council Family Practice, 2013*

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Radboudumc

PHD Portfolio

Name PhD candidate: W.W. Geense
Department: Intensive Care
Graduate School: Radboud Institute for Health Sciences

PhD period: 01-01-2017 – 31-12-2021
Promotors: Prof. J.G. van der Hoeven, Prof. H. Vermeulen
Co-promotor(s): Dr M. Zegers, Dr M. van den Boogaard

TRAINING ACTIVITIES

a) Courses & Workshops	Year(s)	ECTS
- Graduate school specific introductory course (RIHS)	2014	1.5
- Course 'E-Brok Course' (ethics in human research)	2015	1.5
- Course 'Scientific integrity'	2015	1.0
- Course 'Intervention mapping'	2013	1.5
- Course 'Academic writing'	2014	3.0
- Course 'Wetenschappelijk schrijven'	2014	3.0
- Course 'Biometrics'	2015	4.0
- Course 'Qualitative interviewing'	2015	1.0
- Course 'Qualitative analysis'	2017	1.0
- Course 'Systematic review and meta-analysis'	2017	1.5
- Opfriscursus statistiek met SPSS	2018	2.0
- Course 'Longitudinal data analysis'	2019	1.5
- Course' E-Brok recertification'	2019	0.2
- Individual career coaching	2019	1.0
b) Seminars & lectures		
- Presentations for ICU nurses	2019 - 2020	0.2
- Verpleegkundig refereren	2020	0.1
- Radboud Grand Rounds	2017 - 2020	0.6
- Care cursus	2017	0.5
c) Symposia & congresses		
- NFU sturen op kwaliteit	2017	0.2
- Regionale IC samenwerking	2017	0.2
- ESICM Vienna 2017	2017	1.0
- Radboud Gallilei Track: eindsymposium	2018	0.2
- Congres: De kracht van het netwerk -2de landelijke symposium voor ICU-netwerken	2018	0.2
- Post IC syndroom congres	2018	0.2
- ESICM Paris 2018	2018	0.5
- Venticare, Den Bosch	2019	0.5
- ESICM Berlin 2019	2019	1.0
- Congres Leven na de intensive care - 2020	2020	0.2

d) Oral and poster presentations at (inter)national events	Year(s)	ECTS
- ESICM Paris 2018 - Non-pharmacological interventions to prevent adverse outcomes among ICU survivors: a systematic review and meta-analysis	2018	0.5
- ESICM Paris 2018 - What is the patient's health status prior to ICU admission	2018	0.5
- Venticare 2019- Een jaar na IC opname: hoe gaat het met onze patiënten?	2019	0.5
- ESICM Berlin 2019 - Changes in frailty among ICU survivors and associated factors	2019	0.5
- ESICM Berlin 2019 - One year after ICU admission: physical, mental and cognitive outcomes	2019	0.5

e) Other		
- Research meetings Intensive Care Research	2017 - 2020	
- Verpleegkundig refereren	2017 - 2020	
- PhD Meetings nursing science	2017 - 2020	

TEACHING ACTIVITIES

f) Supervision of internships / other		
- Nursing science student	2019-2020	1.0

TOTAL	**33.8**

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