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**PHYSICAL AND PSYCHOLOGICAL PROBLEMS
AFTER CRITICAL ILLNESS
PREDICTION, DETECTION AND TREATMENT**

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CCRN



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To my family

*Pay attention to where you are going,
because without meaning you might get nowhere*

A.A Milne

ABSTRACT

The prevalence of physical and psychological problems after critical illness is high. To improve long-term outcome in Intensive Care Unit (ICU) survivors, follow-up programmes are under development. However, the optimal organization, duration and content of ICU follow-up has not yet been established and the efficacy of ICU follow-up is uncertain.

A new multidisciplinary model for helping ICU survivors by identifying and managing untreated physical and psychological problems was developed. Findings from the first year of follow-up were described and treatment effects of this interventional follow-up were evaluated. Novel methods for predicting patients at risk for physical and psychological problems following critical illness were investigated.

Multidisciplinary screening and treatment of problems was feasible in identifying and helping ICU survivors with untreated physical and psychological problems. Patients screened and treated in the first six months appeared to have little need for further ICU follow-up. Women reported more psychological problems than men after critical illness and multidisciplinary ICU follow-up reduced the prevalence of more severe symptoms of post-traumatic stress and depression in women. Predictive models for use at ICU discharge, separately screening for physical disability and psychological morbidity were developed. Weighted predictors for estimation of the probability of physical or psychological problems two months after ICU discharge were included in the two screening instruments. Significant predictors for new-onset physical disability were low education level, reduced core stability, fractures and an ICU stay >48 hours. Predictors for psychological morbidity were major pre-existing disease, being a parent to children <18 years of age, previous psychological problems, in-ICU agitation, being unemployed/on sick-leave prior to ICU admission and exhibiting depressive symptoms in the ICU. Both instruments had fair predictive accuracy in identifying ICU survivors with morbidity after ICU stay and performed better than ICU length of stay as a method of selecting patients with likely need for support.

Key words: Intensive Care Unit, Critical Care, Follow-up, Physical disability, Post-traumatic stress, Anxiety, Depression

LIST OF PUBLICATIONS

The thesis is based on the following publications and manuscripts, referred to as roman numerals in the text:

- I. Schandl AR, Brattström OR, Svensson-Raskh A, Hellgren EM, Falkenhav MD, Sackey PV.
Screening and treatment of problems after intensive care: A descriptive study of multidisciplinary follow-up.
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- II. Schandl A, Bottai M, Hellgren E, Sundin Ö, Sackey P.
Gender differences in psychological morbidity and treatment in intensive care survivors-a cohort study.
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- III. Schandl A, Bottai M, Hellgren E, Holdar U, Sackey P.
Early screening for new-onset physical disability after intensive care unit stay-a predictive study.
Submitted manuscript
- IV. Schandl A, Bottai M, Hellgren E, Sundin Ö, Sackey P.
Developing an early screening instrument for predicting psychological morbidity after critical illness.
Submitted manuscript

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LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
APACHE	The Acute Physiology and Chronic Health Evaluation
AUROC	The Area Under a Receiver Operating Characteristic
BMI	Body Mass Index
CAM-ICU	Confusion Assessment Method for the Intensive Care Unit
CCI	Charlson Comorbidity Index
ICU	Intensive Care Unit
ICU-MT	Intensive Care Unit Memory Tool
IES	Impact of Event Scale
HADS	Hospital Anxiety and Depression Scale
MAAS	The Motor Activity Assessment Scale
NICE	National Institute for Health and Care Excellence
PTSD	Post-Traumatic Stress Disorder
PTSS-10	Post-Traumatic Stress Symptom Scale 10
RASS	Richmond Agitation and Sedation Scale
SAPS	Simplified Acute Physiology Score
SF-36	Short Form-36

INTRODUCTION

CRITICAL ILLNESS AND INTENSIVE CARE MEDICINE

Critically ill patients suffer from acute physiological instability caused by injury, intoxication or disease, to an extent that urgent treatment is necessary to avoid future disability or death¹. A major purpose of intensive care is to support failing vital functions until the patient has recovered or causal treatment has improved the patient's condition. Treatment should prevent or improve vital organ failure in such way that life continues being meaningful for the patient². Initially, the Intensive Care Unit (ICU) was a postoperative ward specialized in cardiovascular monitoring or providing ventilator support for patients with acute or chronic respiratory failure^{1,3}. Depending on the resources available, modern intensive care medicine stretches from simple postoperative units to advanced ICUs with incorporated intermediate care¹ and with extended medical emergency teams, operating all over the hospital⁴. Organizational changes and new monitoring techniques, together with advances in medical research have permitted more efficient and aggressive treatment of critical illness^{1,5}. Intensive care medicine of today faces new challenges, with a growing population of elderly patients, severely injured patients surviving transport to the hospital and initial resuscitation as well as patients with chronic diseases suffering from acute complications that previously was considered terminal⁶. These patients may initially be treated successfully due to more aggressive intensive care and possibly more liberal admission to the ICU but these ICU survivors may potentially suffer from greater in- and post-ICU morbidity than those previously admitted to ICU's⁶.

THE ICU EXPERIENCE

The ICU context is different from other health care facilities or wards. Patients are continuously monitored and under surveillance by ICU clinicians. Many patients are temporarily dependent on highly technical equipment such as ventilator support, invasive monitoring or renal replacement therapy. Patients with an acute hospital admission may be unprepared for the situation and the potentially stressful or even painful ICU procedures and treatments⁷. The acute onset of life-threatening illness and the extreme physiological and psychological stress caused by injury or illness and ICU treatments may be traumatic for some patients⁸. Moreover, the ICU environment often deprives patients of normal sensory stimuli and instead implies a number of stressful stimuli such as constant noise, bright light and bed-side activity around the clock^{9,10}. Also, patient's awareness of the dependency on ICU clinicians and technical medical equipment for survival and recovery may promote feelings of helplessness, vulnerability and lack of control^{9,11}. To help patients endure ICU treatments and to reduce anxiety and stress, sedation may be required¹². Prolonged periods of unconsciousness and immobility, together with disturbed memory panorama may lead to future physical^{13,14} and psychological complications¹⁵⁻¹⁷.

MORBIDITY AFTER CRITICAL ILLNESS

Traditionally, outcome after critical illness has been reported in terms of short-term mortality. As advances in intensive care medicine have contributed to increased survival, patients' long-term health and well-being after critical illness has received increased attention¹⁸. Several studies have revealed that a substantial proportion of patients suffer from physical and psychological morbidity during the first year^{13,15,19,20}.

Physical disability

A major feature and one of the most important sequelae in ICU survivors, regardless of the reason for ICU admission is muscle weakness^{19,21-23}. Loss of muscle mass and acquired nerve dysfunction during the ICU stay induces complications such as reduced mobility, muscle weakness, and poor balance^{19,24}. Severe weakness associated with critical illness has been named "ICU-acquired weakness" and has been divided in three categories: critical illness myopathy, polyneuropathy and neuromyopathy²⁵. ICU-acquired weakness occurs in approximately 50% of ICU patients with sepsis, multi-organ failure or prolonged mechanical ventilation^{26,27} and has been regarded as a consequence of critical illness, treatments and prolonged immobility^{26,27}. ICU-acquired weakness is associated with increased ICU and hospital stay²⁶, delayed weaning from mechanical ventilation and reduced functional capacity^{28,29} and has been found to be an independent predictor of hospital mortality²¹. Muscle atrophy and weight loss, partly due to immobility, are other frequently observed problems following critical illness^{19,29}. Previous research has demonstrated that bed rest leads to 4-5% reduction of muscle mass per week, especially in the lower extremities³⁰. The interaction between immobility and critical illness appears to result in even more pronounced muscle reduction²⁹ and ICU patients may lose up to 20% of their baseline weight during prolonged ICU stay³¹. This loss of muscle mass may lead to difficulties in basic functions such as breathing and eating²⁰. Physical impairment may even be more pronounced in elderly patients, leading to decreased ability to manage basic activities of daily living (ADL) or even to live independently³². The physical disability may persist from weeks to years after ICU discharge, preventing patients from returning to normal life³³⁻³⁵. Incomplete recovery may lead to reduced quality of life^{18,24,36,37}, impaired daily functioning^{34,35} and delayed return to work^{31,38}. Approximately 50-70% of former ICU patients report functional limitations one year after ICU discharge^{34,35} and as few as 50% of ICU survivors have been reported to be able to return to work one year post ICU³⁹. There may also be other factors that may influence the trajectory of physical recovery, such as reduced physical function before hospitalization⁴⁰ as well as psychological morbidity⁴¹⁻⁴⁵.

Psychological problems

Anxiety, depression and posttraumatic stress symptoms have been widely reported problems after critical illness and ICU stay^{46,47} and may have profound effects on the recovery after critical illness⁴⁸. Many people have intense emotional reactions to the traumatic memories from the ICU. Some cope well with the emotional stress of severe injury, or illness. Others are more susceptible to develop psychological stress reactions after crises and remaining psychological problems are common⁴⁹.

Anxiety disorders

Even in patients with sound coping skills, severe illness or injury requiring ICU treatments is likely to incite some degree of anxiety. Anxiety is defined as a highly unpleasant emotional reaction in response to real or perceived threat, characterized by extreme worrying, nervousness or fear for future uncertainties and related to situations perceived as uncontrollable or unavoidable^{7,50}. The nervousness and dissociation often associated with anxiety may also cause physical symptoms such as tachycardia, increased blood pressure, tremors or shortness of breath⁴⁹. Worldwide, the prevalence of anxiety has been estimated to be approximately 4.5%, with higher prevalence in women (5.2%) than in men (2.8%)⁵¹. In ICU patients, the point prevalence of anxiety has been reported to be 24%¹³ (range 23-48%)^{34,52-54}. Different anxiety disorders such as generalized anxiety disorder, phobic disorder and post-traumatic stress disorder, have their own characteristics and symptoms and require different treatments⁴⁹. Anxiety is often co-morbid with other psychiatric disorders, particularly with depression⁴⁹. Clinical screening instruments, such as the Hospital Anxiety and Depression Scale⁵⁵ can be used to detect anxiety symptoms and may suggest a need for further, formal diagnostic assessment. Early diagnosis and treatment is essential to avoid chronicity and co-morbid psychiatric disorders^{7,49}. Treatment of anxiety disorders includes lifestyle changes as well as psychotherapy and in some cases pharmaceutical therapy⁴⁹.

Post-traumatic stress

Post-Traumatic Stress Disorder (PTSD) is a severe anxiety disorder, typically triggered by a traumatic event^{49,56}. Already in Homer's epic poems the Iliad and the Odyssey, symptoms resembling those of PTSD were described in those who returned after fighting the Trojan War. During the American Civil War, many soldiers reported physical symptoms such as tachycardia, anxiety and shortness of breath after the combat experience. The syndrome was named "Soldiers heart" or "Irritable heart". The psychological long-term consequences of combat was not officially recognized until World War II, when combat survivors, former prisoners of war and survivors from concentration camps reported considerable problems with psychological distress and mood disorders. This was the starting point for the construction of the PTSD diagnosis. However, it was not until after the Vietnam War that PTSD was accepted as a diagnosis and was included in the Diagnostic and Statistical Manual of Mental Disorders III^{49,56}. Today, PTSD is recognized to occur

in people exposed to a wide range of extreme life events, such as sexual assault, life-threatening accidents and sudden deaths of loved ones⁵⁶. PTSD is defined according to the Diagnostic and Statistical Manual of Mental Disorders⁵⁷ as the following: Exposure to a triggering traumatic event involving death, threat of death, threat of physical-, sexual- or psychological integrity to oneself or to someone else, to a degree beyond the ability to cope. The acute response to the trauma includes feelings of intense fear, helplessness and horror. Persistent symptoms of PTSD include three types of symptoms: 1) re-experiencing the trauma, in nightmares or in sudden intense memories, so called flash-backs 2) the avoidance of stimuli associated with the traumatic event 3) hyperarousal behavior such as anger and increased vigilance. Symptoms lasting for more than one month that cause significant impairment in social, occupational or other important areas of functioning are required for PTSD diagnosis⁵⁷.

Approximately 20% of ICU survivors are reported to suffer from PTSD⁴⁶, with prevalence rates ranging from 5-64% in the first year after ICU stay⁵⁸. Several studies have investigated risk factors for the development of post-traumatic stress after critical illness. Female gender^{8,59,60} and younger age^{8,60,61} have been identified as significant predictors of post-traumatic stress after ICU stay. In some follow-up studies, the use of benzodiazepines appears to play a role in development of PTSD^{8,62}. Other described risk factors are the dose of opiates⁶², low serum cortisol levels in ICU⁶³, prolonged duration of mechanical ventilation⁶¹ and long ICU stay⁶⁰. Also, upsetting memories from the traumatic event or from the ICU, as well as psychotic memories have been associated with the development of post-traumatic stress symptoms^{16,17}. Untreated PTSD is associated with reduced quality of life and an increased risk of substance abuse and suicide^{64,65}. PTSD treatments include exposure therapy, cognitive behavioral therapy or Eye Movement Desensitization and Reprocessing⁴⁹. The aim of treatment is to help patients from being anxious of the traumatic event and learning not to interpret reminding stimuli as a return to the trauma and finally to be more engaged in the present. For treatment of severe insomnia or severe anxiety symptoms, antidepressant medication has been used^{49,56}.

Depression

Depression implies severe quality of life impairment⁶⁶. Despair, hopelessness and apathy are common signs of depression, but insomnia and cognitive problems may also be present⁵⁷. Depression may cause physical problems such as tachycardia, stomach ache or dyspnea⁵⁷. Depressive problems have been observed in around 30% of ICU survivors^{47,52}, ranging from 8-57%⁴⁷. The prevalence of depression is clearly higher in ICU survivors than in the general population (7-8%)⁶⁷ or in patients with burn injury (4-13%)⁶⁸. Since many studies of ICU survivors exclude patients with pre-existing psychological problems, these findings suggest that being critically ill and treated in the ICU contributes to the development of depressive

symptoms¹³. In one study, clinical diagnostic interviews were used to determine the incidence of depression in ICU survivors⁶⁹. After pre-existing cases of depression were eliminated, 25-28% of ICU survivors were found to suffer from new-onset depression. Approximately 50% of these patients had major depression. Low educational level, unemployment, pre-ICU physical disability and neuroticism have been reported as pre-disposing risk factors for depression^{41,69-71}. Previous anxiety and depressive disorders as well as early symptoms of depression have also been demonstrated to be strong predictors for post-ICU depression^{47,69,72}. Co-morbidity between post-traumatic stress and depression is frequently observed after a traumatic event⁴⁹. Depression can usually be managed by psychotherapy and/or antidepressant medications⁷³. Untreated depression is associated with reduced quality of life, decreased working capacity and more seriously may lead to drug abuse or suicide^{64,74}.

STRATEGIES TO IMPROVE OUTCOMES IN ICU SURVIVORS

Physical and psychological impairment after critical illness may pass unrecognized by clinicians and may thereby remain inadequately treated⁷⁵. Previously, specific aftercare was rarely available for ICU patients⁷⁵, except for patients with cardiac diseases or brain injuries⁴⁸. In the last decade the problems after ICU stay have been highlighted and strategies to improve outcome and reduce ICU-related complications have started to develop⁷⁶.

In-hospital interventions

In the recent years, several studies have evaluated the efficacy of mobilization and muscle training, already in the ICU. One study evaluated the feasibility of an early mobilization programme for respiratory failure patients⁷⁷. A majority of the patients were able to walk more than 100 feet at discharge from the respiratory ICU. It was concluded that the programme was safe and feasible in preventing or treating neuromuscular weakness after critical illness. In another study evaluating the effectiveness of early activity, a “mobility team” consisting of nurses and physiotherapists initiated training within the first 48 hours of mechanical ventilation⁷⁸. In this study, patients with early mobilization had shorter ICU and hospital length of stay than patients not exposed to the intervention. In a randomized trial, physical therapy and occupational therapy during daily interruption of sedation – within the first days of ICU stay – resulted in better functional outcome at hospital discharge, shorter duration of delirium and more ventilator-free days⁷⁹. In a study with historical controls, a treatment bundle consisting of reduced sedation, more extensive physiotherapy and occupational therapy decreased ICU length of stay and hospital length of stay⁸⁰. In-ICU physical rehabilitation has been found to be safe and feasible⁸¹ but the continuity of rehabilitation after ICU discharge is uncertain⁸². In 2009, the National Institute for Health and Care Excellence (NICE) in the United Kingdom issued recommendations for rehabilitation after critical illness⁷⁵. The guidelines suggest

assessment of risk for physical and psychological problems, while the patient is under ICU treatment and once again after ICU discharge. NICE recommend that patients at risk for physical or non-physical problems should be offered tailored ward-based rehabilitation programmes, developed by a multidisciplinary team⁷⁵. Despite these extensive guidelines from NICE, few hospitals can provide such structured rehabilitation pathways. One study evaluated the feasibility and efficacy of a ward-based rehabilitation programme consisting of physiotherapy and nutrition interventions⁸². The intervention improved the frequency of physiotherapy, but no differences in muscle strength could be seen between treated and untreated groups. To achieve frequent and intense exercise for patients in the ICU or the ward after ICU discharge may sometimes be difficult, as patient may be uncooperative or refuse treatment due to fatigue⁸¹. Despite promising results in single studies, a generally feasible intervention to improve long-term outcomes in a general ICU population is yet to be determined²⁴.

Memories from the ICU stay may be fragmented or delusional and often include nightmares or hallucinations^{83,84}. Many ICU patients with confusing memories find the course of illness difficult to understand⁴⁸. Some patients find the recovery phase to be the most stressful period in the continuum of critical illness, as this is when they realize how seriously ill they have been⁸⁵. An observational study evaluated a newly introduced psychologist service during the ICU stay⁸⁶. The service was available during the entire ICU and hospital stay and included education, counseling and stress management for patients and their relatives. Patients receiving psychologist support had significantly less symptoms of post-traumatic stress compared to historical controls. Another method helping patients manage ICU experiences is the ICU diary⁸⁷. An ICU diary contains text and sometimes photographs of the patient in the ICU. The purpose of the diary is to give patients and their families a comprehensible explanation to ICU treatment and care⁸⁷. The diary may help patients to gain understanding in the course of illness and create realistic expectations about the time needed for recovery⁸⁸. In a recent study, the ICU diary reduced the incidence of post-traumatic stress three months after ICU discharge for a subgroup of patients with high levels of psychological distress⁸⁹. The content and the use of diaries varies in different hospitals and countries⁹⁰.

Outpatient interventions

There is currently little data supporting out-patient interventions in promoting recovery after ICU stay. Home-based programmes or self-help manuals could be a feasible option for ICU survivors as they often suffer from reduced mobility and may find it difficult to participate in hospital-based training⁹¹. Rehabilitation programmes with out-patient classes for ICU survivors have been found to be poorly attended⁸¹. In a randomized controlled trial, the efficacy of a post-ICU disease management programme was evaluated in patients with prolonged ICU stay⁹². The patients underwent a multidisciplinary supportive education programme

during the first two months after ICU discharge. Participants in the intervention group had significantly less days of rehospitalization. Another randomized multicenter trial assessed the effectiveness of a nurse-led ICU follow-up programme⁹³. The intervention consisted of a manual-based, self-directed physical rehabilitation programme starting in hospital and included two outpatient consultations. This study did not indicate that the programme improved quality of life nor was the programme found to be cost-efficient. In yet another randomized trial the feasibility and effect of a six-week self-help rehabilitation manual was evaluated¹⁷. ICU survivors randomized to the self-help rehabilitation improved in physical function assessed as a domain in self-reported quality of life. No significant differences between groups could be seen in anxiety, depression or post-traumatic stress symptoms. A home-based training programme for ICU survivors, with trainer visits and telephone follow-up was evaluated without finding differences in physical function or walking distance between intervention and standard care groups⁹¹.

ICU follow-up

As researchers increasingly include long-term quality of life, physical and psychological assessments as outcome measures, the knowledge of sequelae after critical illness and ICU stay has increased significantly. The awareness of these problems and an increased demand for information among ICU survivors has led to the development of national and international guidelines recommending ICUs to follow up patients after critical illness^{18,75,94,95}. Because of these guidelines, many hospitals around Europe have initiated ICU follow-up in order to help patients manage the multifaceted complications after critical illness. Between 17–44% of hospitals in Scandinavia and United Kingdom inhabit ICU follow-up clinics⁹⁶⁻⁹⁸. However, the organisation of ICU follow-up varies widely, as well as the amount of help the patients is offered⁹⁹. Most follow-up clinics are run by ICU staff^{48,98}, probably due their interest in long-term outcomes of critically ill and possibly greater awareness of the problems following critical illness than that in general practitioners¹⁸. ICU clinicians likely understand the origin of illness- or ICU-related problems and may be able to clarify problems or explain confusing memories and suggest appropriate physical rehabilitation. ICU-led follow-up also enables patient feed-back that can be returned to the ICU and thereby help improve care. Swedish guidelines recommended ICU follow-up at two, six and twelve months post-ICU for patients treated in the ICU for more than four days⁹⁵. ICU length of stay as a predictor of reduced long-term outcome is uncertain¹⁰⁰. The time point for initiating ICU follow-up and the number of appointments varies between hospitals⁹⁸. In spite of different structures of ICU follow-up services in different countries and hospitals, the main purpose of these programmes is generally similar: a) To inform the patients of what happened in the ICU, what treatments they received, while they were unable to give their consent b) To aid patients in managing physical and psychological problems following critical illness and the

ICU stay c) To receive feedback of ICU care and treatment from the patients and relatives.

As stated, a substantial proportion of patients suffer from physical and psychological problems after critical illness. Relatively little is known about what problems are due to ICU care, the illness or injury leading to critical illness or due to underlying characteristics or comorbidities in patients developing critical illness¹⁸. ICU follow-up is believed to improve long-term outcomes. ICU survivors appear to appreciate follow-up and when specifically asked, state that follow-up has improved their recovery from critical illness¹⁰¹⁻¹⁰³. However, the optimal organization, duration and content of follow-up has not yet been established⁹⁷. Any follow-up programme that differs significantly in its characteristics from those previously studied merits evaluation, as it has not yet been clearly established what component of follow-up may be beneficial to patients. Despite guidelines and widespread development of ICU follow-up programmes little is known of which patient will benefit from ICU follow-up⁹⁷. Knowledge of how to identify patients with significant post-ICU morbidity and how best to intervene to reduce the development of new-onset long-term problems would be of clinical benefit to ICU survivors, and also likely increase cost-effectiveness. An ICU follow-up designed for this purpose would improve resource allocation and offer the right patient the appropriate intervention.

AIMS OF THE THESIS

The principal objective of this thesis was to evaluate new methods for prediction, detection and treatment of physical and psychological problems after critical illness.

The specific aims were:

1. To describe the prevalence of physical and psychological problems in patients with prolonged ICU stay and evaluate the feasibility of managing these problems with a multidisciplinary ICU follow-up programme.
2. To compare psychological morbidity and treatment effects between patients enrolled in a multidisciplinary ICU follow-up programme and patients not offered such help.
3. To develop a predictive screening instrument – for use at ICU discharge – to identify patients at risk for new-onset physical disability two months after ICU discharge.
4. To develop a predictive screening instrument – for use at ICU discharge – to identify patients at risk for post-traumatic stress, anxiety or depression two months after ICU discharge.

MATERIAL AND METHODS

STUDY DESIGN

Paper I is a descriptive study¹⁰⁴ of a cohort of ICU survivors', assessing the prevalence of reported problems and interventions performed to help the patients manage these problems during the first year after critical illness. Paper II is a prospective quasi-experimental study¹⁰⁵ evaluating the effect of ICU follow-up. Two groups (follow-up group and control group) were compared concerning long-term psychological outcome following critical illness. To identify patients with increased likelihood for physical disability and psychological problems after critical illness (paper III,IV) we used a prospective cohort design¹⁰⁵. An overview of the material and methods used in the papers is shown in Table 1.

Table 1. Overview of study design, methods and outcome assessments.

Paper	I	II	III	IV
Design	Single center, descriptive cohort study	Single center, prospective quasi-experimental cohort study	Single center, prospective cohort study	Single center, prospective cohort study
Study population	All patients with an ICU stay ≥ 4 days coming for ICU follow-up in 2007	Control group: Patients with an ICU stay ≥ 4 days in 2006 Follow-up group: Patients with an ICU stay ≥ 4 days, 2007-Sept 2008	All patients treated in the General ICU during 6 months in 2011	All patients treated in the General ICU during 6 months in 2011
Participants	$n=92$	Control group: $n=151$ Follow-up group: $n=259$	$n=252$	$n=252$
Intervention	ICU follow-up	ICU follow-up	No intervention	No intervention
Outcome assessment	Physical function tests Questionnaires: IES, HADS, SF-36	Questionnaires: IES, HADS	Questionnaires: ADL-staircase	Questionnaires: PTSS-10, HADS
Time point for evaluation	3, 6, 12 months post-ICU	14 months post-ICU	ICU discharge and 2 months post-ICU	ICU discharge and 2 months post-ICU

ADL=Activities in Daily Living; ICU=Intensive Care Unit; IES=Impact of Event Scale; HADS=Hospital Anxiety and Depression Scale; PTSS-10= Post-Traumatic Stress Symptom Scale 10; SF-36=Short Form-36

SETTING

All studies were performed in the 13-bed General ICU and the ICU follow-up unit at Karolinska University Hospital Solna in Sweden. The hospital is a tertiary care hospital divided in two major sites (Solna and Huddinge) with a total capacity of treating 1600 patients. Since 2006 the hospital is a referral center for trauma patients in Metropolitan Stockholm. Approximately nine hundred adult patients with traumatic injuries, severe infections, surgical or medical diagnoses receive ICU treatment per year in the General ICU. The ICU has a patient to ICU nurse ratio of 1:1. No restraints are used and staff is present in the patient's vicinity at all hours. In 2012, the mean ICU length of stay was 3.4 days. For patients with an ICU stay longer than four days, mean ICU length of stay was 10.9 days⁹⁶. In 2007, an ICU follow-up clinic was established and is run by a multidisciplinary team consisting of nurses, a physiotherapist and doctors from the General ICU.

PARTICIPANTS

Paper I

Patients treated in the General ICU for more than four days during 2007 were included in the study. The patients were invited for ICU follow-up at three occasions during the first year of recovery. The selection of patients was in concordance with the current Swedish guidelines⁹⁵. Patients with shorter ICU stay but expressing a need for follow-up due to clearly ICU-related psychological problems were also included in ICU follow-up programme, as the purpose with ICU follow-up was to help patients cope with their situation. Patients resident in other counties were excluded due to their limited ability to attend to the ICU follow-up. The invitation for ICU follow-up was sent by postal mail to all eligible patients. All patients were asked to contact the follow-up clinic either to arrange time for appointment or to cancel the appointment. Declining patients were interviewed further about the reason for declining follow-up, their health status and memories from the ICU.

Paper II

Patients ≥ 16 years old, treated for more than four days (96 hours) in the General ICU were eligible for consecutive enrolment. Criteria for study inclusion were being resident in Sweden, being Swedish-speaking and not participating in an ICU follow-up programme in another hospital. These patients were considered being able to receive and complete the Swedish version of the evaluation questionnaires. The cohort of patients treated in the ICU during 2006 – when no ICU follow-up was available – constituted the control group. The follow-up cohort consisted of patients treated in the ICU in 2007 until September 2008. Patients in the follow-up group were offered three consultations at the follow-up clinic, at three, six and twelve months post- ICU⁹⁵. All patients offered ICU follow-up were considered being followed up, regardless of active participation in the follow-up programme or

not, in order to simulate the true efficacy (according to an intention to treat principle) of the follow-up programme.

Paper III, IV

For papers III and VI, the participants were recruited to both studies simultaneously. During six months in 2011 all ICU patients – regardless of ICU length of stay – were consecutively enrolled in the studies when discharged from the General ICU. Evaluation of risk factors at ICU discharge was necessary, thus patients transferred to ICUs in other hospitals were excluded. Also, non-Swedish speaking patients and patients with documented cognitive impairment were excluded as they were considered unable to complete the Swedish version of the questionnaires. Five patients were admitted shortly to the ICU for invasive procedures. These patients were not considered being ICU patients more than for administrative and practical reasons and were therefore excluded.

INTERVENTION

In paper I and II, ICU follow-up was considered an intervention. The Swedish Intensive Registry suggested a minimum follow-up for patients with an ICU stay longer than four days at two, six and twelve months post-ICU⁹⁵. Health-related quality of life was the only required assessment. Beyond these recommendations it was up to the individual ICU to develop a suitable follow-up routine. In 2007, we followed these recommendations but went further by setting up a multidisciplinary, interventional follow-up clinic with screening routines to identify untreated problems and established liaisons with specialists for managing these problems. All members of the follow-up team were clinicians working in the General ICU. Patients treated for more than four days in the ICU were visited in the ward by a nurse from the follow-up team within one week from ICU discharge. A brief recapitulation of the ICU stay was made and memories of events in the ICU were clarified. If the patient had an ICU-diary, it was given to the patient during this visit. The patients were then invited for follow-up at three, six and twelve months after ICU discharge. Prior to each visit the patient received four questionnaires by postal mail, to fill out and bring to the consultation. The screening instruments were used to screen for symptoms of anxiety and depression (Hospital Anxiety and Depression Scale), post-traumatic stress (Impact of Event Scale), memory panorama (Intensive Care Unit-Memory Tool) and score health-related quality of life (Short Form-36).

Hospital Anxiety and Depression scale (HADS)⁵⁵

HADS is a reliable screening instrument assessing clinical symptoms of anxiety and depression. It is also found to be a valid measure of severity of these disorders, which makes it a feasible instrument to measure changes in the patients' state with repeated assessments. The instrument is divided into two subscales, consisting of seven items for anxiety and seven for depression. Each subscale has four

alternatives, scoring from 0-3 and the total subscale score ranges from 0 to 21. The subscale scores indicate probable absence, possible presence or probable presence of anxiety or depression. In clinical settings, where the purpose is to include only those patients with a high probability of suffering from the disorders, a subscale score ≥ 11 is recommended. In research settings, when all possible cases are to be included, a subscale score of ≥ 8 is recommended⁵⁵. The Swedish version of HADS is valid in screening for anxiety and depression^{106,107}. HADS is found to have psychometric stability in assessing symptom severity and caseness, in somatic and psychiatric patients¹⁰⁸.

*Impact of Event Scale (IES)*¹⁰⁹

IES is a short self-administered screening instrument measuring symptoms of post-traumatic stress. The questionnaire consists of 15 items divided into two subscales. The first seven items concern intrusive memories and re-experiencing the traumatic event. The second part (eight items) assesses avoiding behavior and thoughts associated with the trauma. A Likert-like scale is used to evaluate how often the symptoms have occurred during the last week: 0=not at all, 1=rarely, 3=sometimes, 5=often. The total score ranges from 0 (no symptoms) to 75 points (maximum). Scores above 25 points are considered moderate to severe symptoms of post-traumatic stress¹⁰⁹. IES has been translated into Swedish¹¹⁰ and is considered to be a psychometrically sound instrument for evaluation of psychological stress in different medical settings^{111,112}. However, the instrument is not considered fully diagnostic of PTSD, as IES does not include hyper-arousal symptoms¹¹².

*Intensive Care Unit-Memory Tool (ICU-MT)*¹¹³

The ICU-MT consists of 14 items concerning the patient's memory panorama before, during and after the ICU stay. A checklist of different memories from the ICU stay allows the patients to mark what they remember. The memories are divided in three different categories: factual, emotional and delusional memories. The questionnaire has been validated and used for ICU follow-up in United Kingdom and Italy^{113,114}. It has been translated into Swedish, validated in a Swedish pilot study¹¹⁵ and is widely used in ICU follow-up.

*Short form general health survey-36 (SF-36)*¹¹⁶

SF-36 is a commonly used and well-validated questionnaire with the purpose to estimate self-reported physical and mental health. The questionnaire measures physical health as well as psychological well-being, summarized as health-related quality of life. SF-36 contains an eight-domain profile consisting of 36 items. The eight domains are: Physical functioning (ten items), Role-Physical (four items), Bodily Pain (two items), General health (five items), Vitality (four items), Social Functioning (two items), Role-Emotional (three items) and Mental health (five items). Each item measures physical or mental limitations and has a weighted response score. The eight domains with scores ranging from 0-100, can be

computed into two general summary scores; physical and mental component summary scores. There is one additional item, not included in the scoring system, assessing health changes during the past year¹¹⁷. SF-36 has been validated in the United States¹¹⁸ and tested in an ICU population in the United Kingdom¹¹⁹. The questionnaire has also been translated into Swedish¹²⁰ and validated in a Swedish general population¹⁰⁶.

At the ICU follow-up consultations, the instruments that the patient had filled out were collected and the scores were entered in a computerized spreadsheet. Thereby, the degree of psychological problems, self-reported quality of life and information regarding the patient's memory panorama from the ICU was computed. Screening scores and information was obtained online and could thereby be used at the consultation. Each clinical appointment included meeting a nurse, a physiotherapist and a doctor.

Meeting the nurse

During the meeting with the nurse, the patient's and relatives' experience of the ICU stay was in focus. Memories from the ICU stay were discussed, in part based on results from the ICU-MT. Some events, such as unreal memories were clarified. All patients were offered a visit to the ICU in order to better understand specific delusions or surreal ICU memories. Moreover, a structured checklist was used for charting the patient's current well-being following the ICU stay, including questions regarding occupational status, cognitive and/or social problems. Specific out of hospital needs such as insurance issues led to a referral to the patient counsellor at the General ICU.

Meeting the physiotherapist

The patients estimated their current ability to manage physical activities and they rated their previous and present level of physical activity with the help of a six-graded activity scale, where 0=no physical activity and 6= hard physical activity four to six days a week¹²¹. Validated function tests were used to measure grip strength, leg-strength and walking ability. Grip strength was assessed with a handheld dynamometer (JAMAR) and calculated as the mean value of three maximal contractions performed with the dominant hand. JAMAR-dynamometry is a reliable and simple method¹²² including normative data¹²³ and have been used as a substitute for overall muscle strength^{21,25}. Evaluation of leg-strength was performed with the Time Stands Test, a reliable and valid measure for lower extremity function¹²⁴. Patients were instructed to stand up as quickly as possible ten times from a chair without arm support and the total time needed was recorded¹²⁵. The six minute walk test is feasible for ICU survivors^{31,126} and assesses walking ability and functional exercise capacity¹²⁷. It is a self-paced test where the patient walks as far as possible in six minutes on a flat track and the distance covered in this time is recorded. In addition to distance walked, assessment of patients'

perceived exertion¹²⁸, self-rated breathlessness and fatigue in the quadriceps as well as heart rate was performed. Reduced physical function, compared with self-reported pre-ICU physical function was identified and those patients were referred to a physiotherapist near their home. Patients with specific physical problems after the ICU stay but considered capable of self-training were instead given instructions for training at home.

Meeting the doctor

The doctor recapitulated the ICU stay and medical investigations and treatments performed during the ICU stay were explained. Scores obtained from the psychological screening instruments (HADS and IES) were discussed with the patient. If the scores exceeded a set cut-off level, a psychiatrist referral was suggested to the patient. The screening instruments were used to identify potential problems rather than as diagnostic tools. Patients with high scores in the questionnaires but declining psychiatrist referral were interviewed further to preclude more severe problems, such as suicidal thoughts or post-traumatic stress symptoms not covered by the IES. These patients with high scores but not ready to visit a psychiatrist were urged to contact the ICU follow-up clinic, if they were to change their mind. Patients with untreated daily pain problems were referred to the pain clinic for further evaluation and treatment. For patients in need for other specialist follow-up, such as orthopaedic or neurosurgeon consultations that were not already planned, patients were encouraged to have a meeting set up.

DATA COLLECTION

Common for all papers, patient characteristics and ICU related data were obtained from medical charts and the local patient data management system.

Paper I

In paper I, follow-up assessments were made at the three follow-up appointments during the first year after intensive care. Physical function tests were performed during every physiotherapist consultation. The SF-36, ICU-MT and psychological screening instruments were sent home to the patients together with the invitation and were completed prior to each consultation. Patients declining follow-up were asked to explain the reason for not attending. Self-reported questionnaire scores and physical function test results were compiled as well as proposed interventions in order to manage the detected impairments.

Paper II

Data were collected prospectively for the participants in both groups. In order to evaluate ICU follow-up as an intervention, three questionnaires (IES, HADS and ICU-MT) were sent to participants in the control group and the follow-up group 14 months after individual ICU discharge (two months after the ICU follow-up contact was completed for the follow-up group). Data collection in paper II was

based on these self-reported assessments. IES and HADS were used to evaluate incidence of symptoms of post-traumatic stress, anxiety and depression. ICU-MT was used to investigate potential differences in memory panorama from ICU between the groups. Data of potential confounders were obtained from the medical chart (age, severity of illness, admission diagnosis, previous psychological problems, length of ICU stay, and length of sedation).

Paper III, IV

Risk factors for physical disability and psychological problems were identified through literature review and were selected in agreement with ICU clinicians, physiotherapists, an occupational therapist and a clinical psychologist. Eighteen potential risk factors were commonly assessed in both studies: Age, gender, marital status, educational level, occupational status, ICU length of stay, Simplified Acute Physiology Score III, diagnosis, comorbidity, previous psychological problems, use of midazolam and propofol, opiate infusions, ventilator treatment, delirium, ability to initiative, depressive symptoms and social support. Five specific potential risk factors for physical disability (fractures, Body Mass Index, oxygen demand, grip strength and core stability) and three specific potential risk factors for psychological problems (parenthood, in-ICU agitation and hallucinations) were included in the respective studies.

Information regarding patients' characteristics was obtained from the medical chart and the patient him/herself or their next of kin. Risk factors related to ICU treatment were assessed by revision of the patient data management system or medical charts. Hallucinations and depressive symptoms were evaluated by asking or observing the patient and ability to perform simple physical tasks were evaluated at by the patient's ICU nurse. Patients with no visits from next of kin were regarded as having reduced social support. To obtain data of the patient's previous physical function, the patient or next of kin was asked to estimate the need for assistance in six basic activities/functions (hygiene, dressing/undressing, toileting, mobility, continence and food intake) two weeks prior to hospitalization. The evaluation was based on the Katz ADL index^{129,130}, a method for basic assessment of functional ability in aged abled or disabled patients¹³¹. Two months after individual ICU discharge, patients received a demographic questionnaire together with the ADL-staircase by post, in order to estimate physical disability (paper III) and the Post-Traumatic Stress Symptom scale 10 and HADS (previously described in the thesis) to evaluate psychological morbidity (paper IV):

Activity of Daily Living Staircase¹³²

Reduced ability to perform activities of daily living was used as an indicator of physical disability. The ADL-staircase is a ten-item questionnaire providing information regarding patients' ability to independently manage basic activities¹³². It is an extended version of the Katz ADL index¹²⁹. The instrument comprises of

six personal ADL items¹²⁹; hygiene, dressing/undressing, toileting, mobility, continence and food intake as defined by the Katz index¹²⁹, extended with four instrumental ADL items; cooking, shopping, transportation and cleaning^{132,133}. Each item is rated on a three-graded scale regarding degree of dependency; independent, partly dependent and dependent. Dependency was defined as assistance from another person. Assessment of a patient's ability to perform these activities independently is considered a reliable and valid measure of functional status^{133,134}. The ADL staircase is a widespread instrument in a clinical context for evaluation of rehabilitation efficacy¹³⁵.

*Post-traumatic Stress Symptom Scale 10 (PTSS-10)*¹³⁶

The PTSS-10 is an ICU-specific self-administered screening instrument for symptoms of post-traumatic stress. It was originally developed from the Post-traumatic Syndrome 10-Questions Inventory¹³⁷ which was based on the Diagnostic Statistical Manual of Mental Disorders criteria⁵⁷. The first part consists of four items identifying possible traumatic incidences connected to the ICU stay i.e. pain, nightmares, anxiety and respiratory distress. The second part includes ten items assessing the intensity of symptoms of post-traumatic stress. Symptoms included are: sleep disturbance, nightmares, depression, hyper-alertness, withdrawal, irritability, frequent mood changes, guilt, muscle tension and avoidance of situations evoking recall of the ICU. The items are rated from 1=never to 7=always, with a total score ranging from 10 to 70 points. With a cut-off value of 35 points or more the sensitivity was 77% and the specificity 97.5% for the PTSD diagnosis¹³⁶. The instrument is considered being a reliable and valid instrument for post-traumatic stress screening in former ICU patients¹³⁶.

In paper III, patients were considered having new-onset physical disability if they had been working prior to the ICU stay and were on sick-leave due to physical impairment two months after ICU discharge or if they reported reduced ADL independency in the ADL staircase compared to pre-ICU physical function. For patients that reported ADL independency prior to the ICU stay and reported only impaired instrumental ADL at two months post-ICU, additional medical chart review and a phone call to the patients was made to confirm that the impairment was new-onset. In paper IV, psychological morbidity two months after ICU discharge was defined as PTSS-10 >35 and/or HADS ≥8.

Classification systems and definitions

The following systems were used to classify or define severity of illness, pre-existing disease, previous psychological problems, ADL status prior to ICU admission and presence of agitation and delirium (paper I-IV):

*The Acute Physiology and Chronic Health Evaluation (APACHE II)*¹³⁸

APACHE II is a system used to classify severity of illness during the first 24 hours of ICU stay¹³⁸. The scoring system estimates the degree of critical illness with fairly good precision and predicts survival in intensive care patients. APACHE II has been validated in different studies^{139,140} and is internationally used. The system is based on the measure of physiologic derangements caused by the injury or disease, but also takes age and comorbidity in account. Data are collected during the patient's first 24 hours in intensive care and the most divergent values of twelve physiological parameters render weighted scores depending on the degree of discrepancy from the normal values. The score range is 0-71, with higher scores implying more severe illness¹³⁸. During the years of study I and II, APACHE II was the scoring system for admission severity of illness used in our unit.

Simplified Acute Physiology Score III (SAPS III)^{141,142}

SAPS III is another scoring system for assessing early severity of illness and predicting mortality in ICU patients^{141,142}. The scoring system includes 20 variables and predicts the probability for hospital mortality. The SAPS III score range is 0-217 and is the arithmetic sum of three categories of admission data. The categories consist firstly of patient characteristics prior to ICU admission, such as age, previous health status and therapy before ICU admission, secondly, data regarding the circumstances for ICU admission and thirdly, deviant physiological values within one hour before or after ICU admission. The SAPS III has shown acceptable validity in discrimination and calibration¹⁴². In 2011, the General ICU changed the severity of illness scoring system at ICU admission from APACHE II to SAPS III.

*Charlson Comorbidity Index (CCI)*¹⁴³

CCI was originally developed to estimate the risk of ten-year mortality for patients with comorbid somatic diseases, for example heart disease or cancer. Each condition is assigned a weighted score of 1, 2, 3 or 6, depending on the mortality risk associated with this condition. The index was developed using survival data for medical in-patients and is commonly used for risk adjustment in ICU patients. The accuracy for CCI in predicting mortality assessed as AUROC curve was 0.63¹⁴⁴. We used the CCI as a system for scoring and comparing the burden of pre-existing diseases in the cohorts (paper I-IV).

Previous psychological problems

Information regarding previous psychological problems was used in paper II-IV and was collected from the medical charts or by asking the patient or next of kin. Our definition of previous psychological problems implied one of the following: a) a history of prior episode of depression or anxiety b) a psychiatric diagnosis in previous medical charts or c) documented alcohol or drug abuse.

The Motor Activity Assessment Scale (MAAS)¹⁴⁵

The MAAS is a sedation scale used for assessing level of arousal or sedation. Responsiveness is assessed and categorizes the patients in seven groups; 0=unresponsive, 1=responsive only to noxious stimuli, 2=responsive to touch or name, 3=calm and cooperative, 4=restless but cooperative, 5=agitated and 6=dangerously agitated and uncooperative. The MAAS has shown satisfactory reliability and validity in mechanically ventilated ICU patients¹⁴⁵. The sedation scale is widely used in ICUs and has been in use in the General ICU since many years. MAAS >4 was used to determine the presence of agitation in paper IV.

Confusion Assessment Method for Intensive Care Unit (CAM-ICU)¹⁴⁶

The CAM-ICU is a screening instrument for monitoring the presence or absence of acute confusion (delirium) in verbal or nonverbal ICU patients^{146,147}. The development of the instrument was based on criteria in the Diagnostic and Statistic Manual of Mental Disorders IV (DSM IV)⁵⁷. Delirium is considered present if the four criteria are fulfilled; 1) acute onset and fluctuating course 2) inability to concentrate or pay attention, 3) disorganized thinking and 4) changed level of consciousness¹⁴⁷. The instrument had good reliability and validity when used by ICU clinicians¹⁴⁸. The validated Swedish version¹⁴⁹ was implemented in the General ICU and used to evaluate delirium as a potential risk factor for functional disability (paper III) or psychological morbidity (paper IV).

STATISTICAL ANALYSES

The statistical analyses were performed using SPSS version 18.0-20.0 (SPSS Inc. Chicago, IL, USA) or Stata version 11 and 12 (StataCorp College Station, TX, USA). In all studies, continuous data were summarized by means \pm standard deviations, ordinal data as medians and interquartile range and categorical data as proportions. When the distribution of the continuous variables was skewed, medians and interquartile range were reported.

Paper I

In describing the follow-up group, differences between enrolled and excluded patients as well as between participating and declining patients were analyzed. Comparisons of demographic and ICU related data were performed with Student's t-test for continuous data, Mann Whitney U-test for ordinal data and Pearson's χ^2 -test for categorical data. Data collected at three, six and twelve months follow-up visits were analyzed over time. Physical function test results and normally distributed interval data in SF-36 were evaluated by using repeated-measures analysis of variance. The non-parametric Friedman's test was used for detecting potential differences in questionnaire scores (ordinal data) for IES and HADS across the three follow-up visits. A p -value<0.05 was considered statistically significant.

Paper II

In a previous study evaluating the effect of a rehabilitation manual after critical illness and intensive care, the intervention group and standard care group reported median IES scores of 15 and 25 points respectively¹⁷. We powered the study to detect a ten-point decrease in median IES score in the intervention group. When the power calculation was performed, the first patients were already invited for ICU follow-up and the number of participants in the control group was already defined. Thus, the power calculation was based on the expected number of control patients and number of patients needed in the follow-up group. With an α -level of 0.05 and >80% power to reject the null-hypothesis if the null hypothesis was false, the required minimum sample was 100 participants. To compensate for an estimated loss to follow up of 30%¹⁵⁰ and 20% mortality¹⁵¹ 150 patients were to be included in the follow-up group.

Student's t-test was used to test for mean differences between groups in normally distributed continuous data (age, APACHE II, CCI and ICU length of stay). Mann Whitney U-test was used for comparing continuous data when the distribution was skewed (length of sedation) and χ^2 -test was used for comparing categorical data (previous psychological problems, diagnosis group and ventilator treatment)¹⁵². Questionnaire scores in IES and HADS were considered ordinal variables, and their median values were reported. Outcome variables were compared between groups based on an intention to treat principle. Logistic quantile regression analysis¹⁵³ was used to assess for the hypothesized difference between men and women and to control for potential confounders (age, comorbidity, previous psychological problems, length of ICU stay, APACHE II, diagnosis groups, length of sedation). Logistic quantile regression analysis allows testing differences between groups with respect to the median, or any chosen percentile, of a bounded outcome variable of interest after adjusting for confounders. We considered the three quartiles (25th, 50th and 75th percentile) of IES and HADS. In our study, scores above the 75th percentile indicated the prevalence of more severe problems of post-traumatic stress (IES) and anxiety/depression (HADS). The follow-up intervention was included as an independent variable in all regression models. The potential confounding effect of the variables was assessed by entering variables one at a time in the models. Variables that changed the estimated coefficient of the follow-up intervention by more than ten percent were kept in the final analysis.

Paper III,IV

The suggested "rule of thumb" sample size to develop predictive models requires around ten cases per predictor¹⁵⁴. We estimated that the model would be developed including no more than ten predictors. With dropouts and mortality taken into consideration, a sample size of 150 patients was considered to likely be sufficient. Differences in continuous and categorical data for responders versus non-

responders were examined with Mann Whitney U-test respectively Fisher's Exact Test. *P*-values <0.05 were considered to indicate statistical significance but for potential predictors, *p*-values of <0.10 in the univariate comparison merited exploration in the predictive model. Analyses were performed separately for physical disability and psychological problems. Missing values in risk factor assessment were considered to imply absence of the specific risk factor. Use of midazolam and propofol as well as ventilator treatment and fractures were first examined as continuous variables, then categorized in three groups and finally dichotomized (0 versus ≥ 1) because of their skewed distribution. Data for all potential risk factors were examined for univariate associations. Univariate associations between risk factors and outcome were assessed in a logistic regression model with one covariate at a time. Variables with a *p*-value >0.10 in the univariate analysis were excluded from further analysis. The remaining variables were entered in a multivariable logistic regression model in order to evaluate predictive power for adverse physical or psychological outcomes. The AUROC curve was utilized as a measure of the predictive accuracy of the two models. The predictors in each model were removed one at a time, and the AUROC curve was recalculated each time. To adjust for potential over-fitting of the predictive accuracy in the screening instrument when applied to a new group of ICU patients, the AUROC curve was internally cross-validated in 1000 random bootstrap samples. The bootstrap samples were generated by random sampling from the original dataset. The AUROC curve for ICU length of stay as an only predictor for psychological problems and physical disability was also calculated, to enable comparisons of the models and screening instruments with the current Swedish guidelines in selection of patients for ICU follow-up. In a post-hoc analysis and for practical reasons, we categorized patients according to their probability to have physical disability and psychological problems in low risk, moderate risk, and high risk groups.

ETHICAL CONSIDERATIONS

The studies were performed in compliance with the fundamental principles of medical research referred to in the World Medical Association's declaration of Helsinki¹⁵⁵. Study participants were treated with respect and their interests were prioritized over scientific needs. All participants received verbal and written information regarding purpose of the study. Voluntariness was emphasized and confidentiality in reporting the data was guaranteed. Paper I and II contain demographic data comparisons between responders and non-responders. Consent from non-attending patients (paper I) and non-responders in the control group (paper II) was not obtained. However, demographic information for the group of non-attending patients was important for the overall interpretation and external validity of the results. In study III and IV, written informed consent was obtained from the participants during the week after ICU discharge. In patients declining study participation, the collected risk factors were immediately removed from the database. However, basic characteristics for patients not completing evaluation

questionnaires two months after ICU discharge were kept in order to compare demographics between responders and non-responders. Completing questionnaires regarding memories and events from the ICU may potentially evoke unpleasant memories and undesirable feelings. Patients in the control group in paper II, without formal follow-up (as this was not operating at the time for their ICU discharge) were asked to contact the ICU follow-up clinic if they perceived the received questions upsetting in any way. All patients in paper III and IV were offered a visit to the ICU follow-up clinic in the letter accompanying the questionnaires. Patients declining ICU follow-up despite reporting high scores (above the cut-off level) in the psychological screening instruments were contacted by the researchers for further information regarding the follow-up service and possible referral to a psychiatrist.

RESULTS

PATIENT CHARACTERISTICS AND RECRUITMENT

Paper I

In 2007, 136 patients were treated for more than four days in the General ICU. According to the Swedish guidelines for ICU follow-up⁹⁵ these patients were entitled ICU follow-up. Ninety-two patients were invited for follow-up after exclusion of patients resident abroad ($n=4$) and patients that died between ICU discharge and three months post-ICU ($n=43$). Patients that died were significantly older, had a longer ICU length of stay and more co-morbidities (higher CCI score) compared to surviving ICU patients. Three patients with an ICU length of stay shorter than four days were invited for follow-up, one with evident in-ICU psychological distress reported by ICU clinicians and two patients that contacted the clinic because of difficulties to cope with stressful ICU memories. In total, sixty-one patients attended the consultations. Declining patients had significantly more co-morbidities. Patients that declined follow-up were asked to specify the reason for declining, and the main stated reason was “no need for follow-up”. Thirty of the attending 61 patients came for all three consultations.

Paper II

As in study I, patients with an ICU stay longer than four days (96 hours)⁹⁵, were consecutively included in the study. The control group and the follow-up group enrolled 151 and 259 patients respectively. After excluding deceased patients and those unable to complete the Swedish version of the questionnaires, 102 and 156 patients in each group remained for evaluation. Four patients from the control group suffered from pronounced psychological problems and contacted the researchers for help. We considered it unethical not to give these control patients support that was available and therefore they were invited for ICU follow-up. According to an intention to treat concept, data from these patients remained in the control group when analyzed. There were no significant differences in baseline characteristics or ICU-related data between the groups. Response rates were 72% in the control group and 63% in follow-up group. Demographic data in responders versus non-responders were similar. No significant differences in baseline data were found between individual gender groups. The internal consistency for IES and HADS was good for the control and follow-up group. In the control group, Cronbach's α for IES was 0.88 for intrusion and 0.87 for avoidance and in the follow-up group 0.81 and 0.82 respectively. For HADS Cronbach's α was 0.88 for anxiety and 0.83 for depression in the control group and in the follow-up group 0.87 for both subscales.

Paper III, IV

Three hundred eighty-nine patients were discharged from the General ICU during the study period and were eligible for inclusion. Thirty-five percent were excluded

because they were readmitted to the ICU ($n=35$), assessment at ICU discharge was not possible ($n=40$), patients were unable to complete questionnaires ($n=54$), too young for participation ($n=2$) and admitted to the ICU for short invasive procedures ($n=5$). Thus, 252 patients were enrolled in the study. In order to effectively use the material, ICU clinicians' time and patient time, study III and IV originated from the same sample of participants. Eighteen of the potential risk factors were considered common for physical and psychological problems after the ICU stay. Sixty-four percent completed the questionnaires. The majority of non-responders did not give a reason for not completing the questionnaires. Fourteen percent withdrew consent to participate. In five patients the next of kin stated that the patient was too sick to participate. Questionnaire results of four patients in paper III and two in paper IV were excluded due to missing items. Questionnaire responders were older and had more pre-existing diseases compared to non-responders. These patients constituted the sample in study III and IV.

DETECTION (PAPER I)

A substantial proportion of patients with prolonged ICU stay suffered from physical or psychological problems after critical illness. Sixty-five percent of patients ($n=40$) had no on-going physical rehabilitation three months after ICU discharge, despite considerable physical disability post-ICU compared to self-reported pre-ICU function. Patients with specific physical impairment and considered capable of self-training ($n=22$) received training instructions from the physiotherapist at the follow-up consultation. Eighteen patients with profound physical disability were referred to a physiotherapist for more extensive training. In patients that came for all three consultations ($n=30$) improvement over the year was seen in leg strength and functional capacity. Fifty-six percent ($n=34$) reported scores above the cut-off value for clinical psychological problems in IES and or HADS. Patients with high scores were significantly younger than patients with low scores. Twelve patients accepted a referral to a psychiatrist. Three patients declined the appointment before meeting the psychiatrist. Three patients were diagnosed with anxiety disorders (PTSD $n=1$, height phobia $n=1$, generalized anxiety disorder $n=1$) of which one suffered from a combination of anxiety and depression and two patients of depression alone. Four patients had recovered spontaneously between time point for referral and the psychiatrist consultation. Symptoms of anxiety seemed to improve over the year in patients coming for all three consultations. However, in health-related quality of life (SF-36) improvement was mainly seen between three and six months. Three patients were referred to the pain clinic for untreated pain problems and four patients with social or practical problems received a referral to the patient counselor. Interventions arranged by the ICU follow-up were mainly performed during the three or six month consultation (Table 2). The majority of patients declining further follow-up stated that they had received help with their current problems and felt no need for further follow-up.

Table 2. Referrals during the first year after ICU stay

Referrals	3 months	6 months	12 months
	<i>n</i> =61	<i>n</i> =43	<i>n</i> =30
Psychiatrist	7	3	2
Pain clinic	1	1	1
Physiotherapy	6	10	2
Training instructions	11	11	0
Patient counselor	3	1	0
Total number	28	26	5

The multidisciplinary model for ICU follow-up was feasible for identifying and managing untreated problems after ICU stay. Most identified physical and psychological problems described by the patients and identified by the follow-up service could be addressed in the pre-set context of ICU follow-up. Physical function tests and psychological screening instruments provided a standardized method to evaluate patients' post-ICU function. The tests and questionnaires facilitated identification of otherwise unsuspected problems and provided an objective base for specialist referrals. The prearranged routes for referrals made it possible for the ICU follow-up to manage most of the identified problems. Referral replies were, according to agreement with referral recipients, directly to the general practitioner, who thereby was involved in further evaluation of the treatment.

TREATMENT (PAPER II)

In paper II, ICU follow-up was evaluated with regard to the prevalence and severity of psychological problems. As hypothesized, sex was an important effect modifier and analyses were therefore performed separately for men and women. In patients with no ICU follow-up (control group), women reported significantly more symptoms of post-traumatic stress (higher IES score) than men in the same group. More importantly, women in the follow-up group had less severe self-reported symptoms of post-traumatic stress than women in the control group. Age and ICU length of stay showed confounding effects. Previous psychological problems predicted later psychological morbidity and have been suggested to confound long-term psychological outcomes and were therefore also treated as a potential confounder. After adjusting for these variables, IES scores remained significantly higher in women in the control group compared to women in the follow-up group. Additionally, the 75th percentile in IES and HADS-depression, corresponding to high scores or high degree of adverse psychological symptoms, was significantly higher in women in the control group than in women in the follow-up group. In men, no significant differences in psychological outcome between the control group and the follow-up group were found. Women receiving psychiatric evaluation and treatment improved significantly in IES and HADS scores between three and 14 months. In treated men no such improvement could be seen which was an uncertain

finding as only three of the referred male patients completed the questionnaires at both time points.

PREDICTION

As stated previously, the current selection of patients invited for ICU follow-up is based on their ICU length of stay ⁹⁵. The accuracy for ICU length of stay as a predictor of new-onset physical disability expressed as AUROC was 0.70 and for psychological morbidity as low as AUROC=0.53. By evaluating risk factors for physical and psychological morbidity at ICU discharge two predictive screening instruments were developed. The first screening instrument identified patients at risk for physical disability and the other identified patients at risk for post-traumatic stress, anxiety or depression.

Prediction of new-onset physical disability (paper III)

In total, twenty-three risk factors for physical disability were evaluated at ICU discharge, of which twelve risk factors with *p*-values <0.1 in the univariate association analysis were entered in the multivariable logistic regression model (Table 3). After modeling, four predictors remained in the model. Low education level, impaired core stability, fractures and an ICU stay longer than two days were predictive of physical disability two months after ICU discharge and were included in the screening instrument.

Table 3. Univariate associations between risk factors and physical disability

Risk factors	Univariate associations (<i>p</i> -values)
Age	<0.01*
Gender	>0.1
Marital status	>0.1
Education level	<0.001*
Occupational status pre-ICU	>0.1
ICU length of stay	<0.001*
SAPS III	<0.1*
Diagnosis	>0.1
Comorbidity	<0.1*
Psychological problems pre-ICU	>0.1
Propofol use	>0.1
Midazolam use	<0.05*
Opiate infusion	>0.1
Ventilator treatment	>0.1
Delirium	<0.05*
Fractures	<0.001*
Body Mass Index	>0.1
Oxygen demand	>0.1
Grip strength	>0.1
Core instability	<0.001*
Ability to initiative	<0.01*
Appears depressed	>0.1
Social support	>0.1

*Included in the multivariable logistic regression model. BMI=Body Mass Index; ICU=Intensive care unit; SAPS III= Simplified Acute Physiology Score III.

ICU length was dichotomized with a cut-off of more than two days as this cut-off demonstrated a distinct divergence in the predictive value. The regression coefficient of each predictor was transformed into a risk score by multiplying it by 30. This simplified the calculation of the risk scores and also made the total risk score relatively similar to the risk of new-onset physical disability in percent. The predictive accuracy of the model expressed as AUROC was 0.82. The cross-validated 1000-bootstrap sample AUROC was 0.80. The screening instrument for use at ICU discharge, identifying patients at risk for new-onset physical disability is presented in Figure 1.

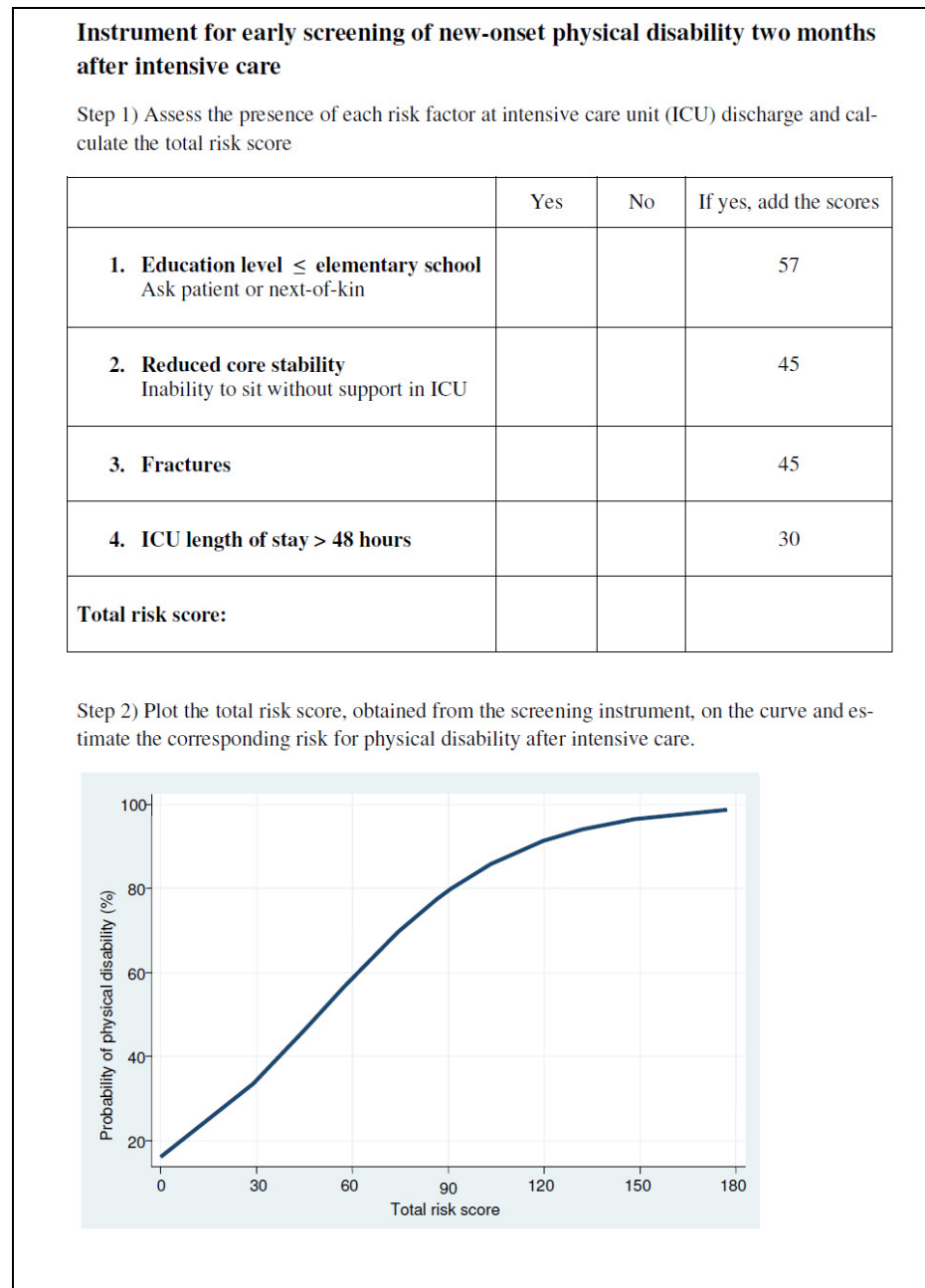


Figure 1. Instrument for early screening of new-onset physical disability two months after ICU stay.

Prediction of psychological morbidity (paper IV)

In total, twenty-one risk factors were evaluated in enrolled patients at ICU discharge, of which seven predictors with $p < 0.1$ in the univariate association analysis remained for inclusion in the multivariable logistic regression model (Table 4). Finally, six variables were associated with and predictive of adverse psychological outcome after critical illness. The predictors were: Major pre-existing diseases (defined as CCI > 3), having children younger than 18 years of age, previous psychological problems, in-ICU agitation, being unemployed or sick-listed at ICU admission and showing depressive symptoms in ICU. Major pre-existing diseases were defined as a total CCI score > 3, as this cut-off showed a distinct divergence in the predictive value. The regression coefficients of these variables were equivalent to their associated probability for adverse psychological outcome. In order to make the coefficients easier to compute and interpret, they were multiplied with 25 and named “risk scores”. The individual and total risk scores were almost equal to the risk of adverse psychological outcome in percent. The predictive accuracy of the model, assessed as the AUROC was 0.77. The cross-validated 1000 bootstrap sample AUROC was 0.72. The screening instrument for psychological morbidity is shown in Figure 2.

Table 4. Univariate associations between risk factors and psychological morbidity

Risk factors	Univariate associations (<i>p</i> -values)
Age	>0.1
Gender	>0.1
Marital status	>0.1
Children < 18 years	<0.05*
Education level	>0.1
Occupational status pre-ICU	<0.05*
ICU length of stay	>0.1
SAPS III	>0.1
Diagnosis	<0.1*
Comorbidity	<0.01*
Psychological problems pre-ICU	<0.01*
Propofol use	>0.1
Midazolam use	>0.1
Opiate infusion	>0.1
Ventilator treatment	>0.1
Delirium	>0.1
Agitation	<0.1*
Hallucinations	>0.1
Ability to initiative	>0.1
Appears depressed	<0.1*
Social support	>0.1

*Included in the multivariable logistic regression model. ICU=Intensive care unit; SAPS III=Simplified Acute Physiology Score III.

Instrument for early screening of psychological morbidity two months after intensive care

The instrument is used for screening at Intensive Care Unit discharge.

Step 1) Assess the presence of each risk factor and calculate the total risk score

	Yes	No	If yes, add the scores
1. The patient has Charlson Co-morbidity Index¹ (CCI) > 3 See table below			50.5
2. The patient has children < 18 years of age			31.5
3. The patient has previous psychological problems Defined as prior episodes of depression, anxiety or having other psychiatric diagnoses and/or documented alcohol or drug abuse. If possible, ask the patient or his/her next-of-kin.			28.5
4. The patient was unemployed or on sick-leave at intensive care unit (ICU) admission			12
5. The patient was agitated <u>in</u> ICU MAAS ² > 4, defined as aggressive behavior with confusion or panic.			20
6. The patient appeared depressed <u>in</u> ICU Defined as sadness, apathy or feelings of hopelessness. If possible, ask the patient if he/she feels depressed.			7.5
Total risk score:			

²Devlin JW, et al. Motor activity assessment scale: A valid and reliable sedation scale for use with mechanically ventilated patients in an adult surgical intensive care unit. *Crit Care Med* 1999;27(7):1271-1275.

Figure 2. Instrument for early screening of psychological morbidity two months after ICU stay, page 1.

¹Identify any pre-existing disease and summarize the total Charlson Co-morbidity Index score (CCI). If the total score exceeds 3 tick yes in the box above.

Medical conditions	Scores
Myocardial infarct	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Ulcer disease	1
Mild liver disease	1
Diabetes	1
Hemiplegia/paraplegia	2
Moderate or severe renal disease ^a	2
Diabetes with end organ damage ^b	2
Any tumor	2
Leukemia/lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumor	6
AIDS	6

Summarized CCI-score

^aPatients on dialysis, with uremia or who have had kidney transplantation. ^bPatients with retinopathy, neuropathy, nephropathy, with juvenile onset or previous episodes of ketoacidosis or hyperosmolar coma.

Step 2) Plot the total risk score obtained from the screening instrument on the curve and estimate the corresponding risk for adverse psychological outcome after intensive care.

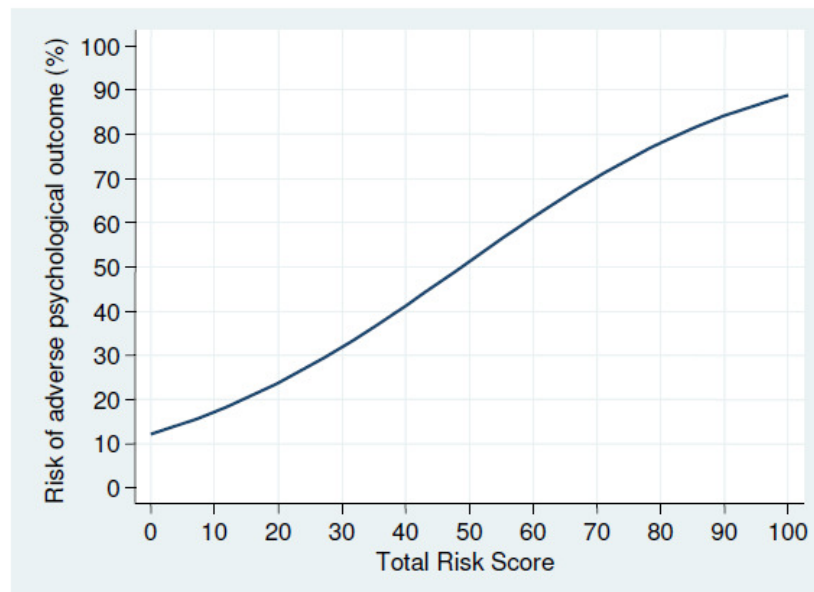


Figure 2. Instrument for early screening of psychological morbidity two months after ICU stay, page 2.

Triage of risk groups

To visualize the risk probability and potential workload associated with different triage cutoffs, patients were categorized in low risk, moderate risk and high risk groups according to their probability for new-onset physical disability or psychological morbidity. Patients were considered at high risk if the probability exceeded 70% for physical disability and 60% for psychological problems.

Utan tvivel är man inte klok
Tage Danielsson

DISCUSSION

METHODOLOGICAL CONSIDERATIONS

Study design

The research question and feasibility in data collection determined the choice of study design. In paper I, we employed a descriptive design¹⁰⁴, as our purpose was to investigate and describe the magnitude of physical and psychological problems after critical illness, rather than to infer cause and effect. The study was intended for ICU clinicians in developing ICU follow-up programmes and interventions for managing these problems. In paper II, a quasi-experimental design¹⁰⁵ without randomization was used in evaluating the efficacy of ICU follow-up in two cohorts. Since Swedish guidelines⁹⁵ recommend ICU follow-up for patients with prolonged ICU stay, we chose not to randomize patients but instead compare patients before and after the introduction of the ICU follow-up programme in 2007. Follow-up data was collected prospectively for the two groups and potential differences in baseline data were controlled for in the analysis. For papers III and IV, a prospective cohort design¹⁰⁵ was used to identify potential predictors for developing the predictive models. The selection of patients and predictors was predefined and enabled prospective recording of risk factors and outcome assessment¹⁵⁴.

Sample size

In paper I, the available sample during one year of ICU follow-up was used to illustrate the magnitude of problems in this cohort. As no inferential goal was intended, no power calculation was performed. In paper II, the power calculation was based on detecting potential differences primarily between the control and follow-up group, and not for stratification of gender. At this time point, the first patients were already invited for ICU follow-up and the control group was already defined. When sample size for the follow-up group was accomplished, inclusion of participants was terminated, as long inclusion time may increase the risk for changes in ICU routines or treatments¹⁰⁵.

Selection bias

In paper I, self-enrolment contributed to that only 60% of invited patients with prolonged ICU stay actually came for follow-up and was eligible for evaluation. The prevalence of psychological problems in these patients was relatively high compared to other studies^{46,47,156,157}, which could indicate a risk for self-selection bias¹⁰⁵. Patients with considerable impaired physical or psychological problems might have chosen to come for ICU follow-up for help and treatment. Healthier ICU survivors might have declined follow-up as they felt no need for help. On the other hand, it may be difficult for patients with reduced mobility and/or considerable physical disability to participate in an outpatient ICU follow-up programme¹⁰³.

Attrition

In paper I, improvement over time was noted in patients with complete data at all three consultations. Patients declining the second or third consultation stated that they were satisfied with received help and perceived no need for further follow-up. In paper II, a higher response rate was obtained in the control group compared to the follow-up group (72% versus 63%). The lower response rate in the follow-up group may have been a result of “study fatigue” as patients coming for the follow-up consultations were requested to fill out the same screening instruments at each consultation as a follow-up routine. A response rate of 60-70% has been considered a realistic goal for postal questionnaires in ICU survivors^{36,158}. Attrition is rarely entirely random¹⁰⁴ and there may be a variety of reasons for loss to follow up and attrition. ICU patients may be a difficult group to study due to the high rates of mortality and morbidity. Moreover, people with psychological problems may be more reluctant to participate in studies investigating psychological morbidities^{159,160} and in trauma research, the difficulty of obtaining high response rates is a familiar problem¹⁶¹. Patients experiencing avoidance symptoms of PTSD or suffering from depression may be less likely to return screening instruments. On the other hand, patients who make a full recovery from an episode of critical illness may be more likely to drop out of the study because they find the research irrelevant to them. Generally, questionnaire non-responders have been associated with being male, younger age, having less formal education and poorer health status¹⁶². In paper III and IV, non-responders were younger and possibly healthier as they had less comorbidity and shorter ICU stay than responders.

Information bias

Measurement error

When developing a model for clinical use, definitions of risk factors that are in line with daily practice should be employed¹⁵⁴. The selection of risk factors in study III and IV was based on relevant literature and only those found to be feasible for evaluation before ICU discharge were chosen. Thus, some relevant risk factors may not have been included. Memories of potentially traumatic events appear to play an important role in the development of post-traumatic stress⁵⁶, but are difficult to assess at ICU discharge as the trauma may still be ongoing. As far as possible we used standardized methods in evaluating the presence of risk factors. Agitation is assessed in most ICUs with a validated sedation-agitation scale^{163,164}. In our ICU, we used MAAS for agitation assessment at the time of the study and agitation was associated with later adverse psychological outcome. While the Richmond Agitation and Sedation Scale (RASS)^{165,166} may be a more widely accepted scale internationally, MAAS and RASS are very similar with regard to the cutoff between a calm and agitated patient. Some potential predictors were not assessed with formal, validated methods. To our knowledge, there is no standardized method for in-ICU assessment of hallucinations and depressive symptoms. Thus, these risk factors were assessed without screening tools. We considered that the nurses were capable to assess the

presence of hallucinations in their clinical routine. Three times daily the patient's nurse assessed the presence of hallucinations by asking the patient if he/she perceived any unreal sensations or hallucinations. A more formal evaluation of hallucinations could have been performed by psychologists or by using validated scales, but we believed it would have precluded everyday completion of the checklist in most units. Depressive symptoms were assessed in communicative patients by asking the patient if he/she felt depressed. For patients verbally unable to express their feelings (e.g. tracheostomy, general fatigue), other signs of depression were noted (apathetic behaviour or crying). Regarding the validity of nurses' assessment of depressive symptoms, previous meta-analysis concluded that different nursing categories have significantly different accuracy, where hospital nurses assessment of depression had a sensitivity of 43% and a specificity of 80%¹⁶⁷. They also stated that proximity to patients may be an important factor in correctly assessing depression. As far as we know, no study has specifically investigated ICU nurses, a nursing group with probably the highest nurse-to-patient ratio in many hospitals. In our study, nurses' assessment proved to be predictive of adverse psychological outcome.

Misclassification

In paper III and IV, several risk factors were dichotomized. Delirium was classified as one or more positive assessments in the CAM-ICU. Another possibility would be to classify delirium as number of delirium-free days or to discriminate between hypo- and hyperactive delirium¹⁶⁸. Assessment of previous psychological problems was performed by using medical records, which may vary in completeness and accuracy. To improve the accuracy of information, we asked the patients or their next of kin, in addition to reading the patient's medical chart. Considering the documented importance this risk factor has for subsequent psychological problems in numerous studies, we considered it important to assess. We felt fairly confident in that our combined approach in assessing previous psychological problems was as effective as is possible in the real life situation and realistic to achieve in the vast majority of patients. As the assessment of physical disability and psychological morbidity was performed with self-reported methods instead of using function tests and psychological interviews, a risk for misclassification may be induced. However, the ability to take care of personal hygiene and needs independently has been considered a credible measure of functional outcome¹⁶⁹. Recovering functional independence after hospitalization is of clinical importance for patient well-being¹⁷⁰. While the ADL-staircase was originally designed to be used by an occupational therapist or a physiotherapist assessing functional status by observing patients perform activities of daily living, the instrument has also been used as a questionnaire for self-reported ADL dependency in ICU survivors¹⁷¹. The instrument is shown to be most effective in an elderly population¹³⁴, probably due to a risk of a ceiling effect in younger patients. It would have been optimal to use the same questionnaire both to estimate the pre-ICU function and physical disability two months post-ICU.

IES was our choice to assess symptoms for post-traumatic stress in paper I and II and is considered to be a valid method for measuring symptoms of post-traumatic stress, but does not assess symptoms of hyper-arousal which is included as a diagnostic criteria for PTSD⁵⁷. For study IV we chose to change our screening tool for post-traumatic stress to PTSS-10, which assesses all three symptom clusters of PTSD and is validated in an ICU population¹³⁶.

Recall bias

Most ICU patients are acutely admitted to the hospital, precluding prospective baseline assessment for previous physical or psychological problems. To estimate pre-ICU function in paper III, patients or their next of kin were asked to rate ADL independency retrospectively on the Katz index which may induce a risk of recall bias. Most patients in this study (95%) rated no functional dependency prior to ICU admission, information we believe might be easier to recall than estimating some degree of dependency on an ADL-scale. Retrospective reporting of functional status have previously been found to correlate well with objective findings¹⁷².

Information pertaining previous psychological problems were obtained from the medical chart of the patient him/herself. In assessing psychological morbidity, under-reporting of psychological problems is commonly seen¹⁷³ possibly because it may be embarrassing for a patient to admit mental health problems¹⁷⁴.

Confounding bias

In paper II, confounding was potentially relevant as patients were not randomized into groups. Data from the comparison group (controls) were collected immediately prior to data for the follow-up group, thereby limiting the risk for bias related to changes in patient case-mix, ICU routines or treatments. In order to compare ICU routines and case-mix, data from the Swedish Intensive Care Registry (www.icuregswe.org) were retrieved. No significant differences in case-mix, sedation routines, ventilator treatment or length of ICU stay were found in ICU patients over the years of the study period. We used logistic regression to control for potential confounders. The possible confounders were identified in the literature: benzodiazepines as sedation routine¹⁷⁵, duration of sedation^{176,177}, pre-existing somatic diseases¹⁷⁸, pre-ICU psychiatric symptoms^{46,47}, younger age^{46,54} and female sex^{46,47,54} were included in the analysis. Also, women in the control group showed higher prevalence of previous psychological problems than women in the follow-up group (29% versus 17%, $p=0.15$) and previous psychological problems were included as a covariate in the analysis.

Interaction between physical disability and psychological morbidity may be present^{179,180}. We included psychological risk factors in predicting physical disability and vice versa. However, we did not control for a potential confounding effect between the two outcome measures (new-onset physical disability and psychological morbidity). In paper III and IV, patients were not requested to specify the degree of help with physical or psychological recovery outside the follow-up. Depending on

diagnosis, social support or education level, rehabilitation may not be equal for all patients, which can influence the trajectory of recovery. A follow-up study after major trauma reported that mainly patients with more severe physical impairment were offered rehabilitation therapy after hospital discharge. Despite rehabilitation these patients reported lower quality of life after five years¹⁸¹. In retrospect – as low education level was a significant predictor for physical disability (paper III) – it would have been valuable to assess the extent of other rehabilitation in patients. Another possible confounding factor for psychological recovery may be the presence of an ICU diary. During the study period ICU diaries were not systematically given to all ICU patients and we did not control for this factor.

Chance

We presented the findings with confidence intervals or significance levels. In paper I, when performing multiple comparisons in domains of quality of life over the year, no significance level was specified. We considered using the Bonferroni correction method^{182,183} for multiple-comparisons but found it too conservative and decided to leave the results for readers to interpret without reporting multiple-comparison-adjusted significance level¹⁵². In paper IV, the 95% CI for three predictors (In-ICU agitation, unemployment or on sick-leave prior to ICU admission and depressive symptoms in ICU) crossed the null value, which may indicate chance or lack of statistical power as possible explanations for the result. Priority was given to the predictive accuracy when deciding whether to include these predictors in the model.

External validity

The variety of medical diagnosis, age, somatic and psychological pre-existing diseases certainly influence the trajectory of recovery after critical illness. Besides ICU length of stay (paper I and II) the studies were not restricted to a specific age or patient group, which implies reasonably good generalizability to mixed ICU populations. However, data for all four studies were collected from one site, which may limit the external validity¹⁰⁵ and other settings may have a different patient case-mix and treatment routines. Generally, larger sample sizes are helpful and might have elucidated differences for subgroups (paper I-II) and also improved the accuracy of the predictive models (paper III and IV). Finally, with a 60-70% response rate, around 30-40% of the eligible patients were not represented in the study.

GENERAL DISCUSSION

Within the context of the stated limitations, the thesis demonstrates that a multidisciplinary ICU follow-up is feasible in identifying and helping ICU survivors with untreated physical and psychological problems (paper I). Moreover, in paper II we found that women reported a higher degree of psychological problems than men after critical illness, and that ICU follow-up may reduce the frequency of more severe symptoms of post-traumatic stress and depression in women. Paper III and IV highlight important predictors for physical and psychological problems after intensive care. Including these predictors in a screening instrument is a feasible method for identifying risk patients at risk for later physical or psychological problems at ICU discharge.

Detecting and managing problems after critical illness (paper I)

For some patients, recovery after critical illness is relatively uncomplicated. However, physical disability and psychological morbidity was found in a significant proportion of patients in paper I-IV. These findings are well confirmed in other studies^{13,15,18-21,31,36,37,41,46,47,52,58,61,62,150,156,171,184,185}. The problems are reported so frequently that a collective term, “post-intensive care syndrome” has been suggested to describe the multifaceted complications after critical illness and intensive care⁷⁶. Paper I describes methods for identifying post-ICU impairment and possible interventions, information warranted in a recent report from a stakeholders’ meeting about how to improve long-term outcomes in ICU survivors⁷⁶. Many ICU follow-up clinics are nurse-led^{97,186,187}, but no optimal model has yet been identified^{97,99}. It appears reasonable that a multidisciplinary approach, with each profession contributing with unique knowledge and perspective of the rehabilitation process is an advantage in identifying and managing post-ICU problems. Interdisciplinary rehabilitation programmes applied in other settings than post-ICU have been found to efficiently improve rehabilitation interventions¹⁸⁸. The structured screening for physical and psychological problems at each ICU follow-up visit provided a comprehensive overview regarding patients’ status and facilitated interpretation of rehabilitation needs. The referral rate supported by the screening results, at three, six and twelve months was 27%, 35% and 16% respectively. In other studies, referral rates in ICU follow-up vary from 7-50%^{99,186,187,189} depending on differences in ICU follow-up organization and follow-up routines. The patients included in our study were asked to describe their pre-ICU functional status. Despite this strategy, some referrals might have been due to pre-existing problems, as we did not systematically screen for new-onset problems. Regardless of the cause for the identified problems, treatments may have provided help in the patients overall recovery. The Swedish guidelines recommending three ICU follow-up consultations⁹⁵ are primarily based on literature and expert opinion, with the primary intention to follow patients recovery during the first year. In clinical practice, two interventional follow-up consultations may be sufficient for longitudinal follow-up with early identification and treatment of problems (first appointment) and later evaluation of the interventions offered or to

identify problems that remain unresolved despite time for spontaneous restitution (second appointment). Given the low rate of referrals and the number of patients declining a final visit in paper I, a third follow-up visit may possibly be superfluous from both a cost-effectiveness and patient perspective.

Gender differences in psychological morbidity (paper II)

In this study, long-term psychological problems appeared to be more frequent in women than in men. Higher rates of PTSD in women have previously been demonstrated after traumatic events¹⁹⁰⁻¹⁹³ and intensive care^{59,194}. Even though traumatic events are more likely to occur in men^{192,195}, women tend to develop PTSD more than twice the rate men do (10% versus 4%)^{192,195} even when exposed to similar types of trauma¹⁹⁶. Moreover, the lifetime prevalence of depression in women is twice the rate for men (20% versus 10%)^{73,197}. Previous research has suggested that there may be systematic gender differences in self-report bias¹⁹⁸. Psychological problems are often wrongly associated with a sign of weakness and excessive emotion. A number of studies have addressed this problem, but no conclusive results have been produced^{174,198}. Clearly there is an underestimation in prevalence of psychological problems in society, irrespective of gender¹⁷⁴. As previously stated, the prevalence of self-reported psychological problems was higher in women. However, there were individual men reporting considerable psychological distress, indicating that men may also need and potentially benefit from treatment.

ICU follow-up may have some similarities with therapies used in treating anxiety disorders. Exposure therapy involves returning to the site of traumatic event but in a less intimidating context, in order to reduce avoidance and overcome the reminder of the traumatic event⁴⁹. ICU follow-up has some resemblance to this therapy, in that patients are exposed to the memories and the ICU environment during less dramatic circumstances while venting their memories and re-visiting the ICU. Cognitive behavioral therapy focuses on changing maladaptive thinking to more realistic thoughts and consequently decreasing emotional distress⁴⁹. One phase of the therapy includes trauma education⁴⁹, to some extent paralleled with recapitulation of the ICU stay performed during ICU follow-up. During the consultation the trauma (ICU stay) and responses to the trauma are explained and patients' reactions are in most cases explained to be normal⁴⁹. The ICU follow-up concept with counseling-like sessions, may possibly appeal to women. In one study, women found counseling or cognitive behavior therapy efficient while men did not. This was explained by the authors as women's greater likelihood and capacity to form treatment alliances in therapy¹⁹⁹. Moreover, women tend to respond better to PTSD treatment than men²⁰⁰, which has been postulated to relate to a generally greater familiarity with a wider range of emotions in women, as well as more extensive experience with interpersonal relationships and a greater likelihood to use coping strategies²⁰¹. Women are more likely to seek help for psychological problems than men¹⁹⁹.

Many patients can cope efficiently with troublesome feelings and behaviours after a traumatic event, which may be of help in psychological recovery after critical illness. Those patients may not need or even benefit from extensive ICU follow-up. For some patients, ICU follow-up could potentially have a negative effect. Repeated reminders of a potential traumatic event may evoke feelings of anxiety in those with other coping strategies than re-exposure, as shown in debriefing studies²⁰². In general, patients with a higher-than-average risk for problems are more likely to benefit from an intervention than patients with lower-than-average risk. Inclusion of only patients with higher risk may contribute to a higher confidence in positive trial results²⁰³. Well-designed studies have failed to demonstrate treatment effects in post-ICU interventions^{91,93}. The outcome might have been different if the intervention would have been concentrated to risk patients, as patients with spontaneous recovery dilute the effect of an intervention^{203,204}. To our knowledge, our study – in which women were found to be a risk group for psychological problems – was the first to evaluate the efficacy of ICU follow-up in relation to gender differences.

Predicting physical disability (paper III)

The trajectory of recovery after critical illness may depend on pre-disposing factors, the injury or illness in itself and factors related to the hospital stay¹⁸. In paper III, four significant predictors for physical disability were included in the screening instrument. The strongest predictor “low level of education” is a pre-disposing factor for impaired physical function, whereas “fractures” may be regarded as the consequence of a traumatic injury. Reduced muscle strength (assessed as core instability) and length of ICU stay are likely consequences of critical illness and ICU treatments. In previous studies, low education level has been associated with a higher mortality and morbidity rate^{205,206} and poor functional outcome²⁰⁷⁻²⁰⁹. The mechanism of which low education level may delay functional recovery is uncertain but has been debated in other rehabilitation settings. Education and income – often paralleled – have been described to be major determinants in the ability and opportunity to control everyday life and affect the future in a positive way²¹⁰. A Swedish report from the Institute for Evaluation of Labour Market and Education Policy demonstrated that during the year after critical illness, the income decrease is as little as 5-6% for patients with high education, while it reaches 9-12% in patients with low education²¹¹. It may be that the economical situation for patients with low education level makes the costs implied with efficient rehabilitation difficult to bear. Also, the use of different coping strategies between educational levels has been suggested to influence outcome after rehabilitation²⁰⁸. Patients with low education are suggested to employ more avoidant coping, while highly educated patients tend to use more problem-oriented coping strategies²¹². Problem-solving and goal-setting strategies are characterized by proactive behavior and improved outcome in rehabilitation²¹³. Besides coping, communication is essential in maintaining efficacious rehabilitation after hospital discharge. The way of communicating has been found to be different depending on socioeconomic status of the patient²¹⁴. In hospital settings, patients

with higher education were found to communicate more actively, expressing their concerns and preferences regarding health status and rehabilitation, while patients with low education received less information²¹⁴. Patients with low education level may also be less prepared or aware of how to navigate through the health care system, especially after severe illness. These patients appear to be less likely to believe that they can influence their outcome²¹⁵. In cardiac rehabilitation, differences in socioeconomic status regarding attendance to training classes were seen, with non-attendance more common in low socioeconomic groups²¹⁵.

Fractures were found to impair physical recovery. Since the Karolinska University Hospital Solna is a trauma referral center, major trauma is a common reason for ICU admission. There is a high incidence of orthopedic injuries in trauma patients²¹⁶ and fractures may play an important part in the trajectory of recovery²¹⁷. In orthopedic trauma patients, recovery in function and quality of life appears to reach a plateau as late as around twelve to 18 months after the trauma²¹⁸. Follow-up studies after major trauma demonstrated that a substantial proportion of patients reported physical impairment¹⁸¹, not being able to return to work or problems preventing regained previous level of activity up to five years after the trauma²¹⁹⁻²²¹.

Muscle weakness is a common problem following critical illness³⁷ and reduced muscle strength is found to be a predictor of mortality and morbidity^{21,222}. It may be challenging to quantify muscle strength in ICU patients, because most manual muscle tests require awake, co-operative and motivated patients²²³. When developing a model for clinical use, included predictors should be available in daily practice and be possible to assess with reasonable precision¹⁵⁴. Thus, we chose to assess proximal muscle strength (core stability) as the ability to sit independently, without physical support, in the ICU. We speculate that patients not able to sit without support in the ICU suffer from more profound muscle weakness that requires longer period of rehabilitation.

Today, patients are offered ICU follow-up depending ICU length of stay⁹⁵. It seems reasonable to believe that prolonged ICU stay is an indicator of deteriorated vital organ function and these patients may require longer time for physical recovery compared to patients with shorter stay²⁸. A study including older patients demonstrated significant physical deterioration as early as the second day in hospital, with no improvement in the majority of patients at hospital discharge and further decline in 10% of patients²²⁴. In paper III, however ICU length of stay >two days was only the fourth strongest of the predictors for physical disability, with an odds ratio of 2.6.

Predicting psychological morbidity (paper IV)

Many variables may interact in the development of psychological morbidity, such as pre-disposing factors for psychological vulnerability, the severity of the trauma stressor and resilience and recovery variables⁴⁹. No post-trauma variables were investigated in paper IV, as the time for screening (at ICU discharge) was in the midst of potential psychological trauma that the hospitalization implied. Moreover,

personality and coping strategy tests were considered not be feasible to assess at ICU discharge. The final screening instrument included six predictors in total. Four predictors; major pre-existing disease, being parent to children younger than 18 years of age, previous psychological problems and being unemployed or on sick-leave before ICU admission, may be considered as predisposing factors and not specific for ICU patients. Most of the predictors may indicate psychological vulnerability. Previous research has demonstrated co-morbidity between chronic physical disorders and depression^{41,179} or anxiety²²⁵. In anxiety disorders, mainly PTSD, panic attacks and agoraphobia were also associated with physical disorders¹⁸⁰. Either patients with pre-existing diseases already suffered from psychological problems before ICU admission, or the disease lowered the threshold for sustaining against new-onset psychological problems when an additional life-threatening situation occurred. In concordance with previous findings, being a parent to young children may predict symptoms of post-traumatic stress²²⁶. We speculate that a heavier burden of responsibility in parents to young children in combination with increased vulnerability after a life-threatening injury or illness, may explain the elevated psychological morbidity for parents of young children.

Patients with previous psychological problems have been found to be susceptible for developing subsequent problems after a traumatic event in several studies^{15,227,228}. While some patients may have suffered from psychological problems before ICU admission, only a minority of the recruited patients were treated in the ICU for reasons related to psychological morbidity, such as suicide attempt. Being unemployed or on sick-leave before ICU admission may be associated with previous psychological susceptibility to some degree^{41,44}. However, being on sick-leave may also be associated with ongoing impaired health status⁴¹. The remaining two factors, agitation and depressive symptoms appearing in the ICU, may be regarded as more intense emotional reactions to a traumatic event. Fear and anxiety may be expressed as agitation in a confused patient during for example sedation withdrawal. Agitation is a state of extreme arousal, irritability and motor restlessness that results from a sense of discomfort or tension and can be caused by many factors, such as pain, delirium, hypoxemia, hypotension and withdrawal from alcohol, illicit drugs or medication¹⁶⁴. An underlying genetic susceptibility may also contribute to development of anxiety²²⁹. Depressive symptoms detected already in the ICU were predictive of subsequent psychological morbidity to some extent. This finding is confirmed in other studies, where early post-ICU depression indicated substantial risk for persistent depression during the first year after ICU^{60,69}. We did not discriminate between pre-ICU or new-onset depression. In a previous study however, around 25% of ICU survivors suffered from new-onset depression two months post-ICU, of which around half was major depression⁶⁹. This indicates that while previous psychological problems may be at play when identifying post-ICU problems, there is likely a substantial proportion of new-onset psychological problems in ICU survivors.

Early detection and treatment of psychological problems can improve long-term outcome significantly²³⁰. Patients with psychological morbidity are more likely to have longer hospital stay and suffer from greater physical disability⁶⁹. Psychological problem after critical illness may lead to poorer adherence to medical treatment²³¹ and decreased motivation and reward from physical rehabilitation²³². The screening instrument developed in paper IV may be of value to identify these patients and apply early rehabilitation or other interventions that may improve recovery.

Feasibility of the screening instruments (paper III,IV)

Presently, patients are invited for ICU follow-up, independent of risk for problems after critical illness. Some patients with low risk may most likely recover uneventfully, while others at high risk for problems are not even invited for ICU follow-up or may decline because of major physical disability or severe psychological problems. Reduced mobility may prevent patients to come to outpatient clinics. Patients suffering from PTSD-related avoidance symptoms may prefer to stay away from the hospital and depressed patients may not have the initiative or energy to participate in any therapy. In these risk patients, the likeliness to receive treatment and achieve higher therapy compliance would probably increase if they were approached already during the hospital stay. The screening instruments were developed with the purpose to identify such risk patients. In order to aid ICU clinicians in deciding potential treatment strategies for these patients, the patients were divided into low risk-, moderate risk- and high risk groups depending on the individual probability to develop problems following critical illness (Table 5). Depending on ICU and follow-up service resources, the choice of which risk probability level or risk category to use for interventions may vary. One possible triage could be the following: Active, more extensive in-hospital follow-up for high risk patients, repeated physical or psychological screening after ICU discharge for moderate risk patients and no in-hospital interventions for low risk patients. According to our model and suggested risk groups, patients considered having low risk (0-29%) for physical or psychological problems might be excluded from early, active, in-hospital follow-up. By excluding patients with low risk for future problems, a smaller number of patients remain for more resource-intensive assessment and treatments by trained clinicians. Such assessment may include an evaluation of what problems are new-onset and related to the recent episode of critical illness and ICU stay. With this suggested triage, some low-risk patients may also benefit from some form of follow-up. Such less resource-intense follow-up could be performed by ICU clinicians and might include recapitulation of the ICU stay and treatments, clarification of delusional memories, and going through the ICU diary.

Table 5. Suggestion of future ICU follow-up strategies

Group	Risk	Intervention
Low risk for problems	0-29%	Recapitulating ICU stay
Intermediate risk for problems	30-69%	Repeated post-ICU screening
High risk for problems	70-100%	Rehabilitation programme

CLINICAL IMPLICATIONS

Critical illness can be regarded as a continuum, ranging from the acute clinical deterioration, through intensive care treatment and continuing even after hospital discharge until the patient's risk of late complications is at the same level as similar patients not receiving intensive care¹⁸. To improve ICU patients' recovery and prevent functional decline as early as possible – preferably already in the ICU – interventions such as early mobilization may be of importance. Awareness of aspects in the patient's social, somatic and psychological background, that may promote or impair physical and psychological recovery is also important. In order to develop efficient patient care rehabilitation programmes for ICU survivors, clinicians may need to deal not only with the patient's immediate ICU-related somatic problems, but also consider a broader context, including patients' previous educational, professional, somatic and psychological situation. Risk assessment and resource allocation, appropriate for the individual patient's needs is a reasonable ambition for a future ICU follow-up. In waiting for more externally validated screening instruments for inclusion in specific rehabilitation pathways, multidisciplinary ICU follow-up can be a feasible approach to aid patients, by identifying and managing untreated problems after critical illness. With this approach, two consultations in the first six months seem to be sufficient for most patients. In conclusion, prediction of risk patients, screening for and detecting problems following critical illness and offering adequate treatment may improve recovery for patients after critical illness and facilitate resource allocation for ICU follow-up.

FUTURE PERSPECTIVES

It is still not fully understood what component in ICU follow-up programme is vital for improved recovery in ICU survivors. In our interventional study, we did not separate the effect of each part of the intervention from the follow-up as a whole. Future research covering this area would be valuable. In order to increase the chance of identifying clinically helpful interventions, disturbing “noise” from patients not at significant risk for problems should be reduced as far as possible. This can be done by identifying risk patients prior to evaluating an intervention. To increase generalizability of the screening instruments (paper III and IV), the predictors need to be confirmed and possibly modified in a larger population, preferably in a multicenter study. Thereafter the screening instruments can be used for interventional studies evaluating the efficacy of potential interventions. Triage of follow-up interventions depending on patients' risk for physical or psychological problem may be one way to design ICU follow-up in a resource-efficient way. Finding a patient-beneficial and cost-effective rehabilitation programme for high risk patients is undoubtedly a future research topic, of great interest not only for patients and clinicians, but also to those funding intensive care and ICU follow-up. Another important area for future research, not investigated in these studies, is risk screening for cognitive problems. These problems are frequently seen in ICU survivors in the

first week after ICU discharge, but in some patients appear to remain a long-term problem²³³.

CONCLUSIONS

- Multidisciplinary ICU follow-up may help patients manage untreated physical and psychological problems by identifying these problems and finding routes of rehabilitation and support. Follow-up in the first six months after ICU discharge appears to suffice for most patients.
- Psychological problems following critical illness appear to be more common in women than in men. Multidisciplinary ICU follow-up attenuates more severe long-term symptoms of post-traumatic stress and depression in women.
- Screening instruments, for use already at ICU discharge can predict physical disability and psychological morbidity two months after critical illness with fair precision.
- Significant predictors for new-onset physical disability two months after critical illness or trauma and intensive care are low education level, reduced core stability, fractures and an ICU stay >48 hours.
- Significant predictors for psychological morbidity two months after critical illness or trauma and intensive care are major pre-existing disease, being a parent to children <18 years of age, previous psychological problems, in-ICU agitation, being unemployed or on sick-leave prior to ICU admission and exhibiting depressive symptoms in the ICU.

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