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PREDICTION OF PSYCHOLOGICAL AND PHYSICAL MORBIDITY AFTER CRITICAL ILLNESS AND INTENSIVE CARE UNIT STAY

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

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For my family with love and gratitude

Live as if you were to die tomorrow, learn as if you were to live forever

Mahatma Gandhi

POPULAR SCIENCE SUMMARY

BACKGROUND

A majority of patients treated in the intensive care unit (ICU) survive, despite the severe illness bringing them to the ICU in the first place. However, more than 50% of patients suffer from psychological, physical and cognitive problems in the months to years after their critical illness, impeding the ability to return to life as it was prior to falling ill. These problems have collectively been named post-intensive care syndrome, PICS. PICS can also affect ICU survivors' family members, then with the addition of F for family.

Many hospitals offer follow-up after ICU stay but resources for follow-up are limited and it is unknown which patients benefit the most from follow-up interventions and what such follow-up should consist of. Current selection of patients for follow-up in Sweden and several other European countries is based on ICU length of stay, in the belief that a longer ICU stay implies more long-term morbidity. There is no evidence supporting the correlation between length of stay in the ICU and the risk of developing PICS. The aim with this thesis was to investigate potential risk factors for psychological and physical problems after ICU stay, develop methods for identification of patients with a high risk of developing such problems and to investigate whether an incomplete patient recovery affect informal caregivers' perceived caregiver burden.

METHODS AND RESULTS

Study I is a multinational cohort study with the aim to develop a screening instrument to be used at discharge from the ICU to predict patients' risk of developing psychological problems three months later. We included 572 ICU survivors of whom 404 responded to follow-up questionnaires. In our cohort, 20% (80 patients) had psychological symptoms such as depression, anxiety or PTS three months after ICU discharge. Risk factors for psychological problems post-ICU were age, where being middle-aged imposed the greatest risk, lack of social support, depressive symptoms and traumatic memories at ICU discharge. A statistical model indicated that the screening instrument based on these risk factors correctly identified 76% of patients with a risk for psychological problems. The current selection method based on time spent in the ICU correctly identified 49% of patients at risk.

Study II is based on the same patient cohort as study I, however this time with the purpose of developing a screening instrument for prediction of new-onset physical disability three months after ICU discharge. In our cohort of ICU survivors responding to the follow-up questionnaires 19% (75 patients) suffered from new-onset physical disability. Impaired functional status at ICU discharge was the single most important risk factor for new-onset physical disability. A statistical model indicated that this early screening correctly identified

68% of patients at risk of physical problems, to be compared with 57% identified with the current selection method time spent in the ICU.

Study III is a Swedish single-center cohort study with the aim to evaluate if an early screening of patients' psychological problems one week after ICU discharge can predict psychological problems three months later. We included 132 patients of which 82 (62%) responded to follow-up questionnaires. We found that early symptoms correlated well with degree of symptoms three months later and a statistical method showed that the early screening correctly identified 90% of patients with post-traumatic stress (PTS) symptoms, 80% of patients with symptoms of anxiety and 75% of patients with depressive symptoms.

Study IV is a cohort study including informal caregivers to patients included in studies I and II, aiming to evaluate if an incomplete psychological or physical patient recovery is associated with a higher perceived caregiver burden three months after ICU discharge. We included 62 informal caregivers of whom 55 (89%) responded to follow-up questionnaires. Caregiver burden was higher in caregivers to patients with an incomplete recovery compared to caregivers to patients with a full recovery. A high caregiver burden correlated with poorer caregiver mental health-related quality of life.

To conclude, the studies in this thesis developed screening instruments for early identification of ICU survivors at risk for an incomplete physical and psychological recovery. This thesis also demonstrated that informal caregivers to patients with an incomplete psychological or physical recovery report a higher caregiver burden, linked to poorer health-related quality of life. These findings offer the possibility to target high-risk patients already at ICU discharge or shortly after ICU stay and offer tailored interventions to these patients and their informal caregivers, potentially increasing the chances to a full recovery. Such a follow-up approach may be more successful and resource-effective than a "one-size fits all" approach.

POPULÄRVETENSKAPLIG SAMMANFATTNING

BAKGRUND

De allra flesta patienter som vårdas på intensivvårdsavdelning överlever vistelsen, trots den svåra sjukdom eller tillstånd som legat till grund för inläggningen. Mer än hälften av patienterna drabbas dock av psykiska, fysiska eller kognitiva besvär i efterförloppet, vilket kan förhindra möjligheten att återgå till det liv de hade innan den svåra sjukdomsepisoden. Dessa besvär har tillsammans kommit att benämnas post-intensive care syndrome (PICS) och kan även drabba närstående till IVA-överlevare, då med tillägget PICS-F för familj.

Många sjukhus erbjuder idag uppföljning efter intensivvård, men vilka patienter som bör kallas till uppföljning och hur sådan uppföljning ska se ut för att ge mest nytta för patienterna vet vi idag inte. I tron att längre vårdtid på IVA innebär en högre risk för PICS, kallas idag patienter som vårdats längre än 72 timmar till uppföljning, enligt rekommendation från svenska intensivvårdsregistret. Urvalet av patienter för uppföljning är liknande i flera andra länder. Det finns dock ingen evidens för att längre vårdtid på IVA innebär en ökad risk för PICS.

Målet med den här avhandlingen var att utvärdera riskfaktorer för psykiska och fysiska problem efter intensivvård, att utveckla metoder för att identifiera de patienter som löper högst risk att drabbas av dessa besvär, och att undersöka huruvida patientens grad av tillfrisknande påverkar belastningen av närstående.

METODER OCH RESULTAT

Studie I är en multinationell kohortstudie, med syfte att ta fram ett screeningverktyg att använda vid utskrivning från IVA för att förutsäga risken för psykiska problem tre månader efter utskrivning från IVA. Vi inkluderade 572 IVA-överlevare, av vilka 404 svarade på uppföljningsenkäterna. I vår kohort hade 20% (n=80) psykiska besvär i form av posttraumatisk stress (PTS), ångest eller depression tre månader efter utskrivningen. De riskfaktorer som visade sig vara förknippade med ökad risk för psykiska problem efter IVA var ålder (högst risk för medelålders patienter), brist på socialt stöd, depressiva symptom och traumatiska minnen från tiden på IVA, vid utskrivningen från IVA. En statistisk modell visade att screeningverktyget baserat på de fyra riskfaktorerna korrekt kunde identifiera 76 % av patienterna med risk för psykiska problem efter IVA. Detta kan jämföras med nuvarande selektionsmetod för uppföljning, vårdtid ≥72 h på IVA, som kunde identifiera 49 % av patienterna.

Studie II är baserad på samma patientgrupp som studie I, men med syfte att förutsäga risken för nytillkomna fysiska besvär tre månader efter IVA. I vår kohort av 404 IVA-överlevare som svarade på uppföljningsenkäterna hade 19 % (n= 75) nytillkomna fysiska besvär. Sämre fysisk funktion vid utskrivning från IVA var förknippad med en signifikant ökad risk för

fysiska problem efter IVA. En statistisk modell visade att vi med hjälp av screeningen korrekt kunde identifiera 68 % av patienterna med ökad risk för fysiska besvär, att jämföra med vårdtid ≥72 h på IVA som identifierade 57% av patienterna.

Studie III är en svensk singel-center kohortstudie med syfte att undersöka om en tidig bedömning av psykiska symptom, en vecka efter utskrivning från IVA, kan förutsäga psykiska problem tre månader efter utskrivning från IVA. Vi inkluderade 132 patienter, av vilka 82 (62 %) svarade på uppföljningsenkäterna. Vi fann att tidiga symptom överensstämde väl med graden av symptom tre månader senare och en statistisk metod visade att den tidiga bedömningen korrekt kunde identifiera 90% av patienterna med symptom på PTS, 80 % av patienterna med ångestsymptom och 75% av patienterna med depressionssymptom.

Studie IV är en kohortstudie där närstående till en del av de patienter som medverkat i studie I och II inkluderats med syfte att undersöka huruvida den upplevda belastningen av närstående var högre bland närstående till patienter med psykiska eller fysiska problem tre månader efter intensivvården. Vi inkluderade 62 närstående, varav 55 (89 %) svarade på uppföljningsenkäterna. Belastningen av närstående var högre hos närstående till patienter med en otillräcklig psykisk eller fysisk återhämtning, jämfört med belastningen hos närstående till patienter som tillfrisknat utan dessa problem. En högre belastning av närstående var också kopplad till en sämre hälsorelaterad livskvalitet.

Sammanfattningsvis har studierna i den här avhandlingen bidragit till att ta fram nya metoder för att kunna identifiera IVA-överlevare med förhöjd risk för otillräcklig psykisk och fysisk återhämtning. Avhandlingen har också kunnat visa att närstående till patienter med otillräcklig återhämtning upplever ökad belastning vilket är kopplat till en ökad risk för sämre hälsorelaterad livskvalitet. Fynden innebär att riskpatienter och deras närstående kan erbjudas skräddarsydd uppföljning redan vid utskrivning från IVA eller strax därefter, vilket kan leda till en förbättrad återhämtning. Tidigt insatt, individualiserad uppföljning skulle kunna visa sig vara mer framgångsrik och resurssparande än nuvarande IVA-uppföljning.

ABSTRACT

A large proportion of survivors of critical illness and intensive care unit stay suffer from post-intensive care syndrome (PICS), consisting of psychological, physical and cognitive problems. These problems can persist for months to years and impede the return to life as it was prior to falling ill. Psychological problems such as depression, anxiety and post-traumatic stress (PTS), can also affect informal caregivers to ICU patients. In order to detect and hopefully treat these problems, an increasing number of hospitals are offering follow-up in the months after ICU stay. Resources for ICU follow-up are limited and it is unknown which patients are at the highest risk of developing PICS. ICU length of stay longer than 3-4 days is currently the most commonly used and recommended method for selection of patients for follow-up, but evidence is lacking regarding the accuracy of this method in finding patients with the highest risk for PICS. The aim with this thesis was to assess risk factors for psychological and physical sequelae after ICU stay, and to develop instruments to predict individual patients' risk of these adverse outcomes, as well as investigate the effect of patient outcome on the wellbeing of their informal caregivers.

Study I is a multicenter prospective observational cohort study assessing risk factors for psychological problems (PTS, depression and anxiety) three months post-ICU in order to develop a discharge screening instrument for identification of patients for psychological ICU follow-up. We included 572 patients at ten ICUs in Sweden, Denmark and the Netherlands. Among 404 (78%) responders, 20% developed significant symptoms of any of the assessed psychological entities. After univariable and multivariable logistic regression modeling, the remaining predictors for adverse psychological outcome three months post-ICU were: age (with the highest risk in ages 49-65 years), lack of social support, symptoms of depression and traumatic memories at ICU discharge. The area under the receiver operating characteristics curve (AUC) for the screening instrument was 0.76 (95% CI 0.70-0.81).

Study II is a multicenter prospective observational cohort study assessing risk factors for new-onset physical disability three months post-ICU in order to develop a discharge screening instrument for identification of patients for physical ICU follow-up. Included patients are the same as in study I. Among the 404 responding ICU survivors, 19% reported new-onset physical disability. After univariable and multivariable logistic regression modeling, the sole remaining predictor for an adverse outcome was physical status at ICU discharge, with an AUC of 0.68 (95% CI 0.61-0.76).

Study III is a single-center prospective observational cohort study evaluating the predictive value of an early psychological assessment one week after ICU discharge on three-month psychological outcome regarding symptoms of PTS, depression and anxiety. Among 132 included patients, there are follow-up data on 82 (62%). In our cohort, 13% suffered from clinically significant symptoms of PTS, 21% from symptoms of depression and 16% from symptoms of anxiety at three months. Correlation between early scores in the ward and three

months scores were moderate to strong. The predictive value of the early screening as assessed with the AUC was 0.90 (95% CI 0.81 to 0.99) for symptoms of PTS, 0.80 (95% CI 0.64 to 0.95) for symptoms of anxiety and 0.75 (95% CI 0.64 to 0.87) for depressive symptoms.

Study IV is a multicenter prospective observational cohort study including cohabiting informal caregivers to 62 ICU survivors included in study I/II. The primary outcome was to assess whether an adverse psychological or physical patient outcome was associated with a higher degree of caregiver burden three months post-ICU. Response rate was 89% (n=55). Of included patients, 17 (33%) had an adverse outcome. Caregiver burden was significantly higher in caregivers to patients with an adverse outcome, caregiver burden scale score mean (±SD) 52 (11) compared to caregivers caring for patients without an adverse outcome, mean 41 (13), p=0.006. A higher caregiver burden also correlated with a reduced caregiver mental health-related quality of life.

This thesis developed methods for prediction of psychological and physical sequelae in ICU survivors three months post-ICU, as well as assessed the effect of an incomplete patient recovery on caregiver burden and mental health problems in informal caregivers. The results of this thesis provides clinicians with tools to better anticipate the trajectory of recovery for their patients in order to initiate early interventions in high-risk patients and their informal caregivers and potentially reduce long-term suffering. This triage of patients also allows for enrichment of high-risk cohorts for future interventional studies of ICU follow-up interventions.

LIST OF SCIENTIFIC PAPERS

I. Milton A, Schandl A, Soliman IW, Meijers K, van den Boogaard M, Larsson IM, Brorsson C, Östberg U, Oxenbøll-Collet M, Savilampi J, Paskins S, Bottai M, Sackey P.
Development of an ICU discharge instrument predicting psychological morbidity: a multinational study
Intensive Care Medicine 2018;44(12):2038-47

II. Milton A, Schandl A, Soliman IW, Joelsson-Alm E, van den Boogaard M, Wallin E, Brorsson C, Östberg U, Latocha K, Savilampi J, Paskins S, Bottai M, Sackey P.
ICU discharge screening for prediction of new-onset physical disability – a multinational cohort study
ACTA Anaesthesiologica Scandinavica 2020;64(6):789-797

III. Milton A, Brück E, Schandl A, Bottai M, Sackey P.
Early psychological screening of intensive care unit survivors: a prospective cohort study
Critical Care 2017;21(1):273

IV. Milton A, Schandl A, Larsson IM, Wallin E, Savilampi J, Meijers K, Joelsson-Alm E, Bottai M, Sackey P.
Caregiver burden and emotional wellbeing in informal caregivers to ICU survivors – a prospective cohort study
Submitted manuscript

CONTENTS

LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
APACHE	Acute Physiology And Chronic Health Evaluation
AUC	Area Under the Receiver Operating Characteristics Curve
BI	Barthel Index
CBS	Caregiver Burden Scale
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CPAx	Chelsea Critical Care Physical Assessment Tool
HADS	Hospital Anxiety and Depression Scale
HRQOL	Health-Related Quality Of Life
HRQL	Health-Related Quality Of Life
IADL	Instrumental Activities of Daily Living
ICU	Intensive Care Unit
IQR	Interquartile Range
LOS	Length Of Stay
MCS	Mental Component Score
NPV	Negative Predictive Value
PCS	Physical Component Score
PICS	Post Intensive Care Syndrome
PHQ-2	Patient Health Questionnaire 2-items
PPV	Positive Predictive Value
PTS	Post-Traumatic Stress
PTSS-10/14	Post-Traumatic Stress Symptom 10/14-Question Inventory
ROC	Receiver Operating Characteristics
SAPS	Simplified Acute Physiology Score
SD	Standard Deviation

1 INTRODUCTION

INTENSIVE CARE MEDICINE

Intensive care medicine developed in the 1950s, initially as a post-operative ward with extended cardiovascular monitoring or invasive mechanical ventilator support for patients with respiratory failure [1]. Over the years the care for the critically ill patients has evolved due to technical advances and medical research, increasing knowledge among staff and health care providers. Common diagnoses treated in the ICU are sepsis and other infections, major trauma, severe cardiac conditions and postoperative complications, all leading to different levels of organ failure and the need for urgent interventions. Intensive care is very resource-intense with advanced monitoring and a high nurse to patient ratio. Although patients treated in the ICU today are older and have more comorbidities than before, most patients survive their episode of critical illness [2]. Despite different diagnoses being the reason for the ICU stay, patients share the experience of a potentially life-threatening condition. The ICU offers a highly technological environment with many machines, devices and noise, which may be stressful and frightening for many patients [3]. Being sedated and potentially in a state between fully awake and unconscious, not knowing what is real and not, can further add to a frightening and traumatic experience. Immobility due to critical illness and sedatives may lead to weakness and impaired physical capacity. The ICU experience, even though lifesaving, can negatively affect patients' recovery and, together with other risk factors lead to considerable morbidity in the months to years post-ICU. ICU survivorship is still poorly understood. Support after ICU stay is evolving as a means to help patients relate to their experience and there is hope that post-ICU interventions may attenuate psychological and physical morbidity after ICU stay.

2 LITERATURE REVIEW

2.1 MORBIDITY AFTER CRITICAL ILLNESS – THE POST-INTENSIVE CARE SYNDROME

ICU survivors suffer from substantial post-ICU morbidity, including physical, psychological and cognitive sequelae. These problems have collectively been referred to as post-intensive care syndrome (PICS) and have shown to persist for months to years [4,5]. Health-related quality of life (HRQL) is also reduced in ICU survivors compared to the general population [6]. With critical care evolving, the scope of care is moving beyond just saving lives, but also focusing on making that life as similar as possible to life as it was prior to falling ill. Awareness is increasing with regards to PICS and different initiatives from societies, former patients and health care professionals working with ICU survivors are evolving, such as apps and homepages with information to patients, family members and health care providers, describing potential PICS problems and possible referrals, also connecting former patients and family members with other ICU survivors and their families [7,8]. Stakeholders meetings and conferences gathering ICU specialists are taking place, raising awareness about PICS and identifying future research questions to address within this area [5]. One important topic described is defining risk factors in order to identify patients at risk of developing PICS [4,9,10]. An increasing number of hospitals are now dealing with the aftermaths of intensive care offering different kinds of follow-up after ICU stay, but the optimal design and timing of such follow-up has not yet been established.

2.1.1 Psychological morbidity

Psychological problems affect approximately one in three patients treated in the ICU [11,12], and are evenly distributed across different subgroups of ICU survivors [13]. Problems predominantly consist of post-traumatic stress (PTS), anxiety and depression. ICU survivors with substantial psychological morbidity report significantly lower health-related quality of life than the general population [14-16]. Risk factors for psychological morbidity appears to vary, in part related to the specific diagnosis, but are important to recognise in order to identify patients at high risk and possibly diminish modifiable factors already during the ICU stay.

2.1.1.1 Depression

Depressive symptoms have been reported by 29-30% of ICU survivors according to a systematic review and meta-analysis. Numbers are consistent through assessment time points at 2-3, 6 and 12 months post-ICU [17]. Compared to the general population the prevalence of depressive symptoms in ICU survivors is threefold [18]. The prevalence however, is similar to

that of hospitalized medical patients [19]. Typical symptoms of depression include feeling sad, worthless, hopelessness, experiencing fatigue, insomnia or hypersomnia and a diminished interest and pleasure in most activities [20]. Depressive symptoms post-ICU have been associated with a 50% increased two-year mortality risk according to one study, after adjusting for other factors such as age, male sex and severity of illness [21].

2.1.1.2 Anxiety

The prevalence of anxiety in ICU survivors has shown to be 32% at 2-3 months, 40% at 6 months and 34% at 12-14 months post-ICU [22]. This can be compared with a 12-month incidence in the general population within the European Union of 14% [23]. Anxiety is characterized as an unpleasant emotional reaction to a situation interpreted as threatening, or anticipation of such a situation, with feelings of tension, excessive worrying and uneasiness [24]. The emotional stress can cause difficulty concentrating, irritability and insomnia as well as physical reactions such as increased blood pressure, muscle tensions and tachycardia [20].

2.1.1.3 Post-traumatic stress (PTS)

PTS symptoms occur in approximately one fifth of ICU survivors, with prevalence of 17-44% during the first year after ICU stay, with the higher incidence in the first six months post-ICU [25]. Individuals who have experienced or witnessed a life-threatening traumatic event can develop symptoms of PTS. These symptoms typically include reliving the event through unwanted intrusive memories, flashbacks and nightmares, experiencing physical reactions, hyper vigilance and avoiding situations and places reminding of the traumatic event [20]. PTS has typically been described in war veterans and was accepted as a diagnosis and included in the Diagnostic and Statistical Manual of Mental Disorders III in 1980 [26].

2.1.2 Physical disability and activities of daily living (ADL)

Impaired physical function is common after ICU stay and has been associated with increased ICU and in-hospital mortality [27,28]. As many as 50% of ICU patients suffer from general weakness as a result of decreased muscle synthesis paired with skeletal muscle wasting and nerve dysfunction [29,30]. Prevalence in the range from 25-100% have been reported, depending on the cohort studied and the chosen diagnostic criteria [31]. Muscle weakness occurs after prolonged bedrest or mechanical ventilation, with the interaction of critical illness and multiorgan failure, giving rise to critical illness myopathy, polyneuropathy and myoneuropathy [32]. These impairments have collectively been named ICU-acquired weakness (ICUAW) [33]. Proximal limbs are most typically affected [31], but ICUAW also affects

respiratory muscles, increasing the duration of time weaning from mechanical ventilation [34]. ICUAW has been associated with higher ICU and hospital mortality in patients with longer duration of mechanical ventilation [28] and in septic patients with multiorgan failure and >21 days of mechanical ventilation [27].

Impaired physical function can affect patients' ability to perform activities of daily living (ADL), instrumental activities of daily living (IADL) and potentially the ability to live independently [35]. ADLs include the ability to take care of regular activities such as bathing, dressing, personal hygiene, mobility, continence and feeding [36]. IADLs include using a phone, modes of transportation, shopping and doing laundry as well as handling finances, food preparation and housekeeping [37]. Functional limitations with restrictions in performing ADL have been reported by as many as 54-69 % of ICU survivors one year after ICU stay [38,39] and only 50% of patients ventilated for >48 hours had returned to work one year post-ICU [39]. Another study reported 68% of ICU survivors to be back at work 2 years after ICU stay. This study did not assess ICUAW per se, but longer time spent in the ICU and the need for mechanical ventilation was associated with a reduced chance of being back at work [40].

A commonly used assessment of physical function in ICU survivors is the 6-minute walk distance (6MWD), which has shown to be reduced up to 24 months post-ICU [41]. ICU survivors with impaired physical function also report lower HRQL than the general population [41] and have higher healthcare-related hospitalization costs [42].

2.1.3 Cognitive problems

The third element of PICS is cognitive problems. In one study, 57% of ICU survivors had cognitive problems six months after ICU stay [43] and in another study of acute respiratory distress syndrome patients, 46% had cognitive deficit one year after ICU stay and 47% after two years [44]. Cognitive problems include memory and executive dysfunction as well as impaired attention [4,43]. Cognitive impairment is a major hurdle for patients to return to work and is also associated with a reduced HRQL [44,45]. Risk factors for cognitive problems include delirium during ICU stay [46,47], where a longer duration of delirium appears to be associated with worse cognitive function [48]. Sepsis [49], hyper/hypoglycaemia [50] and lower educational level pre-ICU [51] are other described risk factors for cognitive dysfunction. Results are not consistent regarding the effect of mechanical ventilation [45,52-54] and ICU LOS on the risk of developing cognitive dysfunction post-ICU [45,54].

2.1.4 Family members/Informal caregivers

Not only patients cared for in the ICU, but also family members (hereafter referred to as informal caregivers) can suffer from PICS, termed PICS-F where F stands for family [5,55]. PICS-F concerns mental health problems and consists of anxiety, PTS, depressive symptoms

and complicated grief [5]. Informal caregivers also report loss of employment, financial burden, lifestyle interference and reduced mental HRQL [56]. Approximately one third of informal caregivers suffer from PICS-F, and problems tend to co-occur within individuals as well as families [55]. Prevalence of psychological problems three months post-ICU among informal caregivers has shown to be 30-42% for clinical symptoms of PTS, 24-63% for anxiety and 12-26% for depressive symptoms, although numbers vary between studies [55-57]. While an interventional study offering a 6-week self-help manual and two visits to the ICU follow-up clinic at 2 and 6 months post-ICU did not demonstrate any beneficial effect from the intervention offered in patients nor informal caregivers, it did show a significant correlation between psychological distress in patients at recruitment and at follow-up after six months as well as with symptoms of PTS in relatives [58]. It has been suggested that screening of informal caregivers for increased psychosocial burden should be performed and that follow-up should be offered not only to patients at risk but also to their informal caregivers [55,56,58,59].

2.1.5 Risk factors for PICS components

Several studies have assessed risk factors for PICS, but included risk factors have varied, as well as the timing and measurement of the outcome, thereby reducing the ability to compare studies and draw valid conclusions.

2.1.5.1 Depression

Risk factors for depression in ICU survivors have been assessed in several studies and can be attributable to patient characteristics or factors related to the ICU stay. Previous psychological problems have found to be a significant risk factor for post-ICU depression in several studies [11,12,52,60,61]. There are conflicting results regarding age as a risk factor for depressive symptoms, where a few studies show an increased risk with increased age [60] while others show no association [52,61-66]. Sex, severity of illness and ICU and hospital LOS have demonstrated not to be associated with an increased risk for post-ICU depression in several studies [17]. A pessimistic personality has demonstrated to be predictive of post-ICU depression in two studies by the same research group [64,67]. In-ICU mood and agitation [12,52,61] have also shown to be predictive of depression in ICU survivors. Other significant predictors among patient characteristics that have been described are low educational level and unemployment [12,64,68,69].

2.1.5.2 Anxiety

Among described risk factors for anxiety post-ICU are psychiatric symptoms in the ICU and in-hospital [61,63] as well as previous psychological problems [61]. Other potential risk factors such as age, sex, severity of disease, admission diagnosis, ICU and hospital length-of-stay

have not demonstrated significant association with symptoms of anxiety post-ICU in several studies [61,62,70]. However, one study reported higher anxiety questionnaire scores among younger and female patients [63]. Unemployment and a pessimistic personality trait also seem to be predictive of post-ICU anxiety [64,67,69]. One study found an association between somatic comorbidities and an increased risk for anxiety [71]. The association between being unemployed or on sick leave or having more comorbidities and post-ICU psychological morbidity is in line with another study with a mixed psychological outcome (depression, anxiety and/or PTS) [12].

2.1.5.3 Post-traumatic stress

Several studies have assessed risk factors for PTS in ICU survivors, but few risk factors have been consistent across studies. Younger age has been described as a risk factor in some studies [72-75] while older age was a reported risk factor in one study [64]. There are also conflicting results regarding gender as a risk factor. Female sex was a risk factor for post-ICU symptoms of PTS in some studies [69,72,74,76-78], whereas other studies did not find this association [60,61,63,64,73-75,79,80]. Previous psychiatric problems have been a relatively consistent risk factor for PTS in ICU survivors [11,60,61,73,81-84]. A few smaller studies did not show this association however [80,85,86]. In-ICU mood and acute stress symptoms were reported risk factors in a number of studies [52,61,77] as well as traumatic memories of the ICU stay [72,87]. Pre-ICU characteristics such as unemployment and low educational level were also associated with post-ICU PTS [64,67]. Some studies suggest an association between benzodiazepine use in the ICU [74,84,88] and PTS, but it is difficult to determine if patients prone to anxiety or agitation in-ICU receive more benzodiazepines or if there is in fact causality between high benzodiazepine doses and subsequent PTS. One study showed an association between duration of sedation and PTS [61]. In the majority of follow-up studies, potential ICU-related risk factors such as severity of disease, admission diagnosis, number of days with mechanical ventilation and ICU LOS did not appear to impact occurrence of post-traumatic stress symptoms [25].

2.1.5.4 Physical disability and impairment of ADL

In one study, prolonged bed rest was the single most important risk factor for muscle weakness and long-term physical disability up to 24 months [41], and it has been reported a significant risk factor in several others [29,89]. Another study concluded that mechanical ventilation >8 days, age ≥ 65 years and being admitted due to trauma were factors associated with increased risk for impaired ability to perform ADL [90]. Older age and longer ICU LOS were found to be risk factors for physical disability post-ICU in previous studies [91,92]. Longer duration of mechanical ventilation was a risk factor in two studies assessing risk factors for IADL dependencies [37,93], as well as in one small study assessing disability in arm and leg

function in daily activities 6-24 months post-ICU [94]. Other described risk factors for physical disability post-ICU include the use of corticosteroids [89,92,95], neuromuscular blocking agents [27], hyperglycaemia [96], and early versus late parenteral feeding [97]. However, data regarding these risk factors are conflicting, with some studies reporting no adverse effect regarding the use of steroids [41], neuromuscular blocking agents [98] and hyperglycaemia [41]. Tight glycaemic control through intensive insulin therapy has since been abandoned due to harmful hypoglycaemic events [99].

2.2 IMPROVING LIFE AFTER CRITICAL ILLNESS

With greater awareness of the physical, psychological and cognitive problems many ICU survivors face, strategies to reduce these problems and to improve outcome are gaining importance. Studies of interventions aiming at reducing impairments are being conducted but most interventional studies so far have failed to prove any significant benefit, likely in part due to poor selection of the population at risk; patient inclusion typically being based on a minimum time spent in the ICU or minimum duration of mechanical ventilation, factors not proven to be associated with a higher risk for PICS. The lack of methods to identify high-risk patients may dilute potential beneficial effects from interventional studies, with the inclusion of patients recovering without follow-up interventions as well, not targeting only high-risk patients. It is still unknown what interventions are the most effective and give the most benefit for the patients and their informal caregivers.

2.2.1 In-hospital interventions

Several studies have examined the effect of early mobilization in the ICU on a number of short-term patient outcomes, such as duration of mechanical ventilation, ICU and hospital LOS as well as physical functioning and mortality [100]. In some studies, early mobility therapy has been associated with patients being ambulatory earlier, improved functional status at hospital discharge as well as significantly shorter ICU and hospital LOS, while being as safe and with the same amount of complications as standard care [101-106]. No effect of physical therapy was seen on mortality, neither in-hospital nor up to six months after discharge [100,107]. Few studies have assessed long-term outcomes of in-hospital interventions, but one study showed better results in some of the physical function tests six months post-discharge after an in-ICU rehabilitation intervention [108]. Another study compared early goal-directed mobilization with standard care. No differences between groups regarding HRQL, depression, anxiety, ADL and return to work after six months was found [109].

A randomized clinical trial including 240 ICU patients with mechanical ventilation for a minimum of 48 hours, with the intervention group receiving more intensive in-hospital rehabilitation, individualized goal setting and more information, all delivered by a rehabilitation practitioner, did not show any benefit of the intervention on physical nor

psychological outcomes 3-12 months after discharge [110]. Patients in the intervention group however, reported higher patient satisfaction with several of the outcome measures. Patients in the control group received physical therapy, occupational therapy and a self-help ICU rehabilitation manual as recommended in the UK guidelines. One possible explanation for the lack of positive results may be that the intervention and standard care were too similar to show a real difference on the outcome [111].

However, a Cochrane review in 2017 concluded that due to included studies being small, not blinded and with varying outcome measures, hard evidence is lacking regarding the efficacy of early mobility in-ICU [112].

Few studies have assessed in-hospital interventions aiming at improved psychological outcome which limits the ability to draw conclusions about the benefit of such interventions. A multicentre randomized controlled trial evaluating the effect of a complex nurse-led psychological intervention on patients' level of PTS symptoms six months post-ICU did not show an effect of the intervention [113]. A single-centre study assessing an in-ICU clinical psychologist intervention only in trauma patients found a reduced risk for developing PTS as well as a reduced risk of being on psychiatric medication 12 months after discharge [114]. A narrative review of mixed quality and methodological studies assessing different psychological interventions concluded that psychological support in-ICU was associated with positive short-term and long-term psychological outcomes, but included studies were underpowered to detect significant interventional effect [115]. Larger studies assessing psychological interventions are needed.

2.2.2 Outpatient interventions

ICU survivors have been reported to appreciate follow-up after intensive care [116,117], but there is no strong evidence regarding the potential beneficial effects of such follow-up in terms of measurable physical, psychological or cognitive improvements [118,119]. A few qualitative studies have shown increased patient satisfaction and motivation with mixed interventions even though failing to prove substantial measurable effects on physical and/or emotional outcome [110,120,121]. One study assessing a nurse-led intervention with regards to HRQL 12 months after ICU stay and the cost-effectiveness of such an intervention did not show any effect on the outcome, or any economic benefit [122]. Another randomized controlled trial of ICU survivors, aiming to improve HRQL at 6 and 12 months through a nurse-led psychological outpatient intervention, showed no benefit of the intervention on the predefined primary and secondary outcomes, but a per protocol analysis showed significant reduction in number of patients above cut-off in the HADS Anxiety subscale in the intervention group at three months post-ICU [123]. The selection of patients in these trials however, was not based on risk assessment at inclusion.

A home-based physical rehabilitation intervention showed no effect on physical functioning or HRQL six months after hospital discharge [124]. Another interventional study with a 2x2 factorial design evaluated the effect of supplemental amino acids and outpatient physiotherapy classes. Patients in the intervention groups showed an improved physical recovery and a reduced rate of anxiety and depression [125]. Nevertheless, the study was underpowered and included only patients able to walk 30 m unaided at ICU discharge, a rather selected group of ICU survivors questioning generalizability and most probably omitting high-risk patients for physical disability.

In yet another study assessing the effect of a self-help rehabilitation manual on HRQL, PTS, depression and anxiety, the intervention group had improved physical HRQL but no statistically significant differences were seen between intervention and control group regarding the psychological outcomes [126]. A small study examining the feasibility of outpatient physiotherapy found improvements in physical functioning compared to baseline as well as reduced symptoms of anxiety and depression, but there was no control group for comparison and hence improvements could potentially be due to normal recovery [127]. Another interventional study randomized patients and their caregivers to either a disease management program or standard care. The disease management program consisted of an 8-week program with emotional and instrumental support from a dedicated nurse. When patient death and caregiver drop-out was accounted for, there was a statistically significant difference in favour of the intervention, with a higher proportion of patients categorised as having no or mild depression in the intervention group than in the control group, even though differences in the mean (SD) of the outcome questionnaire was not different between the groups [128].

A recent randomized controlled trial assessed the effect of a six-week telephone- and web-based coping skills training program compared to a critical illness education program and the effect on patient and family psychological distress[129]. They found no effect of the coping skill intervention, except in a subgroup of patients with high baseline distress, suggesting that future interventional studies should target high-risk populations.

The use of ICU diaries has, in some studies, proven to be an effective psychological intervention. One study evaluating the effect of ICU diaries demonstrated significantly fewer patients diagnosed with new-onset PTS in the intervention group three months post-ICU, and a post-hoc analysis showed a greater reduction in PTS symptoms in a subgroup of patients with initial high symptom scores of PTS, indicating a larger treatment effect in a high-risk group of patients [79]. Another study by the same group showed significant reduction in PTS symptom scores at three months post-ICU in caregivers to patients who received a diary compared to caregivers to patients with no diary [130] (even though scores at both baseline and follow-up were below the defined cut-off for clinically significant symptoms of PTS). Another pilot ICU diary study showed a reduction of PTS symptom scores at 12 months post-ICU in survivors and their caregivers, but no effect on depression or anxiety [80]. Yet another pilot diary study without adequate power revealed lower prevalence of substantial symptoms of anxiety at three months in ICU survivors receiving a diary, but no effect on symptoms of

depression and PTS [131]. A more recent randomized clinical trial including patients receiving mechanical ventilation for at least 48 hours compared the use of ICU diaries with no diaries and could not demonstrate a significant difference of significant PTS symptoms between groups, neither in anxiety or depression among patients nor family members [132]. Only 51% of patients responded at follow-up, raising concerns about the validity of the results. Furthermore, as stated previously, mechanical ventilation does not appear to constitute a risk factor for PTS, which further makes interpretation of the negative finding difficult. Perhaps restricting inclusion to high-risk patients would have yielded a different result. A Cochrane systematic review from 2015 concluded that the evidence for ICU diaries for improving psychological outcomes for patients and caregivers was minimal [133].

Another Cochrane review concluded that the evidence was unclear regarding the effects of education and information in-ICU upon patients' symptoms of depression, anxiety and health-related quality of life and upon caregivers' symptoms of depression, anxiety or satisfaction [134].

To summarize, outpatient interventions that have been studied to date are heterogeneous both when it comes to type and timing of intervention and the outcome measured, making conclusions of any potential benefit difficult to draw. The common denominator for patient selection in all of the above-mentioned interventional studies was a predefined minimum time spent in the ICU or with mechanical ventilation before inclusion, which intuitively may be a good method of selection but lacks evidence in this regard, making it unlikely to be the best way to select patients with the highest risk for an adverse outcome and most likely to benefit from follow-up interventions. Not targeting high-risk patients could have affected the lack of positive results, due to dilution. Future interventional studies need to focus on patients at risk and use standardized interventions that differ from standard care. Further, outcome measurements may benefit from harmonization, facilitating comparisons between studies.

2.2.3 Follow-up after intensive care

Although there is increasing awareness of PICS and follow-up after ICU stay is evolving, many hospitals still lack such services [135-138]. The timing and setup of follow-up varies between hospitals and countries, and it is still unknown what interventions are most effective [139]. National guidelines recommend assessment of patients' physical, cognitive and emotional status in ICU, before discharge from the ICU and initiation of a personalized rehabilitation already in the regular ward [140]. The most effective and favourable structure of such follow-up remains unknown.

Interventional studies have not been able to demonstrate substantial benefits of follow-up interventions, when these have been applied in relatively unselected ICU survivor populations. Patient selection for follow-up has typically been based on ICU LOS [135-138], a factor not associated with adverse psychological outcome after ICU stay [12]. It would be of

value to be able to identify patients at high risk for long-term physical and psychological problems at discharge from the ICU. Small studies, evaluating different methods to screen patients for psychological problems post-ICU exist, but to date no method has gained widespread use. Some screened patients at later time points [141,142], and other only assessed subgroups of patients [87,143]. One study evaluating a newly developed screening tool for ICU patients with ICU LOS > 48 hours showed acceptable predictive value for three-month psychological morbidity with an area under the receiver operating characteristics curve (AUC) of 0.70 [144]. The screening tool needs further validation and does not take into account the potential risk of later problems for the cohort of patients with ICU stay <48 hours. A single-centre study from our research group developed a preliminary screening instrument for new-onset physical disability after ICU stay, with an AUC of 0.80 [145] and yet another study developed a preliminary instrument for screening of psychological problems, with an AUC of 0.77 [12]. Focusing follow-up on high-risk individuals could enable early interventions in risk populations, optimizing resources for ICU follow-up and increasing the possibility of improving the long-term outcome and quality of life in survivors of critical illness and ICU stay.

3 RESEARCH AIMS

The overall objective of this thesis was to improve the recovery for ICU survivors and their informal caregivers through early identification of patients at risk for psychological and physical disability after ICU stay.

The specific aims of the included studies were:

- To develop an ICU discharge screening instrument for prediction of psychological problems three months after ICU discharge

- To develop an ICU discharge screening instrument for prediction of new-onset physical disability three months after ICU discharge

- To evaluate if in-hospital screening of psychological problems one week after ICU discharge can predict psychological problems three months later

- To assess whether an incomplete psychological or physical patient recovery after ICU stay affects caregiver burden and emotional wellbeing in informal caregivers

4 MATERIALS AND METHODS

4.1 ETHICAL CONSIDERATONS

All studies in this thesis were approved by regional ethical review boards and the studies were performed in accordance with the standards laid down in the World Medical Association's 1964 Declaration of Helsinki and its later amendments. Studies I, II and IV were registered at clinicaltrials.gov, registration number NCT02679157 for studies I and II, and number NCT02712541 for study IV. Ethical approval number for studies I, II and IV was 2015/1799-31 and for study III 2012/35-31/2. Informed consent was sought from all participating patients. Patients who later declined participation had their data removed. Data from patients dropping out were kept in order to perform comparative analyses between drop-outs and patients remaining in the study, in order to better understand reasons for attrition and assess potential selection bias. All included studies were observational, implying minor discomfort in participating, except from the possibility of provoking unpleasant emotions and memories when answering the follow-up questionnaires.

4.2 OVERVIEW

Table 1. Overview of methods of included studies

	Study I	Study II	Study III	Study IV
Short title	Prediction model for psychological problems post-ICU	Prediction model for new-onset physical disability post-ICU	Early psychological screening of ICU survivors	Caregiver burden in informal caregivers to ICU survivors
Design	Multicenter prospective cohort study	Multicenter prospective cohort study	Single-center prospective cohort study	Multicenter prospective cohort study
Study participants	ICU survivors with ICU stay ≥12 hours n=572	ICU survivors with ICU stay ≥12 hours n=572	ICU survivors with ICU stay ≥24 hours n=132	Informal caregivers to ICU survivors included in study I/II n=62
Exposure/Risk factors	Age, sex, educational level, employment status, children <18 years old, comorbidities, previous psychological problems, social support, severity of disease, admission diagnosis, acute/elective ICU admission, agitation, coma, severe sepsis, duration of invasive ventilation, ICU LOS, depressive symptoms and traumatic memories at ICU discharge	Age, sex, educational level, employment status, comorbidities, social support, physical status pre-ICU, severity of disease, admission diagnosis, coma, severe sepsis, duration of invasive ventilation, ICU LOS, fractures, physical status at ICU discharge	Early scores in psychological questionnaires one week post-ICU	Being an informal caregiver to a patient with or without an adverse psychological and/or physical recovery post-ICU
Primary outcome assessment	Psychological problems three months post-ICU: PTSS-14, HADS	New-onset physical disability three months post-ICU: BI	Psychological problems three months post-ICU: PTSS-10, HADS	Caregiver burden in relation to patient outcome three months post-ICU: CBS
Secondary outcome(s)	Mental HRQL (RAND-36)	Physical HRQL (RAND-36)		Psychological problems in informal caregivers, (PTSS-14, HADS) correlation between caregiver burden and mental HRQL (RAND-36)
Main statistical analysis	Univariable and multivariable logistic regression, prediction modeling	Univariable and multivariable logistic regression, prediction modeling	Spearman's rank correlation, ROC curves	Linear regression, Spearman's rank correlation

Abbreviations: ICU Intensive Care Unit, APACHE Acute Physiology And Chronic Health Evaluation, LOS Length Of Stay, PTSS-14 Post-Traumatic Stress Syndrome 14- Questions Inventory, HADS Hospital Anxiety and Depression Scale, BI Barthel Index, CBS Caregiver Burden Scale, HRQL Health Related Quality Of Life, ROC Receiver Operating Characteristics

4.3 CLASSIFICATIONS AND OUTCOME QUESTIONNAIRES

Charlson Comorbidity Index (CCI) (Studies I, II and IV)

The CCI was developed to estimate the 1 and 10-year mortality due to comorbidities in medical patients. It contains 17 different diagnosis categories of which each is weighted based on the mortality risk. It has been validated and updated to fit the ICD-10 definitions since its development, and has a predictive value assessed as the AUC of 0.86 [146,147]. In this thesis it was used as an estimation of the burden of comorbidities of patients included in studies I, II and IV.

Simplified Acute Physiology Score III (SAPS III) (Studies I-II)

SAPS III is a system for assessing severity of illness and predicting ICU patients' vital status at hospital discharge by scoring prior comorbidities, specific characteristics and vital parameters at ICU admission [148]. We chose to include only Box I as an additional measure of severity of disease due to comorbidities, since other parts of the SAPS III requires specific laboratory analyses and all participating hospitals were not using the SAPS III in clinical practice.

Acute Physiology And Chronic Health Evaluation II (APACHE) (Studies I-IV)

The APACHE II is another classification scoring the severity of illness based on previous health status, age and physiologic parameters during the first 24 hours of ICU stay, in order to predict in-hospital mortality [149]. It has been widely used and was in these studies used to describe the severity of illness of included ICU patients.

Patient Health Questionnaire 2-items (PHQ-2) (Studies I-II)

The PHQ-2 is a validated two-item questionnaire assessing the frequency of depressive symptoms and anhedonia. Scores ranges from 0-3 per question, rendering a total score of 6. A score ≥3 showed high sensitivity and specificity for major depression when compared to a mental health professional interview [150]. The original question and answers were slightly changed in order to better adapt to the time frame in the ICU for the included patients, to assess depressive symptoms at ICU discharge.

Post-Traumatic Stress Syndrome 10/14-Question Inventory (PTSS-10/14) (Studies I-IV)

The PTSS-10 and PTSS-14 are validated tools assessing symptoms of post-traumatic stress (PTS) in ICU survivors. The PTSS-10 was the instrument in clinical use when performing study III and consists of two parts, part A with four questions answered yes or no assessing traumatic memories and part B with ten questions rating PTS symptoms from 1 (never) to 7 (always). Scores range from 7-70 in the 10-item version and from 7-98 in the 14- item version. It is based on the diagnostic criteria in the American Psychiatry Association's Diagnostic and Statistical Manual of Mental Disorders 3rd edition (DSM-III), with a revision made to better suit the ICU environment [151]. The PTSS-14 was developed to adapt to the updated diagnostic criteria in the DSM-IV, adding four questions in the part B regarding numbing, flashbacks and avoiding [141]. A PTSS-10 part B score >34 and a PTSS-14 part B score >45 is indicative of clinically significant symptoms of PTS [83,141].

Hospital Anxiety and Depression Scale (HADS) (Studies I-IV)

The HADS is a validated tool assessing symptoms of anxiety and depression in general medical as well as ICU patients. It consists of 7 questions assessing depressive symptoms and 7 assessing anxiety symptoms, each subscale generating a score ranging from 0-21. A subscale score ≥8 has been suggested to identify possible cases of clinically significant symptoms of depression or anxiety and a subscale score ≥10 indicates a probable case [152].

RAND-36 (Studies I-IV)

The RAND-36 is a 36-item validated questionnaire assessing health-related quality of life, developed from the widely used Medical Outcomes Study Short Form-36 (SF-36) [153,154]. Questions can be divided into eight domains, further divided into two component scores, the mental health component score (MCS) and the physical health component score (PCS). Scores range from 0-100, a higher score indicating a higher HRQL.

Chelsea Critical Care Physical Assessment Tool (CPAx) (Studies II and IV)

The CPAx was developed to measure physical morbidity in an adult ICU population, assessing ten different areas of physical functioning and grading them from 0-5 depending on the level of dependency in performing the activity [155]. In study II we used the five first items in order to assess physical status at ICU discharge. The first five items are: need for respiratory support/oxygen therapy, ability to cough/clear secretions, ability to roll in the bed, to move from laying to sitting and dynamic sitting on the edge of the bed. The last five items include standing balance, moving from sitting to standing, transferring from bed to chair,

stepping and grip strength. Total score range from 0-50, a higher score indicating better function.

Barthel Index (BI) (Studies II and IV)

The Barthel Index is a 10-item validated questionnaire assessing the dependency or independency in performing activities of daily living (ADL), such as feeding, dressing and showering [156]. Scores range from 0-100, a higher score indicating better physical functioning. A score reduction of 9.25 has been suggested a minimal clinically important difference in BI score [157].

Caregiver Burden Scale (CBS) (Study IV)

To assess caregiver burden in study IV, we used the CBS, originally developed in a population of caregivers to stroke patients. It consists of 22 questions assessing the caregivers' situation regarding isolation, general strain, disappointment, emotional involvement and environment due to taking care of the patient. Each question generates 1-4 points [158].

4.4 STUDY DESIGN

4.4.1 Study I

Design

This was a multi-center prospective observational cohort study of patients admitted to one of ten participating ICUs in tertiary-care hospitals in Sweden, Denmark and the Netherlands.

Study cohort

Patients were eligible for study inclusion if ≥18 years old and admitted for 12 hours or more to the ICU (≥24 hours for planned, postoperative ICU admissions) and surviving to ICU discharge. Exclusion criteria were the need for neurointensive care, inability to communicate in the language of the study site, documented substantial cognitive problems including dementia, multiple limitations of treatment, lacking a formal home address or admitted to the ICU solely for an invasive procedure (such as epidural line placement, central vein catheterization).

Data collection/Predictors

Data were collected in-ICU through patient data management systems, medical charts and patients or their next-of-kin. Risk factors were chosen after a literature review of potential

risk factors for psychological problems post-ICU also taking into account the feasibility of assessing the risk factor bedside at ICU discharge. Assessed risk factors were patient age, sex, level of education, being a caretaker to children <18 years old, employment status, comorbidities assessed with the Charlson Comorbidity Index (CCI) and the Simplified Acute Physiology Score (SAPS) III box 1, social support, previous psychological problems, severity of disease assessed with the Acute Physiology And Chronic Health Evaluation (APACHE) II, admission diagnosis, acute or elective reason for ICU admission, days with coma, agitation in-ICU, severe sepsis, duration of mechanical ventilation and ICU length of stay (LOS) as well as depressive symptoms (assessed with the 2-item Patient Health Questionnaire, PHQ-2) and traumatic memories (assessed with the four questions in the PTSS-14 part A) at ICU discharge.

Outcome

Outcome questionnaires were posted to patients three months after ICU discharge, including validated tools assessing symptoms of depression, anxiety and post-traumatic stress (PTS) with the Hospital Anxiety and Depression Scale (HADS) and the Post-Traumatic Stress Syndrome 14-Question Inventory (PTSS-14). Also included was the RAND-36, assessing health-related quality of life (HRQL). Primary outcome was psychological problems three months post-ICU, defined as HADS Subscale score ≥10 or PTSS-14 score >45. Secondary outcome was mental HRQL, assessed with the four mental domains in the RAND-36; emotional role limitations, social functioning, energy/fatigue and emotional wellbeing. Based on resulting risk factors a screening instrument for prediction of psychological problems post-ICU was developed.

Statistical Analysis

Assessed risk factors were analyzed with univariable and multivariable logistic regression modeling for association with the primary outcome. Supervised, non-automatic stepwise selection was performed, rendering the predictive instrument. Predictors included in the final prediction model were presented with odds ratios (OR) and 95 % confidence intervals (CI) and the predictive value of the model was assessed with the area under the receiver operating characteristics (ROC) curve (AUC). Selection bias due to non-response was handled with a weighted model, applied to all subsequent analyses.

4.4.2 Study II

Design

Same as Study I.

Study cohort

Same as Study I.

Data collection

Assessed risk factors for new-onset physical disability post-ICU were: patient age, sex, education level, employment status, pre-ICU physical function assessed with the Barthel Index (BI), comorbidities (assessed with CCI + SAPS III), social support, severity of disease (assessed with the APACHE II), admission diagnosis, coma days, fractures, severe sepsis, duration of invasive mechanical ventilation, ICU LOS and physical status at ICU discharge assessed with the Chelsea Critical Care Physical Assessment Tool (CPAx).

Outcome

Three months after ICU discharge patients received outcome questionnaires by postal mail, in addition to those in Study I, the BI assessing physical function. The BI is a 10-item questionnaire, assessing the level of dependence in performing activities of daily living (ADL). A BI score reduction ≥10 compared to pre-ICU BI score was the definition of the primary outcome, new-onset physical disability three months post-ICU. Secondary outcome was physical HRQL, assessed with the four physical domains in the RAND-36; physical role limitations, bodily pain, physical functioning and general health.

Statistical Analysis

Assessed risk factors were analyzed with univariable and multivariable regression modelling with backwards elimination, for association with the outcome. The resulting predictor for the outcome was included in a prediction model and presented with OR (95% CI). The predictive value of the instrument was assessed with the AUC.

4.4.3 Study III

Design

This was a prospective observational single-center cohort study performed in the general ICU in Karolinska Hospital Solna.

Study cohort

Adult patients admitted ≥24 hours to the ICU and surviving to discharge were eligible for inclusion. Patients with aphasia, unable to communicate in Swedish, with intellectual disability or with severe visual or auditory disorders were excluded.

Data collection

In-ICU data such as patients' age, sex, admission diagnosis, APACHE II score and ICU LOS were collected from the medical chart and patient data management system. Within one week from ICU discharge, a nurse visited patients in the general ward and assessed symptoms of depression, anxiety and PTS with validated questionnaires (HADS, PTSS-10).

Outcome

Three months after ICU discharge, patients received the same questionnaires by postal mail, assessing symptoms of depression, anxiety and PTS. Patients were considered to have clinically significant psychological problems if HADS subscale score was ≥8 or PTSS-10 score >34. Primary outcome was predictive value of the early assessment on three-month psychological problems.

Statistical Analysis

The predictive value of the early assessment on three-month questionnaire scores was analyzed with the AUC. Correlation between early scores and three-month scores was assessed with Spearman's rank correlation.

4.4.4 Study IV

Design

This study was a multicenter prospective observational cohort study including patients and caregivers from four of the ten participating study sites for studies I/II.

Study cohort

Informal caregivers cohabiting with patients included in study I/II at four Swedish study sites were included.

Data collection

Data regarding caregivers' age and sex as well as relation to the patient and baseline HRQL (assessed with the RAND-36) was gathered in-ICU in addition to patient data collected for study I/II.

Outcome

Three months post-ICU outcome questionnaires were sent by postal mail to informal caregivers, assessing caregiver burden with the Caregiver Burden Scale (CBS) and symptoms of depression, anxiety (HADS), PTS (PTSS-14) as well as mental HRQL with the RAND-36. Primary outcome was to compare caregiver burden in caregivers to patients with and without an adverse psychological and/or physical outcome. Secondary outcome was correlation between caregiver burden and caregivers' mental HRQL.

Statistical Analysis

The association between difference in caregiver burden and patients' adverse psychological/physical outcome was assessed with linear regression analysis. Correlation

between caregiver burden and informal caregivers' mental HRQL was analyzed with Spearman's rank correlation.

5 RESULTS

5.1 STUDY I

Of 2193 screened patients, 572 patients were included in study I/II, of which there are follow-up data on 404, 78% of patients who survived to the time of follow-up. Among 404 patients responding to the outcome questionnaires, 61% were male with a median (IQR) age of 65 (53-73) years and median APACHE II score was 18 (13-23). Of included patients, 60% received mechanical ventilation for a median duration of 50 (13-137) hours and median ICU LOS was 62 (30-140) hours. The prevalence of psychological problems three months post-ICU was 20% (n=80). Significant predictors for an adverse psychological outcome were age, lack of social support, depressive symptoms and traumatic memories at ICU discharge (Table 2).

Table 2. Odds ratios and confidence intervals for risk factors included in the multivariable model. Regression coefficients for risk factors in the final predictive model

Risk factor	Odds ratio	95% CI		p-value	Regression coefficient
Lack of social support	3.28	1.47	7.32	<0.01	15.71
Psychological problems pre-ICU	2.17	1.22	3.85	>0.05	
Depressive symptoms (PHQ-2)	1.29	1.10	1.50	<0.01	3.39 per point
Traumatic memories (PTSS-14A)	1.44	1.13	1.82	<0.01	4.84 per point
Age	Separate table				0-58

CI, confidence interval; CPAx, Chelsea Critical Care Physical Assessment tool; ICU, intensive care unit; PHQ-2, patient health questionnaire; PTSS-14A, Post-traumatic symptoms checklist 14 part A

The predictive value of the instrument assessed with the area under the curve was 0.76 (95% CI 0.70 to 0.81). The final prediction instrument is depicted in Figure 1.

Figure 1. The psychological risk prediction instrument for use at ICU discharge

Age

Point correlating to patient's age is the age score

Age	Points	Age	Points	Age	Points	Age	Points
≤ 20	**0**	34	**36**	49-50	**56**	80-81	**46**
21	**2**	35	**38**	51-53	**57**	82	**45**
22	**6**	36	**40**	54-60	**58**	83	**44**
23	**8**	37	**42**	61-63	**57**	84-85	**43**
24	**11**	38	**44**	64-65	**56**	86	**42**
25	**14**	39	**46**	66-67	**55**	87	**41**
26	**17**	40	**47**	68-69	**54**	88-89	**40**
27	**18**	41	**48**	70-71	**53**	90-91	**39**
28	**22**	42	**50**	72	**52**	92	**38**
29	**24**	43	**51**	73-74	**51**	93	**37**
30	**27**	44	**52**	75	**50**	94-95	**36**
31	**29**	45	**53**	76-77	**49**	96	**35**
32	**31**	46	**54**	78	**48**	97	**34**
33	**34**	47-48	**55**	79	**47**	98-99	**33**

TOTAL AGE SCORE: _____

Post-traumatic stress symptoms (PTSS14-A)

When you think back to the time of your severe illness and the time you spent in the Intensive Care Unit (ICU), do you remember:

	YES	NO
Nightmares	☐	☐
Severe anxiety	☐	☐
Severe pain	☐	☐
Trouble to breathe, feelings of suffocation	☐	☐

MULTIPLY NUMBER OF YES WITH 5 FOR TOTAL PTSS-14A RISK SCORE **TOTAL PTSS-14A SCORE: _____**

Depressive symptoms (PHQ-2)

Over the last days, how often have you been bothered by any of the following problems?

	Not at all (0 points)	Occasionally (1 point)	More than half of the time (2 points)	Nearly all the time (3 points)
Little interest or pleasure in doing things	☐	☐	☐	☐
Feeling down, depressed or hopeless	☐	☐	☐	☐

MULTIPLY SUM OF PHQ-2 POINTS WITH 3 FOR TOTAL PHQ-2 RISK SCORE **TOTAL PHQ-2 SCORE: _____**

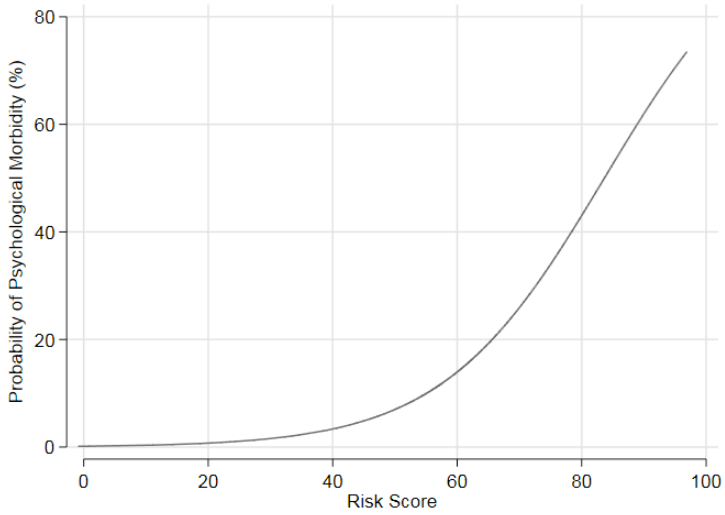
Social support	YES	NO
Do you have a family member or close friend who cares about you and your health who can help you when you leave the hospital?	☐	☐

IF YES ADD 0 POINTS, IF NO ADD 16 POINTS FOR SOCIAL SUPPORT SCORE **TOTAL SOCIAL SUPPORT SCORE: _____**

TOTAL RISK SCORE (SUM OF SCORES FROM AGE, PTSS-14A, PHQ-2 AND SOCIAL SUPPORT): _____

Risk graph

Plot total risk score to get patient's probability of psychological problems three months post-ICU



5.2 STUDY II

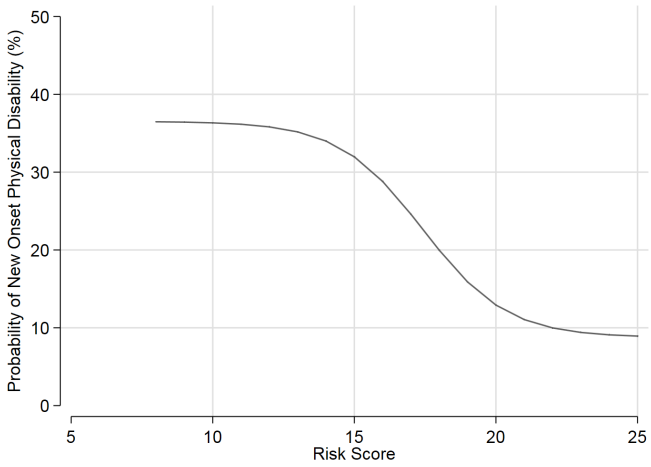
The number of included patients and patient characteristics are the same as in study I. Prevalence of new-onset physical disability three months post-ICU was 19% (n=75). The sole remaining predictor for an adverse physical outcome was physical status at ICU discharge, assessed with the first five items of the CPAx, OR 0.87 (95% CI 0.81 to 0.93), p <0.001, a lower score indicating worse physical function. The predictive value of the screening instrument assessed with the AUC was 0.68 (95% CI 0.61 to 0.76). Negative predictive value for a low-risk group with CPAx score >18 was 0.88 and positive predictive value for a high-risk group with CPAx score ≤18 was 0.32. The final prediction instrument is depicted in Figure 2.

Figure 2. The physical risk prediction instrument for use at ICU discharge

1. Assess patient's physical status and score according to level achieved

Aspect of physicality	0 points	1 point	2 points	3 points	4 points	5 points
Respiratory function	Complete ventilator dependence. Mandatory breaths only. May be fully sedated/paralysed	Ventilator dependence. Mandatory breaths with some spontaneous effort	Spontaneously breathing with continuous invasive or non-invasive ventilator support	Spontaneously breathing with intermittent invasive or non-invasive ventilator support or continuous high flow oxygen (>15 l)	Receiving standard oxygen therapy (<15 l)	Self-ventilating with no oxygen therapy
Cough	Absent cough, may be fully sedated or paralysed	Cough stimulated on deep suctioning only	Weak ineffective voluntary cough, unable to clear secretions independently (e.g. requires deep suction)	Weak, partially effective voluntary cough, sometimes able to clear secretions (e.g. requires Yankauer suctioning)	Effective cough, clearing secretions with airways clearance techniques	Consistent effective, voluntary cough, clearing secretions independently
Moving within the bed (e.g. rolling)	Unable, may be fully sedated/paralysed	Initiates movement. Requires assistance of two or more people (maximal)	Initiates movement. Requires assistance of at least one person (moderate)	Initiates movement. Requires assistance of one person (minimal)	Independent in ≥3 seconds	Independent in <3 seconds
Supine to sitting on the edge of the bed	Dynamic Unable/unstable	Initiates movement. Requires assistance of two or more people (maximal)	Initiates movement. Requires assistance of at least one person (moderate)	Initiates movement. Requires assistance of one person (minimal)	Independent in ≥3 seconds	Independent in <3 seconds
Dynamic sitting (i.e. when sitting on the edge of the bed/ unsupported sitting)	Unable/unstable	Requires assistance of two or more people (maximal)	Requires assistance of at least one person (moderate)	Requires assistance of one person (minimal)	Independent with some dynamic sitting balance (i.e. able to alter trunk position within base of support)	Independent with full dynamic sitting balance (i.e. able to reach out of base of support)

2. Add total score from all five items and plot the score in the graph to obtain patient's probability of new-onset physical disability three months post-ICU



5.3 STUDY III

Of 132 included ICU survivors, response rate was 62% (n=82). Among those, 55 (42%) were female and median (IQR) age was 62 (41-70) years. Median APACHE score was 10 (7-14) and median length of stay in the ICU was 3 (2-6) days. The three-month prevalence of symptoms of PTS was 13% (n=11) and the predictive value of the early screening as assessed with the AUC was 0.90 (95% CI 0.80 to 0.99). Prevalence of symptoms of anxiety was 16% (n=13) and the resulting AUC was 0.80 (95% CI 0.64 to 0.95). Prevalence of depressive symptoms was 21% (n=17) and the AUC was 0.75 (95% CI 0.64 to 0.87). Correlation between the early assessment and three-month scores was moderate to strong (Table 3).

Table 3. Questionnaire scores and correlation between early assessment and follow-up

Questionnaire	Early scores responders n=82	Early scores non-responders n=50	Three months' scores	Patients with symptoms at follow-up, %	Correlation (p-value)
PTSS-10 B	20 (15-29)	25 (19-37)	17 (13-30)	13	0.60 (<0.001)
HADS-Anxiety	3 (1-7)	5.5 (2-10)	2 (1-5)	16	0.48 (<0.001)
HADS-Depression	4 (1-7)	6 (3-11)	4 (1-6)	21	0.56 (<0.001)

Scores are presented as median values (interquartile range) unless otherwise stated. Cut-off for symptoms of PTSS-10 B >34 points. Cut-off for symptoms of HADS-Anxiety and HADS-Depression >7 points. Correlation between early assessment and three-month follow-up calculated with Spearman's rank correlation coefficient.

PTSS-10 B: Post-Traumatic Stress Symptoms 10-Questions Inventory Part B

HADS: Hospital Anxiety and Depression Scale

5.4 STUDY IV

Of 62 included informal caregivers, 55 (89%) responded to the outcome questionnaires. Caregiver Burden Scale scores were significantly higher, indicating a higher caregiver burden, in caregivers to patients with an adverse psychological or physical recovery, mean (SD) 52 (11) compared to caregivers to patients without an adverse outcome, mean 41 (13), p=0.003 (Table 4). There was a strong negative correlation between caregiver burden and caregivers' mental HRQL, r_s= -0.74, p=0.000. Prevalence of PTS in caregivers was significantly higher than that of included patients, 11 (21%) compared to 5 (9%), p=0.048. There were moderate to strong correlations between caregiver burden and informal caregivers' own mental problems, r_s = 0.68 (95% CI 0.52 to 0.84, p<0.001) for depression, r_s =0.62 (95% CI 0.42 to 0.81, p<0.001) for anxiety and r_s = 0.72 (95% CI 0.56 to 0.89, p<0.001) for PTS.

Table 4. Outcome scores for informal caregivers to patients with and without adverse outcome with crude and adjusted mean differences

Informal caregiver outcome questionnaire	Informal caregivers to patients with adverse outcome[1]	Informal caregivers to patients without adverse outcome	Crude mean difference	p-value[2]	Adjusted mean difference[3] (95% CI)
CBS Score, mean (±SD)	52 (11)	41 (13)	11.2	0.003*	12.81 (5.67 to 19.95)
HADS Depression subscale score, median (IQR)	6 (4-10)	4 (2-7)	1.92	0.085	2.21 (0.05 to 4.36)
HADS Anxiety subscale score, median (IQR)	6 (3-9)	4 (2-9)	1.16	0.383	2.12 (-0.26 to 4.49)
PTSS-14 score, median (IQR)	35 (22-54)	28 (18-38)	6.90	0.239	9.21 (-0.73 to 19.16)
RAND-36 MCS score at follow-up, median (IQR)	53 (37-89)	79 (55-92)	-13.98	0.118	-17.41 (-34.08 to -0.74)

[1] Definition of adverse outcome: HADS Depression subscale score ≥11, HADS Anxiety subscale score ≥11, PTSS-14 part B score >45 and/or BI ≥10 score reduction compared to baseline.
[2]p-value for the difference between patients with and without adverse outcome from the crude mean difference analysis
[3]Adjusted for informal caregiver age and sex
*significant p-value
CBS caregiver Burden Scale, SD Standard Deviation, HADS Hospital Anxiety and Depression Scale, IQR Interquartile Range, PTSS-14 Post-Traumatic Stress Syndrome 14-Questions Inventory, MCS Mental Component Score

6 METHODOLOGICAL CONSIDERATIONS

6.1 STUDY DESIGN

The first question to pose when planning a study is what study design will help answer the study question. To test a hypothesis, an analytical study of some kind, either observational or experimental is needed. The choice depends upon what exposure and what outcome is in focus. Observational studies give the possibility of studying rare and multiple exposures and multiple outcomes, with a distinct time relation between exposure and outcome. The study questions in this thesis could all best be answered with a prospective observational study design, with the opportunity to study multiple exposures (risk factors) and their potential effect on the outcome. The broad inclusion made possible by the observational design can increase the generalizability and enable inference of study results on a large and heterogeneous group of ICU survivors.

6.2 INTERNAL VALIDITY

There are three possible explanations for the results of a study, a true association, association by chance (random error) and a systematic error (bias) explaining the association. Systematic errors are further divided into selection bias, information bias and confounding. Internal validity refers to how well the results or proven association in the sampled study population actually represents the true association in the source population one wished to study, i.e. the degree to which systematic error explains the results. High internal validity implies low risk of systematic errors.

6.2.1 Random error

Random errors are best avoided with an adequate study population size, increasing the precision of a study. The larger the study size, the smaller the risk of random errors and the higher the precision. However, the study size is limited because of economic, ethical and feasibility reasons, so that no individuals should be included unnecessarily. These are the reasons why a sample size calculation should be performed before starting a study. For studies I and II, a sample size calculation was performed based on the number of risk factors assessed and the putative prevalence of the outcome, aiming for a power of 80% and a two-sided significance level of 0.05. Study size calculations rendered a projected inclusion of 800 patients that was not reached due to limited resources and more patients than expected fulfilling exclusion criteria and being transferred to other ICUs, possibly affecting the precision of the results. For study III no power calculation was performed, instead study size was dependent on the number of patients admitted to the ICU during the predetermined inclusion period, a rather common pragmatic strategy in observational studies. For study IV, a power calculation was performed based on the assumed difference in caregiver burden

between the two groups of caregivers, rendering a study cohort of 50 participants with full data, aiming at a power of 80% and a two-sided significance level of 0.05. The calculated number of included participants to reach sufficient power was reached.

6.2.2 Selection bias

Selection bias is a systematic error that occurs when the selected sample is not representative of the population one wishes to make inference upon. Volunteer bias is such an example, attrition bias another. The risk of attrition bias is evident when potential study participants decline participation or dropout of the study for reasons that may be related to the exposure or the outcome.

Reasons for non-participation or dropping out in the studies in this thesis is unknown, but could be due to a higher degree of psychological or physical problems, making the individual more reluctant to answer questionnaires about their health status, possibly evoking difficult psychological emotions or traumatic memories. Non-responding could also be due to a good recovery, making the individual less prone to participate when there is no need for improvement. Attrition bias is a potential risk in all studies in this thesis. In studies I and II, potential attrition bias was handled through inverse probability weighting. Potential predictors associated with the probability of responding where analyzed through univariable and multivariable regression analysis. The resulting weighted model was applied to all subsequent analyses in order to minimize selection bias due to non-responding. In study III, patients who were drop-outs had higher symptom scores in the early assessment, indicating that patients with more pronounced psychological problems were more likely to be lost-to-follow-up. This could have affected the results, potentially by diluting them. In study IV, potential selection bias could be introduced due to the convenience sampling of caregivers visiting the ICU at times when research staff was available. The reasons for accepting participation and for being a non-responder might not be completely random, possibly introducing selection bias.

6.2.3 Information bias

Information bias refers to the information of the exposure or the outcome being erroneous, depending on a measurement error of any of the two. Different types of information bias are measurement error, misclassification and recall bias.

Measurement error occurs when we do not correctly measure what we actually want to measure. A potential source for measurement error in these studies could be the subjective reporting of symptoms at follow-up, in filling out the questionnaires by the patients. Another potential measurement error is the assessment of the physical function at ICU discharge with

the CPAx. In order to assess measurement error, we performed an interrater reliability rating for the CPAx, comparing different raters scoring the same items in the same patient.

Misclassification occurs when study participants are erroneously placed into a certain category or group and can be either differential or non-differential, affecting the result in different ways. The differential, or non-random misclassification can either hide a true association or create an association that is not true. The measurement error is not random, indicating that exposure status affects the measurement of the outcome, or having the outcome affects the measurement of the exposure. The non-differential, or random misclassification on the other hand, is unrelated to exposure or outcome status, the probability is similar across groups, and typically dilutes an association. The effect on the result is best described as "bias towards the null". The number of exposures together with the prospective design in these studies minimizes the risk for differential misclassification. The risk of non-differential misclassification is possible if patients misunderstood questions in the follow-up questionnaires or filled them out wrong, affecting both exposed and unexposed groups of patients.

Recall bias occurs when study participants are prone to recall or report an exposure differently, depending on whether or not they have the outcome. This is mostly a problem in case-control studies and retrospective studies, where participants diagnosed with a disease might recall some exposure they think could be predisposing of the disease. In study I and II we asked patients in-ICU about prior psychological problems and pre-ICU physical status, a retrospective reporting that could be subject to misclassification or recall bias, but still reported before the assessment of the outcome three months later, and thereby probably not affecting the measurement of the outcome. In study IV, caregivers were asked in-ICU to assess HRQL two weeks prior to hospital admission of the patient, as a baseline assessment. The fact that HRQL was rated higher three months post-ICU by most caregivers may indicate that the in-ICU rating of HRQL might not have been correctly mirroring their wellbeing at baseline (before the family member fell ill), but potentially negatively affected by the acute illness of their family member.

6.2.4 Confounding

A confounder is a variable that is associated with the exposure and with the outcome but is not an intermediate link in the postulated causal pathway between the two. Confounding can either strengthen or weaken an association. When designing a study, it is important to take into account potential confounders and how to deal with those in order to minimize confounding and produce valid results. In studies I and II, logistic regression modeling was used to handle potential confounding, where potential confounders were included as covariates in the models. Confounding was not specifically assessed in study III, since we did not aim at explaining causation, but merely correlation between early and late symptom scores. Confounding was handled with regression modeling in study IV, assessing age and

sex as potential confounders. Common to all the studies, not knowing each patient's way to recovery after being discharged from the hospital, with different coping strategies, personality traits, health care contacts and rehabilitation interventions outside the hospital leaves for potential residual confounding. Residual confounding is a problem in most studies, as we cannot foresee or control for all possible variables potentially affecting the outcome.

6.3 EXTERNAL VALIDITY

External validity refers to how generalizable the results are to another population than the one studied. A high external validity requires high internal validity, i.e. a low degree of systematic error. The multicentre design, and the broad inclusion of mixed ICU patients in studies I, II and IV should imply a good generalizability to other ICU patient cohorts, at least in health care settings with similar resources. Dropout rate was 38% in study III, which potentially could have introduced selection bias and thereby impacting the internal and hence the external validity of the results.

7 DISCUSSION

Great resources are allocated to patients treated in the intensive care unit, and despite admitted patients being of older age and having more comorbidities than before, an increasing number of patients survive their critical illness [2]. Life after critical illness however, has shown to be challenging for many patients, with PICS components affecting the recovery for patients as well as family members [5,55]. With millions of patients surviving intensive care each year and increased interest in long-term outcomes in these patients, the scope of intensive care is expanding, from barely saving lives to reducing post-ICU morbidity. As a result of this and growing awareness of PICS, follow-up after ICU stay has evolved, in the belief that this may be a way to help patients get back to their life as it was prior to the episode of critical illness. One important step in this development however, has not been addressed appropriately: the selection of patients for follow-up. Not all patients are in need of post-ICU interventions, and resources for follow-up are limited. Thus, methods to identify patients with the highest risk for an incomplete recovery are necessary. Evidence are lacking regarding ICU length of stay, the current selection method in many countries for ICU follow-up, including Sweden [135,137,138]. The rationale behind choosing ICU LOS was a way to limit the number of patients for follow-up and also the belief that a longer time spent in the ICU implied greater morbidity post-ICU. While this may have been a good starting point, the knowledge about this subject has expanded and it may be time to revise and update these guidelines. Parts of this thesis, as well as previous studies, have shown that ICU LOS is an overly simplified and ineffective method for ICU follow-up triage. With the screening methods and early evaluation suggested in this thesis, there is a possibility to identify patients

at risk for an incomplete recovery already at ICU discharge, re-evaluate them in the regular ward and initiate early, in-hospital interventions, also including their informal caregivers. By using this novel approach, hopefully fewer patients and caregivers will suffer from long-term PICS and PICS-F components and health care resources can be used more efficiently. A next step would be to evaluate interventions in the high risk patients that these prediction instruments help identify.

7.1 STUDY I

The screening instrument developed in study I can aid in the identification of patients in need of psychological interventions post-ICU. It performs better as a predictor than ICU LOS, the current selection method for ICU follow-up. Identified predictors for psychological problems were age (with a peak risk at ages 49-65 years), lack of social support, depressive symptoms and traumatic memories at ICU discharge. Previous studies assessing age as a risk factor for psychological problems post-ICU have shown varying results, and younger age have in some studies been associated with increased psychological morbidity [17,25]. In our cohort, being middle-aged was the strongest risk factor for an adverse psychological outcome, a somewhat surprising result. Data from some studies suggest that being middle-aged is associated with lower ratings of happiness and life satisfaction [159], perhaps implying an increased vulnerability to life changing events such as critical illness and the aftermaths thereof. The finding of lack of social support as a risk factor is in concordance with previous studies [160,161]. Depressive symptoms and traumatic memories in-ICU have also previously been described as risk factors for an adverse psychological outcome [12,61,160]. Previous psychological problems has been identified as a risk factor [12,63], but was not significant when included in the multivariable model. Since there was a strong association between previous psychological problems and in-ICU symptoms, pre-ICU psychological problems was likely accounted for in the in-ICU assessment. In some previous studies, patients with a history of psychological problems were excluded, in order to identify new-onset problems. However, this vulnerability for aggravated or recurring symptoms, even though not entirely dependent on factors related to the ICU stay, still seems important to recognize and potentially treat.

Other potential risk factors described in the literature, such as pessimistic personality trait [64,67], amount of benzodiazepines [74,88] or morphine or other sedatives given in ICU [61,81] were left out of this study, since evidence is contradictory and the aim was to create a feasible screening instrument, easy to perform bedside at the day of ICU discharge. There are also a number of suggested but poorly evaluated potential risk factors such as coping strategies, vulnerability and different social and family situations possibly affecting the ability to identify the need for help and rehabilitation that may well play a role in the development of psychological sequelae after ICU stay. We tried to account for these by including previous psychological problems among the potential risk factors and by assessing the patients' perception of social support after discharge, but other important factors, more difficult to assess may still have remained unidentified. Psychological problems after critical illness have

shown to be persistent for months to years [44,67] and may lead to substantial morbidity for the patients, negatively affecting HRQL [4] and reducing the ability to work implying a financial burden besides the emotional burden.

7.2 STUDY II

In study II a screening instrument for new-onset physical disability post-ICU was developed, where physical function at ICU discharge was the one remaining risk factor after univariable and multivariable regression modeling. The predictive accuracy of the method was moderate but outperformed ICU LOS with regards to AUC, sensitivity, specificity, PPV and NPV. The NPV was higher than the PPV, indicating that the screening method might be better at ruling out patients not likely in need of follow-up interventions.

There is no consensus with regards to how physical disability post-ICU should be measured. A previous study used any reduction in ADL as a definition of disability [145] and others used independency in performing six ADLs and walking without assistance [104,107]. With the chosen outcome definition in study II we aimed to find a significant reduction in ADL compared to pre-ICU status. A BI ≥10 score reduction indicates going from independent to completely dependent in activities such as dressing, going to the toilet or taking a shower, with a major impact on the everyday life for the patient and is slightly above the suggested minimal clinically important difference for the BI [157]. Reporting the minimal clinically important difference is a way of assessing a meaningful difference for patients in outcome or follow-up studies, rather than just reporting a statistically significant difference that might not be of clinical value to patients or clinicians.

Physical function at discharge was assessed with the first five items of the CPAx, including the need for respiratory aids such as supplementary oxygen, the ability to cough and clear secretions, move within the bed, move from laying to sitting on the edge of the bed and dynamic, unsupported sitting. The reason for omitting the last five items in the CPAx was that these are more cumbersome to perform, requiring more staff and a specific device, impacting the feasibility of the instrument. We also aimed at including a validated assessment of core strength that is among the first five items, a previously described risk factor for physical disability after critical illness [145]. A longer ICU stay implies longer bedrest and a greater burden of critical illness, negatively affecting muscle waste and most probably physical function at discharge [162]. ICU length of stay has previously been described as a risk factor for physical disability post-ICU [145] but was not significant in the multivariable analysis in our cohort. An interpretation of this is that multiple risk factors converge into poor physical function at discharge, making this a better predictor of individual risk for later disability than merely ICU LOS. This early in-ICU screening provides clinicians with a valuable individual risk assessment of the patient. Given the moderate predictive value, albeit higher than that for ICU LOS, a reassessment in the regular ward is a recommended next step. This second screening could be performed by a physiotherapist and/or occupational therapist, further

evaluating the specific needs of the patient and facilitating tailored follow-up interventions already in-hospital.

7.3 STUDY III

In study III, an early assessment of psychological symptoms one week from ICU discharge was a good predictor for level of psychological symptoms three months later. High negative predictive values for the suggested early cut-offs in all three outcome questionnaires imply that few patients classified as low-risk and left out of further follow-up interventions would later develop psychological symptoms. The assessment can be used as a valuable subsequent triage method for ICU follow-up, a psychological re-evaluation performed sometime after the initial ICU discharge screening suggested in studies I and II. This is also in agreement with the early, in-hospital assessment recommended in the British national guidelines and by a stakeholders meeting aiming to raise awareness about PICS and improve patient and family outcomes [140,163]. This reassessment provides specific information regarding what type of psychological symptoms the patient exhibits, which can guide health care personnel towards more appropriate referrals and adequate treatment. The reassessment also gives the opportunity to see the patient and his/her family members shortly after discharge from the ICU in order to provide support for vulnerable ICU survivors and their family. The identification of high-risk individuals as suggested in studies I and II, and subsequent re-evaluation suggested in study III, can facilitate early interventions, already in-hospital, potentially impeding longer-term psychological morbidity. A similar assessment method for secondary triage of patients post-ICU discharge with regards to physical morbidity would also be valuable and is a potential future research area.

7.4 STUDY IV

The results from study IV showed a significantly higher degree of caregiver burden in caregivers to ICU patients with an adverse physical or psychological recovery post-ICU. The higher caregiver burden correlated with a reduced caregiver mental HRQL. Prevalence of PTS symptoms was higher in informal caregivers than patients, indicating that being by the bedside when a loved one is critically ill might be a greater trauma than being ill. A caregiver with a reduced mental health is likely not in their full capacity to take care of and support a disabled family member, possibly affecting the chances of a full patient recovery. However, correlation does not automatically imply causation and the interaction between mental health in caregivers and incomplete patient recovery is yet to be fully understood and merits further investigation. Informal caregivers suffer from PICS-F components to a high extent and our results imply that caregivers to patients with an increased risk of post-ICU morbidity should be assessed for psychological problems and offered inclusion in ICU follow-up programs.

Identifying and managing PICS and PICS-F is of potential benefit for both patient and informal caregiver outcomes.

In conclusion, a holistic approach to the patient should be encouraged, beyond the first critical step of saving the patient's life. Already early on in the ICU admission, clinicians should consider measures to prevent aggravated cognitive, psychological and physical sequelae and also to include the informal caregivers on the patients' path to recovery. The stay in the ICU is only a brief period of time in the patient's long journey from falling ill, through hospitalization and rehabilitation to returning to life as it was prior to falling ill.

Questions have been raised regarding who should be responsible for follow-up services. Does it have to be ICU staff planning for and initiating follow-up interventions or could it be administered by staff at the regular ward or primary care facilities once the patient has been discharged from the hospital? Many times, economical restraints and staffing issues constitutes obstacles for ICU follow-up services. Vulnerable ICU survivors likely benefit from multidisciplinary support and rehabilitation beyond the ICU stay. With regards to this heterogeneous group of patients, ICU clinicians - doctors and nurses, possess the best knowledge about critically ill patients and their trajectory of recovery. Most research on short- and long-term outcomes in ICU survivors have been conducted by intensivists, identifying problems related to critical illness and ICU stay and initiating follow-up clinics as a response to post-ICU morbidity. In the author's view, they should be the ones organizing multidisciplinary ICU follow-up services, in close collaboration with other clinical entities such as physiotherapy/occupational therapy, clinical psychology/psychiatry and rehabilitation medicine providing tailored interventions to high-risk patients and their informal caregivers. The difficulties with presenting substantial evidence for the benefit of ICU follow-up despite patient satisfaction and staff intuition implies that the "one-size-fits-all" approach may not be the most appropriate and that we need to focus our resources on patients at risk for an incomplete recovery. We may also need to reconsider what to measure and at what time points.

8 POINTS OF PERSPECTIVES

8.1 CLINICAL IMPLICATIONS

As of today, there are no evidence-based methods for the selection of patients for ICU follow-up, or specific guidelines regarding the content and timing of such follow-up. By implementing the screening methods developed in this thesis at ICU discharge and reevaluating patients in the ward shortly thereafter, high-risk and low-risk cohorts of patients can be identified, enabling resources to be concentrated on those in need of post-ICU interventions. The results also suggest that informal caregivers to high-risk patients should be screened for psychological morbidity and included in follow-up. The early identification of risk-patients enables interventions to be initiated promptly after ICU discharge, with a

continuum stretching over hospital discharge, possible rehabilitation/nursing home and into the primary care facilities when the patient is discharged back home. Hopefully, these early interventions in high-risk cohorts can improve patient and caregiver outcome while ameliorating resource-effectiveness for ICU follow-up clinics.

8.2 FUTURE PERSPECTIVES

The prediction instruments need external validation before widespread use. Patients in previous studies have typically been included after a certain time with invasive mechanical ventilation or ICU length of stay, not on strong evidence that they belong to a high-risk population. Including patients with no physical or psychological sequelae implies improvement over time in many patients in both intervention and control arms, potentially diluting the effects of the studied interventions. With the identification of risk-patients, interventional studies and randomized controlled trials can be performed in high-risk cohorts, with greater likelihood to find potential beneficial effects. In other words, the question of the efficacy of ICU follow-up interventions deserves to be revisited, with better selection of patients that may merit from treatment. This thesis offers such a possibility. The outcome of interventional trials in high-risk patients may lead to useful and resource-effective interventions and better evidence-based ICU follow-up guidelines, ultimately improving the long-term outcome for ICU survivors and their families.

9 CONCLUSIONS

- Predicting psychological morbidity post-ICU already at ICU discharge is feasible and has fairly good predictive accuracy. Predictors for psychological morbidity three months post-ICU includes being middle-aged, lacking social support and experiencing depressive symtoms and traumatic memories at ICU discharge.

- Predicting new-onset physical disability post-ICU already at ICU discharge is feasible and has moderate predictive accuracy. The strongest predictor for physical disability three months post-ICU is physical function at ICU discharge.

- The use of screening instruments at ICU discharge can aid in the triage for follow-up, concentrating resources to high-risk patients

- Early in-hospital screening of psychological symptoms in patients after ICU discharge, with validated screening instruments correlates well with psychological symptoms three months later.

- Informal caregivers to patients with an adverse psychological or physical outcome post-ICU report higher caregiver burden and reduced mental HRQL.

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