The Post-Intensive Care Syndrome (PICS)
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CHAPTER 7

General discussion
Each year, about 28,000 individuals are discharged from intensive care units (ICUs) encountering physical, mental and/or cognitive disorders as part of the post-intensive care syndrome (PICS). The general aim of this thesis was to explore the course and prognosis of functioning in ICU survivors during the first year after ICU discharge, and to investigate means for early identification of PICS. The studies included in this thesis focused on adult ICU-patients, who were mechanically ventilated more than 48 hours in a closed format mixed medical-surgical ICU. In this chapter the main findings and methodological issues of the presented studies are reviewed, implications for clinical practice are discussed, and recommendations for rehabilitation care as well as for future research are provided.

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

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

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

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

Coping with the consequences of critical illness

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

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

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

Besides the high prevalence of symptoms of PICS in ICU survivors, we also found a high burden of care and psychological distress in close relatives (PICS-F), 1 to 3 months after ICU discharge. Up to one fifth of the partners and children of ICU survivors reported a high burden of care, whereby items such as ‘other demands on time, changes in personal plans, and family adjustments’ were mentioned most frequently. Sixteen percent of the close relatives had symptoms of PTSD (chapter 6). Also, in more recent studies high occurrence rates of psychosocial symptoms (e.g., depression, anxiety, post-traumatic stress), and decreased HRQoL has been reported. These findings underscore the importance to pay attention to close relatives of ICU survivors in the recovery process.
The use of validated screening instruments, such as the Short Form Health Survey (SF-36), Hospital Anxiety and Depression Scale (HADS), Trauma Screening Questionnaire (TSQ), Malnutrition Universal Screening Tool (MUST), and Caregiver Strain Index (CSI) with pre-defined cut-off points enabled the identification of ICU survivors and their close relatives with symptoms of PICS. In addition, patients and close relatives highly appreciated the provision of information about ICU-related problems in daily functioning and the recovery process. We concluded that our post-ICU clinic was feasible to identify symptoms of PICS in former ICU-patients and their close relatives, and to facilitate referral for further treatment, in order to support the continuity of care after hospital discharge.

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

METHODOLOGICAL CONSIDERATIONS

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

We also found that patients, who completed the questionnaires and visited the post-ICU clinic for measurements, were patients in relatively good health (chapter 3, 4, 5, 6). To improve external validity, we compared the baseline characteristic of study participants and non-respondents (chapter 3, 5), and between patients on different follow-up moments (chapter 4). Because no differences were found, we assume that bias due to selection of patients was limited.
Study design
The prospective observational design of our studies allowed us to gain insight into the recovery process of ICU survivors from shortly after ICU discharge up to 1 year thereafter. However, in our longitudinal study comparing patients with and without ICU-AW (chapter 4), the population evaluated at 3, 6 and 12 months consisted of different subgroups as a result of death and loss to follow-up. Due to skewed data, mixed model analyses were not attainable to analyze the course of functional recovery at different time points. Another methodological shortcoming is that in chapter 3 and 4 we did not collect information on all potential confounders such as functioning prior to ICU admission, medical complications and rehabilitation treatment that might have affected the course of recovery after hospital discharge. Furthermore, we did not correct for covariates as intermediate between ICU-AW and physical impairments, such as length of stay in the ICU. This might have resulted in residual bias. However, we assume that this had only little effect on the observed association between ICU-AW and physical impairments, because we included a control group and adjusted for a priori selected covariates derived from the literature such as age, gender, co-morbidity, presence of septic shock, APACHE IV score and maximal SOFA score during admission.

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

Generalizability
The generalizability of our findings might be limited as most of the studies included in this thesis were conducted in only one university medical center in the Netherlands. Also, in most studies, participants were assessed at a single time point only. However, since the patient characteristics of the cohorts in this thesis were comparable to other cohort-studies in ICU survivors in the Netherlands\(^ {31-33}\) and other Western countries,\(^ {6,13,34,35}\) our findings can be considered representative for ICU survivors, who have been mechanically ventilated for more than 48 hours. In our post-ICU- and coping study (chapter 5 and 6), patients with neurological disease as admission diagnosis, and patients who were transferred
to rehabilitation facilities were excluded, potentially limiting the generalizability of our findings. We hypothesize that the prevalence and severity of impairments, limitations and restrictions might be even higher in those patients who were transferred to a rehabilitation facility. We recommend that this assumption should be investigated in future research.

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

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

Although clear criteria for the early identification of ICU survivors at risk for poor functional outcome are lacking in literature, we found that patients with prolonged ICU-stay, longer duration of mechanical ventilation, and/or ICU-AW, have a higher risk of short- and long-term functional impairments, limitations in activities and restrictions in participation. These findings imply that such patients should be closely monitored after discharge from the ICU to initiate adequate rehabilitation treatment in time to optimally support their recovery process. Patients with an emotion-oriented coping style may have the greatest need for targeted psycho-educational interventions and should be identified early after discharge from hospital to facilitate their recovery. Post-ICU clinics are useful to identify symptoms of PICS, and to monitor the long-term recovery process after hospital discharge, using standardized comprehensive assessments. Early in-hospital risk stratification followed by a post-ICU clinic evaluation 1 to 3 months after hospital discharge is a beneficial approach to improve the continuum of targeted care after critical illness.
Figure 7.1 Categorization of components of PICS according to the ICF framework
Strategies to improve outcome

To achieve the best long-term functional outcome in ICU survivors with symptoms of PICS, two valuable strategies can be distinguished: prevention and treatment. Interventions that address prevention or mitigation of ICU-related symptoms particularly focus on the reduction of risk factors, such as immobilization, sedation, medication, delirium, sepsis, multi-organ failure, ARDS, hypoglycemia, hypoxia, length of mechanical ventilation, and length of stay in the ICU. To minimize the likelihood of developing PICS, the application of the ABCDEFGH bundle has been promoted, which addresses different aspects of risk reduction and treatment options, such as Airway management, Breathing trials, Coordination of care, Delirium assessment, Early mobilization and rehabilitation, Family involvement, Follow-up referrals and Functional reconciliation, Good handoff communication and Handout materials on PICS and PICS-F. Early ambulation and early physical and occupational rehabilitation are beneficial to improve physical functioning and decrease cognitive impairments and psychiatric morbidity. However, rehabilitation care should also be intensively continued after discharge from ICU. Therefore, we propose a structured, stepped care rehabilitation approach, which should start as soon as clinically possible within the ICU, and be continued throughout the recovery process. Such an approach requires an interdisciplinary team of health care professionals with the appropriate competencies to coordinate the patients’ rehabilitation care pathway: doctors, nurses, rehabilitation physicians, physical therapists, occupational therapists, psychologists, social workers, speech therapists, and dieticians.

Given the fact that this thesis focuses on functioning after ICU discharge, and that early rehabilitation interventions in the ICU have been extensively described in the literature, our recommendations for a rehabilitation care pathway for ICU survivors target the period after discharge from the ICU. Figure 7.2 illustrates the proposed stepped care rehabilitation pathway.
Figure 7.2 Interdisciplinary stepped care rehabilitation pathway for ICU survivors
Recommendations for an interdisciplinary stepped care rehabilitation pathway for ICU-survivors after discharge from ICU

**During hospital stay**

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

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

Besides the focus on limb muscle function, also respiratory muscles should be addressed during the rehabilitation program. Respiratory muscle dysfunction is observed in 80% of the patients with ICU-AW, but to date little attention has been given to specific interventions to enhance strength and endurance of the respiratory muscles. Inspiratory muscle training (IMT) might be a promising intervention to improve respiratory muscle function in patients with ICU-AW.
In order to set individual rehabilitation goals, it is also important to inventory, retrospectively or by proxy, the patient’s premorbid (physical, mental, cognitive) functional status. Previous studies showed that health status prior to ICU-admission has a fundamental impact on overall post-ICU quality of life. The Katz-ADL has shown to be useful to investigate the functional status prior to ICU-admission. The Katz ADL should also be used during hospital stay, to monitor the recovery process. In comparison with the Barthel Index, which has been developed for stroke patients, the Katz ADL is broader applicable for general hospital patients. Limitations in basic and instrumental (I)ADL should be treated by occupational therapists. Patients with speech and/or swallowing difficulties should be further assessed and treated by speech therapists. Dieticians should be involved for patients at risk for undernourishment. The Malnutrition Universal Screening Tool (MUST) is feasible to identify patients at risk.

The high incidence of cognitive impairments (e.g., problems with concentration, attention, and short memory deficits) within the first week after ICU discharge implies, that cognitive training by an occupational therapist should also be started early to improve the recovery process. The Mini-Mental State Examination (MMSE) is a commonly used screening test in both clinical practice and research to identify cognitive deficits. In patients with signs of mood disturbances, the Hospital Anxiety and Depression Scale (HADS) can be used to identify mental health problems (i.e., anxiety and/or depression). This self-reported questionnaire can be administered by nurses or physical/occupational therapists. Patients with symptoms of anxiety and/or depression (HADS domain score ≥8) should be referred to a psychologist, psychiatrist or social worker for further diagnosis and treatment. Cognitive and psychological sequelae can impact survivors’ capacities to re-integrate into traditional family and societal roles as well as actively engaging in their recovery.

Besides targeted psychological methods to address mental health problems (e.g., psycho-educational interventions and self-management strategies), the use of positive suggestion techniques and actively engaging ICU patients in their treatment as early as possible, have been recommended. Additionally, providing information about PICS, using ICU diaries, offering self-directed rehabilitation manuals, and involving family members in the care process will help in accepting and anticipating the long-term course of recovery and reducing the risk of PICS-F. In that context, close relatives should be observed carefully, and be screened for mental health problems (HADS), in order to identify PICS-F and to facilitate support or treatment.

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

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

At 1-3 months after hospital discharge

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

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

In close relatives mental health, caregiver burden, and issues regarding employment and social life should be addressed to identify symptoms of PICS-F and to facilitate appropriate support. The HADS, TSQ, Caregiver Strain Index (CSI), and further anamnestic questions should be used for this purpose, respectively.
### Table 7.1 Proposed screening instruments and treatment for symptoms of PICS/PICS-F within the stepped care rehabilitation pathway for ICU survivors

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

**Abbreviations:** CISS-21, Coping Inventory for Stressful Situations; CSI, Caregiver Strain Index; D, dietician; DEMMI, De Morton Mobility Index; FAC, Functional Ambulation Categories; HADS, Hospital Anxiety and Depression Scale; ICU-AW, Intensive Care Unit acquired weakness; MFI-20, Multidimensional Fatigue Inventory; MMSE, Mini-Mental State Examination; MRC-SS, Medical Research Council sum score; MUST, Malnutrition Universal Screening Tool; 2 or 6 MWT, 2 or 6 Minute Walk-Test; NSA, Nottingham Sensory Assessment; NPRS, Numeric Pain Rating Scale; OT, occupational therapist; PS, psychologist; PT, physical therapist; ROM, Range of Motion; RP, rehabilitation physician; SF-36, Short-Form (36) Health Survey; SIP 68, Sickness Impact Profile; ST, speech therapist; SW, social worker; TSQ, Trauma Screening Questionnaire.
At 6-12 months after hospital discharge

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

Barriers to an interdisciplinary stepped care rehabilitation pathway

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

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

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

**SUGGESTIONS FOR FUTURE RESEARCH**

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

*Continuing large longitudinal observational studies*

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

*Need for intervention studies*

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

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

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


