The Post-Intensive Care Syndrome (PICS)
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CHAPTER 1

General introduction
Each year about 86,000 adults are admitted to intensive care units (ICUs) in the Netherlands. The advancements in critical care in the last decades have resulted in higher survival rates, despite an ageing population and an increased severity of illness. However, surviving critical illness has shown to be associated with a wide range of long-lasting negative health outcomes, which include physical and cognitive impairments, as well as mental health problems, which negatively affect daily functioning and health-related quality of life (HRQoL). Early rehabilitation in the ICU is beneficial in reducing physical impairments and ICU and hospital length of stay. Evidence for the effectiveness of interventions for ICU survivors after ICU and hospital discharge is limited. Moreover, the optimal care pathway addressing the whole spectrum of ICU-related physical, cognitive and mental consequences has yet to be determined. This thesis aims to explore the course and prognosis of functioning in ICU survivors, and to investigate means for early identification of patients with need for rehabilitation care. This knowledge will contribute to the development of an optimal care pathway, in order to improve the quality of survivorship. This chapter describes the background and rationale underlying the aims of this thesis.

Post-Intensive Care Syndrome
Due to the increase in survival rates of ICU patients, the long-term consequences of critical illness have become increasingly recognized as an important healthcare issue. In 2012, the Society of Critical Care Medicine introduced the term ‘Post-Intensive Care Syndrome’ (PICS), to describe the complex of “new or worsening impairments in physical, cognitive, or mental health status arising after critical illness and persisting beyond acute care hospitalization”. The term can be applied to a survivor (PICS) or family member (PICS-F) (Figure 1). Although the exact prevalence of PICS among ICU survivors is unknown, it is estimated that 25-50% of patients will suffer from some component of PICS after ICU and hospital discharge.
The concept of PICS includes all domains of the World Health Organization’s International Classification of Functioning, Disability and Health (ICF). The ICF provides a conceptual framework for the definition and measurement of health and disability. It describes a person’s level of functioning (i.e., body structures and functions, activities and participation in society) as a dynamic interaction between health conditions (i.e., disorder or disease), environmental factors, and personal factors (Figure 2). Disability is complementary to functioning and encompasses impairments, limitations in activities, and restrictions in participation. Integrating the concept of PICS into the ICF framework is beneficial to further describe the impact of critical illness on functioning and disability.

**Impairments**

Physical impairments following critical illness include loss of muscle mass, neuromuscular weakness, sensory and nociceptive changes, impaired lung function, fatigue and weight loss. Intensive care unit acquired weakness (ICU-AW) is the most common form of physical impairment with an estimated incidence of 46% (95% CI: 43-49) in patients with sepsis, prolonged mechanical ventilation or multiple organ failure. ICU-AW is defined as muscle weakness with a diffuse (symmetric and flaccid) pattern, which develops after the onset of critical illness. A Medical Research Council sum score (MRC-SS) of < 48 is used as a cut-off for the diagnosis of ICU-AW.
Besides physical impairments, many patients develop delirious states or experience delusional memories regarding their time in ICU, which can lead to mental health problems, such as anxiety, depression, and post-traumatic stress disorder (PTSD). Furthermore, cognitive impairments (e.g., problems with concentration, attention, memory, executive functions) are common in survivors of critical illness.

**Limitations in activities**

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

**Restrictions in participation**

The functional limitations, in turn, can lead to restrictions in fulfilling domestic roles, and to participate in social activities. Around 50% of patients have not returned to work 1 year after ICU discharge. Moreover, the long-term consequences of critical illness in ICU survivors can also affect family members, resulting in psychological, physical, and social problems (PICS-F). The persisting disabilities also negatively affect health-
related quality of life (HRQoL) in ICU survivors.\textsuperscript{4-6,21,42} Although, QoL improves over time, it remains lower in the first year in comparison with the general population. Moreover, many people do not return to the same functional level as before ICU admission.\textsuperscript{8,18,43,44}

Ultimately, surviving critical illness has large social and financial implications for patients, their families, caregivers, and society.\textsuperscript{20,36,41,45-48} Therefore, reducing the prevalence of PICS and improving the functional outcome in ICU survivors should be the ultimate goal in the care for ICU patients. Given the broad spectrum of different health domains of PICS, the expertise of rehabilitation medicine provides a valuable contribution to develop and manage optimal multidisciplinary care for this vulnerable patient group.

**Functional recovery after ICU discharge**

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

**Impact of ICU-AW on functional recovery**

Based on the fact that many, but not all ICU survivors develop PICS after critical illness, the question arises whether patients with the most severe ICU-related impairments at ICU discharge are - by definition - the patients with the worst long-term outcome. ICU-AW is a frequently occurring neuromuscular complication in ICU-patients,\textsuperscript{29} and can be further differentiated into critical illness polyneuropathy (CIP), critical illness myopathy (CIM), or critical illness neuro-myopathy (CINM).\textsuperscript{30,50} The exact pathophysiological mechanisms underlying ICU-AW have not yet been fully elucidated, but are believed to be multifactorial.\textsuperscript{51} Possible mechanisms include microvascular ischemia,\textsuperscript{52-54} mitochondrial dysfunction,\textsuperscript{55,56} and sodium channelopathy\textsuperscript{57} leading to neuronal injury and axonal degeneration. Several studies in patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) have shown that ICU-AW negatively influences physical functioning and is associated with higher mortality rates.\textsuperscript{8,58-60} However, the impact of ICU-AW on long-term physical functioning and mortality in a general critically ill population is unknown, because many studies\textsuperscript{61-63} lacked a properly selected control group or did not adjust for confounders. With an improved life expectancy, a larger aging population, and improvements in the delivery of healthcare, the demand for critical care also increases,\textsuperscript{64} and ICU-AW becomes an extensive and complex health problem requiring comprehensive care. Recent studies suggested that patients with ICU-AW should be closely monitored following ICU- and
hospital discharge to support recovery and improve outcome. In order to support informed decision-making concerning the rehabilitation care pathway for ICU survivors with and without ICU-AW, more insight into the short- and long term functional status, with regard to physical, psychological and social functioning is needed.

**Coping with the consequences of critical illness**

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

**Post-Intensive Care Unit Clinics**

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

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

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

Chapter 2 describes the functional status of ICU survivors immediately after discharge from ICU. In this observational study, basic activities of daily living, muscle strength, sensitivity of the limbs, walking capacity, and cognitive functioning were assessed. In addition, the predictive value of functional status prior to ICU-admission, age, severity of illness, and duration of mechanical ventilation as potential determinants for functional status within the first week after ICU discharge was examined. The next chapters concern studies which compared functional outcome between patients with and without ICU-acquired weakness (ICU-AW). We hypothesized that survivors with ICU-AW have more short- and long-term physical impairments and functional disabilities than ICU survivors without weakness.

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

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

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

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

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


