# Being awake upright and moving as the basis for physiotherapy in the intensive care unit

**Ólöf Ragna Ámundadóttir**

**Thesis for the degree of Philosophiae Doctor**

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UNIVERSITY OF ICELAND
SCHOOL OF HEALTH SCIENCES
FACULTY OF MEDICINE

# Vakandi og virkur og í uppréttri stöðu í öndunarvél á gjörgæsludeild

**Ólöf Ragna Ámundadóttir**

**Ritgerð til doktorsgráðu**

**Leiðbeinendur:**
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This thesis is dedicated to four extraordinary women whose kindness, brilliance, independence and strength have always been an inspiration to me.

My mother

Sigrún Þórisdóttir, 1936 - 2017

My cousin and friend

Kolbrún Jónsdóttir, 1956 - 2020

My grandmothers

Ragnheiður Bjarnadóttir, 1918 - 2011

Laufey Þórmundardóttir, 1908 - 1999

# Ágrip

**Bakgrunnur**: Framfarir í meðferð alvarlega veikra sjúklinga og hækkaður lífaldur hefur leitt til þess að fleira fólk lifir nú af bráð og alvarleg veikindi en áður. Afleiðingar veikindanna ásamt gjörgæslulegunni geta haft áhrif á líkamlegt og sálrænt heilsufar sjúklinga sem oft finna fyrir hægum og ónógum bata. Sjúklingar sem eru lengi rúmliggjandi á gjörgæsludeild eiga við meiri skerðingu á líkamlegri heilsu að stríða eftir gjörgæslulegu en þeir sem liggja skemur. Sjúkraþjálfun sem felur í sér í sér hreyfingu og uppréttra stöðu er fýsilegur kostur til að draga úr rúmlegu sjúklinga, en sú tegund þjálfunar er bæði illa skilgreind og vannýtt. Of fáum gjörgæslusjúklingum er hjálpað í upprétta stöðu sitjandi á rúmstokk eða í standandi stöðu á meðan þeir eru í öndunarvél, þrátt fyrir niðurstöður viðurkenndra rannsókna á öryggi, fýsileika og nauðsynleika þess.

**Markmið**: Markmið þessarar doktorsrannsóknar var þríþætt: Að draga fram þætti í klínískri rökhugsun og ákvarðanatöku sjúkraþjálfara þegar þeir aðstoða sjúklinga sem eru alvarlega veikir við það að setjast fram á rúmstokk og veita þeim viðeigandi þjálfun. Í öðru lagi að rannsaka skammtíma- og langtímaárangur sjúkraþjálfunar með hreyfingu í upprétta stöðu sem hefst á þriðja degi eftir upphaf öndunarvélameðferðar og er framkvæmd tvisvar á dag, borið saman við sjúkraþjálfun sem hefst á fimmta degi og er framkvæmd einu sinni á dag. Í þriðja lagi að greina forspáþætti fyrir skertum líkamlegum endurbata sjúklinga ári eftir útskrift af gjörgæslu.

**Aðferðir**: Ritgerðin samanstendur af þremur vísindagreinum. Sú fyrsta byggðist á eigindlegri rannsókn sem var framkvæmd á 12 sjúkraþjálfurum. Áhorfsathugun var framkvæmd á sérhverjum sjúkraþjálfara, fyrir, á meðan og eftir að hann eða hún veitti sjúkraþjálfun á gjörgæsludeild, sem samanstóð af því að aðstoða alvarlega veikan sjúkling við að setjast fram á rúmstokk. Síðar sama dag var tekið djúpviðtal við sama sjúkraþjálfarann. Gögnin voru greind með eigindlegri innihaldsgreiningu. Vísindagrein II byggðist á slembiraðaðri, einblindri samanburðarrannsókn þar sem borin var saman árangur aukinnar hreyfingar í upprétta stöðu hjá fullorðnum sjúklingum sem voru sjálfbjarga og á fótum fyrir alvarleg veikindi sem kröfðust gjörgæslulegu með öndunar-vélameðferð lengur en 48 klukkustundir. Sjúklingunum var skipt með tilviljunarúrtaki í tvo hópa: Aukin hreyfing tvisvar á dag (n=29) og hreyfing einu sinni á dag (n=21). Útkomumælingar voru lengd meðferðar í öndunarvél, lengd gjörgæslu- og sjúkrahúslegu, innihald sjúkraþjálfunarinnar, heilsutengd

lífsgæði (mæld með Short Form-36 version 2 (SF-36v2) heilsukvarðanum) og líkamleg geta (þol mælt með 6 mínútna gönguprófi, vöðvastyrkur mældur með Medical Research Council - sum score (MRC-SS) og sjálfsbjargargeta mæld með Modified Barthel Index (MBI)), mæld á fimm tímapunktum frá útskrift af gjörgæsludeild þar til ári eftir útskrift. Vísindagrein III byggðist á aðhvarfsgreiningu sem gerð var á útkomu einstaklinganna í grein II til að greina forspáþætti fyrir slakri líkamlegri heilsu ári eftir útskrift af gjörgæsludeild. Mögulegir forspáþættir voru greindir frá grunnbreytum sjúklinganna, breytum sem mátu alvarleika veikindanna, breytum tengdum gjörgæslulegunni, og lengd gjörgæslu- og sjúkrahúslegu. Aðhvarfsgreining var notuð til að meta tengsl á milli forspáþáttanna og þriggja breyta sem endurspegluðu líkamlegt heilsufar ári eftir útskrift af gjörgæsludeild. Þær breytur voru vöðvastyrkur (mældur með MRC-SS), þol (mælt með 6 mínútna gönguprófi) og líkamleg virkni (mæld með SF-36v2 heilsukvarðanum, undirkvarði: Líkamleg virkni).

**Niðurstöður**: Vísindagrein I leiddi í ljós sex flokka og fjóra umlykjandi þætti sem leiðbeindu sjúkraþjálfurunum við klíníska rökhugsun og ákvarðanatöku við að hreyfa og þjálfa alvarlega veikan sjúkling í uppréttri stöðu. Flokkarnir voru: 1) Sjúklingur, 2) Gjörgæsla, 3) Sjúkraþjálfari, 4) Flutningur í upprétta stöðu, 5) Þjálfunin og 6) Áætluð niðurstaða. Umlykjandi þættirnir voru: i) Öryggi & vellíðan, ii) Skoðun & meðferð samtvinnuð, iii) Einstaklingsbundin þjálfun byggð á viðbrögðum sjúklings og iv) Hindranir & lausnir. Vísindagrein II: Tilraunahópurinn hóf hreyfingu í upprétta stöðu á sjöunda degi eftir að öndunarvélameðferð hófst og fengu sjúklingarnir sjúkraþjálfun með hreyfingu í upprétta stöðu í 31% gjörgæsludaga samanborið við viðmiðunarhópinn sem hóf hreyfingu í upprétta stöðu á áttunda degi ($p \geq 0.05$) og fengu sjúklingarnir sjúkraþjálfun sem innihélt hreyfingu í upprétta stöðu í 22% gjörgæsludaga ($p=0.03$). Djúp slæving svo dögum skipti eftir upphaf öndunarvélameðferðar gæti hafa hindrað hreyfingu í upprétta stöðu í rannsóknarhópnum. Enginn munur kom fram á milli hópa á lengd öndunarvélameðferðar, gjörgæslu- og sjúkrahúslegu, né í heilsutengdum lífsgæðum og líkamlegri getu á þeim tímum sem mælingar fóru fram á allt að ári eftir útskrift af gjörgæslu. Vísindagrein III: Þeir sem lifðu af alvarleg veikindi áttu við lélega líkamlega heilsu að stríða ári eftir útskrift af gjörgæsludeild. Tengsl fundust á milli þess að vera kona og hafa skertan vöðvastyrk ($p=0.003$), minna þol ($p<0.001$) og einnig mátu konur líkamlega virkni ($p=0.01$) sína verri en karlar ári eftir útskrift af gjörgæsludeild. Aðrir forspáþættir fyrir skertu líkamlegu heilsufari ári eftir útskrift af gjörgæsludeild, eftir að leiðrétt var fyrir kyni og aldri, voru: hærri líkamsþyngdarstuðull (BMI), minni sjálfsbjargargeta (MBI), fleiri líkamlegir

sjúkdómar fyrir (FCI), og skert líkamleg virkni fyrir upphaf veikinda, vöðvaveikleiki við útskrift af gjörgæsludeild og lengri sjúkrahúsdvöl.

**Ályktanir**: Sjúkraþjálfararnir sem tóku þátt í rannsókninni veittu gjörgæslusjúklingunum einstaklingsbundna hreyfingu í upprétta stöðu og byggðu stignun þjálfunarinnar á viðbrögðum sjúklinganna. Þetta styður mikilvægi þess að sjúkraþjálfarar nýti sér leiðbeinandi reglur frekar en skipulagðar verklegsreglur þegar þeir aðstoða alvarlega veika sjúklinga við að setjast í upprétta stöðu. Niðurstöður styðja það að samhæfa minnkun á slævingu við hreyfingu í upprétta stöðu hjá sjúklingum sem eru í öndunarvél, en óljóst er hvort ein eða tvær meðferðir á dag eða hvaða þjálfunarþættir (val á æfingum/hreyfingu, tímalengd þjálfunar, ákefð og fjöldi meðferða yfir daginn) skila bestum árangri fyrir hvern sjúkling. Konur reyndust líklegri til að fá hægan og ónógan líkamlegan bata samanborið við karlmenn. Þekking á forspáþáttum um skertan líkamlegan bata mun auðvelda sjúkaþjálfurum að finna þá gjörgæslusjúklinga sem þurfa meiri þjálfun og veita þeim sérhæfðari sjúkraþjálfun á réttum tímapunkti.

**Lykilorð:**

Gjörgæsludeild, hreyfing, klínísk ákvarðanataka, klínísk rökhugsun, líkamleg geta, líkamlegt heilsufar, sjúkraþjálfun

# Abstract

**Background:** Advances in critical care and ageing have led to more survivors of critical illness, many of whom experience incomplete physical and psychological recovery due to the consequences of critical illness and the intensive care unit (ICU) stay. Bed rest in the ICU is associated with long-term physical impairments. Mobilisation is advocated in ICU physiotherapy, yet it remains poorly defined and is inconsistently practised. Of particular concern is that patients in the ICU are inconsistently mobilised to an upright position during mechanical ventilation (MV) despite evidence supporting its safety, necessity and feasibility.

**Aim:** The aim of this thesis was threefold. First, to elucidate the factors involved in physiotherapists' clinical reasoning and decision-making processes when initiating and progressing mobilisation in patients who are critically ill. Second, to investigate the short- and long-term outcomes of intensive twice-daily upright mobilisation starting on day three after MV initiation in critically ill patients compared with once-daily mobilisation starting on day five. And third, to identify predictors of poor physical recovery in survivors one year after ICU discharge.

**Methods:** The thesis consists of three studies. Study I is a qualitative study of 12 physiotherapists practising in a tertiary care university hospital. Each of them was observed before, during, and after a mobilisation session with one ICU patient, and these observations were followed by a semi-structured interview. Manual data analysis was conducted using conventional content analysis. Study II is a randomised controlled trial (RCT) that compared patient outcomes in adult, previously ambulating patients who were mechanically ventilated for over 48 hours. They were randomly assigned to intensive twice-daily mobilisation (n=29) or once-daily mobilisation (n=21). Outcomes were duration of MV, ICU length of stay (LOS), hospital LOS, parameters of the physiotherapy intervention, self-reported health-related quality of life (Short-Form-36 version 2 Health Survey (SF-36v2)) and performance-based physical function, measured with the six-minute walk (6MW) distance, the Medical Research Council sum score (MRC-SS), and the Modified Barthel Index (MBI) measured at five time-points up to one year after ICU discharge. Study III is a secondary analysis of the RCT cohort designed to identify exposure variables for poor long-term physical recovery from baseline characteristic variables, severity of illness variables, ICU-related variables and LOS. Linear regression analysis was used to evaluate independent associations of exposure variables with three physical recovery outcomes, measured one year after ICU discharge. These outcomes were

muscle strength (MRC-SS), exercise capacity (6MW distance), and self-reported physical function (SF-35v2 Physical Function domain).

**Results:** Study I: Six categories and four encompassing factors were identified as important in guiding physiotherapists' clinical reasoning and decision-making processes when mobilising their patients. The categories were: 1) Patient, 2) ICU context, 3) Physiotherapist, 4) Transfer, 5) FITT parameters (frequency, intensity, type, and time), and 6) Expected outcome. The encompassing factors identified were: i) Safety & wellbeing, ii) Continuous assessment & intervention intertwined, iii) Individualised & response-driven intervention, and iv) Barriers & solutions. Study II: The twice-daily mobilisation group began upright mobilisation on day seven of the ICU stay, and were mobilised upright during physiotherapy on 31% of ICU days whereas the once-daily mobilisation group began upright mobilisation on day eight ($p \geq 0.05$), and were mobilised upright on 22% of ICU days ($p=0.03$). Prolonged deep sedation after initiation of MV may have hindered the initiation of mobilisation in the twice-daily mobilisation group. No difference was observed between groups in duration of MV, in ICU or hospital LOS, or in self-reported health-related quality of life or performance-based physical function across time-points measured, over one year. Study III: Survivors had poor long-term physical recovery, and the female gender was associated with low muscle strength ($p=0.003$), low exercise capacity ($p<0.001$), and poorer self-reported physical function ($p=0.01$) one year after ICU discharge. Other predictive variables for poor physical recovery, after adjusting for gender and age, were higher body mass index (BMI) at baseline, lower functional independence at baseline, functional comorbidities (FCI), lower self-reported physical function at baseline; muscle weakness at ICU discharge, and longer hospital LOS.

**Conclusion:** The physiotherapists in the study individualised mobilising and positioning their ICU patients upright and progressed them based on patient response. This supports the need for guiding principles of moving and positioning patients, rather than structured protocols. Moving and getting patients upright was supported as an intervention of choice for mechanically ventilated patients, coordinated with periods of lightening of sedation, but distinctions between one or two daily sessions remain to be established along with the optimal parameters (type, intensity, duration and frequency) for a given patient. Women appear to be at greater risk of delayed physical recovery, compared with men. Knowledge of such risk factors will enable physiotherapists to better target and tailor their mobilisation interventions for ICU patients.

**Keywords:**

Clinical reasoning, clinical decision-making, critical care, intensive care unit, mobilisation, physical function, physical long-term outcome, physiotherapy

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The research was carried out in the two intensive care units and in the two physiotherapy departments that are situated in the acute care service at Fossvogur and Hringbraut in Landspitali - The National University Hospital of Iceland, Reykjavik. I would like to thank the managers for their support and for giving me the opportunity, time and facilities to start this project and see it through. I sincerely thank the number of professionals in Landspitali who participated in various parts of the project for their time and support. Special thanks go to the physiotherapists who participated in implementing the intervention and those who performed the blinded outcome measurements in the randomised control trial. The physiotherapists in other health institutions who opened up their clinic for our follow-up data collection have my deepest gratitude. I sincerely appreciate the involvement of Sara Hafsteinsdóttir, Harpa Sigurðardóttir, Kristinn Sigvaldason, Ester Gunnsteinsdóttir and Brynja Haraldsdóttir whose contributions to the project were invaluable. And to Rannveig J Jónasdóttir for endless discussions, reflections, support and help, thank you for sharing the vision.

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# Contents

# List of abbreviations

| | |
|---|---|
| 6MW test | Six-minute walk test |
| ADL | Activities of daily life |
| APACHE II | Acute Physiology and Chronic Health Evaluation II |
| ARDS | Acute respiratory distress syndrome |
| BI | Barthel Index |
| BMI | Body Mass Index |
| CCI | Charlson Comorbidity Index |
| CI | Confidence interval |
| CIM | Critical illness myopathy |
| CIP | Critical illness polyneuropathy |
| EMG | Electromyography |
| ETT | Endotracheal tube |
| FCI | Functional Comorbidity Index |
| $FiO_2$ | Fraction of inspired oxygen |
| FITT | Frequency, intensity, time, type |
| ICF | World Health Organization´s International Classification of Functioning, Disability and Health |
| ICU | Intensive care unit |
| ICU-AW | ICU acquired weakness |
| ISCED | The International Standard Classification of Education |
| IQR | Interquartile range |
| LOS | Length of stay |
| MV | Mechanical ventilation |
| MRC | Medical Research Council |
| MRC-SS | Medical Research Council sum score |

| | |
|---|---|
| MET | The metabolic equivalent of task |
| MBI | Modified Barthel Index |
| RASS | Richmond Agitation Sedation Scale |
| RCT | Randomised controlled trial |
| SD | Standard deviation |
| SF-36v2 | Short-Form 36 version 2® Health Survey |
| SF-36v2 MCS | SF-36v2 Mental Component Score |
| SF-36v2 PCS | SF-36v2 Physical Component Score |
| SF-36v2 PF | SF-36v2 Physical Function domain |
| $VO_2$max | Maximal oxygen uptake (mL/kg/min) |

# List of figures

# List of tables

## List of original papers

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (I-III):

I. Olof R. Amundadottir, Helga Jonsdottir, Gisli H. Sigurdsson, Elizabeth Dean. Physical Therapists' Clinical Reasoning and Decision-Making Processes when Mobilizing Patients Who Are Critically Ill: A Qualitative Study. *Cardiopulmonary Physical Therapy Journal,* 2018, 29:13-25. DOI: 10.1097/CPT.0000000000000066. *

II. Olof R. Amundadottir, Rannveig J. Jónasdóttir, Kristinn Sigvaldason, Ester Gunnsteinsdottir, Brynja Haraldsdottir, Thorarinn Sveinsson, Gisli H. Sigurdsson and Elizabeth Dean: Effects of intensive upright mobilisation on outcomes of mechanically ventilated patients in the intensive care unit: a randomised controlled trial with 12-months follow-up. *European Journal of Physiotherapy*, published online: 29. July 2019. DOI: 10.1080/21679169.2019.1645880. **

III. Olof R. Amundadottir, Rannveig J. Jónasdóttir, Kristinn Sigvaldason, Helga Jonsdottir, Alma D. Moller, Elizabeth Dean, Thorarinn Sveinsson, Gisli H. Sigurdsson (2019). Female gender predicts poor long-term physical recovery after intensive care unit stay. Manuscript is under review at Acta Anaesthesiologica Scandinavica.

## Declaration of contribution

Study I: Ólöf Ragna Ámundadóttir (ÓRÁ), Helga Jónsdóttir (HJ), Elizabeth Dean (ED) and Gísli Heimir Sigurðsson (GHS) were responsible for the study conception and its design. ÓRÁ performed the initial literature search and conducted the study. ÓRÁ performed the content analysis and interpretation of the results with assistance from HJ and ED. ÓRÁ was responsible for drafting the manuscript with supervision from ED, HJ and GHS, who made critical revisions to the article for important scientific content.

Study II: The concept and study design were the work of ÓRÁ, GHS, ED, Thorarinn Sveinsson (ThS), Kristinn Sigvaldason (KS) and Rannveig Jóna Jónasóttir (RJJ). ÓRÁ performed the initial literature search and preparation for the study. ÓRÁ and ED developed the intervention. ÓRÁ conducted the study, and trained and directed the physiotherapists who participated in the blinded assessment. Brynja Haraldsdóttir and Ester Gunnsteinsdóttir directed and performed the intervention for the two study groups. ÓRÁ and ThS performed the statistical analysis. ÓRÁ was responsible for interpretation of the results and drafting the manuscript with supervision from ED and GHS. ED, GHS, ThS, KS and RJJ made critical revisions to the article for important scientific content.

Study III: ÓRÁ, ED, GHS and ThS were responsible for the concept of the study. ÓRÁ performed the initial literature search and preparation for the study. The statistical analysis and interpretation of the results was the work of ÓRÁ and ThS. ÓRÁ drafted the manuscript and ED, GHS, ThS, HJ, Alma Dagbjört Möller (ADM), KS and RJJ made critical revisions to the article for important scientific content.

# 1 Introduction

Critically ill patients that have threatening or established vital organ dysfunction are frequently admitted to an intensive care unit (ICU), for intensive monitoring and management. This may include stabilisation of their physiological responses to illness and injury, with the use of cardiac-, circulatory, ventilatory, or renal support (Doiron et al., 2018). The speciality of intensive care medicine developed after World War II and during the poliomyelitis epidemic in the early 1950s (Vincent, 2013). The first ICUs emerged in the United States, Europe and Australasia. They were designed to closely monitor critically ill or injured patients. Over the following decades, ICUs became multidisciplinary and included intensivists, nurses, physiotherapists, and other specialties (Kelly et al., 2014). The first ICU in Iceland was established in Borgarspitali, in 1970 (Sigvaldason et al., 2000), followed by a second ICU in Landspitali in 1974. Today, three ICUs operate in Iceland, two in Landspitali - The National University Hospital of Iceland, with 1400-1500 patients admitted each year with approximately half of them intubated and mechanically ventilated, and one in Akureyri Hospital, with 491 admissions, and 27 mechanically ventilated patients in 2018 (Sjúkrahúsið á Akureyri, 2019). Physiotherapists have been a part of the multidisciplinary ICU teams in Iceland from the beginning.

Initially, the focus of ICU care during the first decades was on immediate medical outcomes related to short-term mortality (Angus et al., 2003). Indeed, the survival rate of critically ill patients has improved markedly over the years (Vincent, 2013). However, the 2002 Brussels Roundtable, ‘Surviving Intensive Care’, highlighted the high prevalence of poor physical and psychological long-term outcomes of ICU survivors (Angus et al., 2003). It called for research to examine to what extent such poor outcomes were due to the characteristics of the patient, the conditions that lead to the ICU admission, or the ICU care. In 2003, a cohort study reported long-term functional limitations one year after ICU discharge in survivors of the acute respiratory distress syndrome (ARDS) (Herridge et al., 2003). They reported that muscle wasting and weakness were the most serious concerns for patients in terms of their recovery. Furthermore, they called for a study to elucidate the nature of ICU-related muscle wasting and weakness and to establish whether the problem was specific to ARDS. Later, Needham reported a growing interest in understanding whether prolonged bed rest contributes to long-term neuromuscular complications in ICU patients who are mechanically ventilated (Needham, 2008). He reported

encouraging results from feasibility studies aimed at decreasing sedation and increasing mobilisation soon after ICU admission. He called for research and evaluation of current medical practice related to mechanically ventilated patients.

## 1.1 Bed rest in the intensive care unit

As a medical intervention, bed rest was introduced in the nineteenth century (Pavy-Le Traon et al., 2007). Any lack of recovery was attributed to the illness. Clinicians noticed that immobilisation and inactivity were harmful to one´s health in the poliomyelitis epidemic in the first half of the twentieth century and during World War II. Physicians observed that soldiers who ambulated soon after injury or surgery showed faster recovery than those who remained in bed.

Bed rest has been well established to have an association with impairments in physical function that are commonly observed after critical illness (Fan, Dowdy, et al., 2014; Hashem, Parker, et al., 2016). Muscle wasting has been observed in critically ill patients as early as within the first week of ICU stay (Parry & Puthucheary, 2015; Puthucheary et al., 2013). Such wasting appears to be associated with bed rest duration (Fan, Dowdy, et al., 2014; Hashem, Parker, et al., 2016; Pfoh et al., 2016) and the severity of acute illness (Lodeserto & Yende, 2014; Puthucheary et al., 2013). Most muscle loss, measured in the quadriceps femoris muscle by ultrasound, seems to occur during the first two to three weeks of the ICU stay (Gruther et al., 2008). Bed rest as a medical treatment became less common in the second half of the twentieth century (Pavy-Le Traon et al., 2007). Despite the known harmful effects of immobility and bed rest on body systems, such as muscle mass and bone mineral density (Parry & Puthucheary, 2015), bed rest in the ICU remains commonly used (Hodgson et al., 2018; Needham, 2008).

## 1.2 Intensive care unit acquired weakness

Symmetrical muscle weakness, a complication that develops during an ICU admission, has been termed ‘intensive care unit acquired weakness’ (ICU-AW) (Hermans & Van den Berghe, 2015; Kress & Hall, 2014; Sidiras et al., 2019). Muscles atrophy early in an ICU stay (Parotto et al., 2018) which may contribute to slow and incomplete long-term functional recovery and prolonged reduced quality of life in survivors (Hermans & Van den Berghe, 2015; Sidiras et al., 2019; Wieske et al., 2015). Women have shown a higher incidence of ICU-AW than men (Sidiras et al., 2019; Yang et al., 2018). In addition, ICU-AW is associated with increased mortality during a hospital stay (Ali et al., 2008; Wieske et al., 2015). A recent systematic review and meta-analysis identified

risk factors for developing ICU-AW (Yang et al., 2018). The risk factors, some of which are preventable, are female sex, higher severity of illness measured with the APACHE II score, multiple organ failure, systemic inflammatory response syndrome, sepsis, medications (e.g., neuromuscular blocking agents, norepinephrine, aminoglycosides), duration of mechanical ventilation (MV), parental nutrition during the first week in the ICU, hyperglycaemia, electrolyte disturbances, hyperosmolarity, and high lactate levels.

The pathophysiology of ICU-AW is unknown (Zorowitz, 2016) but recognised underlying causes include muscle breakdown (Puthucheary et al., 2013) and depressed protein synthesis (Lodeserto & Yende, 2014; Puthucheary et al., 2013). Patients with multi-organ failure have been reported to have more severe muscle wasting than patients with single organ failure (Puthucheary et al., 2013).The ICU-AW can present clinically in patients who are critically ill, as critical illness polyneuropathy (CIP), critical illness myopathy (CIM), or a combination (Latronico & Bolton, 2011). The prognosis for CIM is believed to be better than for CIP or the combination of the two conditions (Koch et al., 2014). The diagnosis is established with manual muscle testing (most commonly the Medical Research Council sum score (MRC-SS)) (De Jonghe et al., 2002; Fan, Cheek, et al., 2014), electromyography (EMG) (Fan, Cheek, et al., 2014; Zorowitz, 2016), or nerve conduction examination (Fan, Cheek, et al., 2014). Clinical muscle testing of a patient in the ICU may be challenging due to sedation, use of neuromuscular blocking agents, and delirium (Hodgson & Tipping, 2017). Despite high inter-observer agreement, the MRC-SS has been reported to be an insufficiently robust tool to diagnose ICU-AW, due to lack of discrimination in identifying weak patients with a rehabilitation potential after hospital discharge (Connolly et al., 2015).

As yet, no specific intervention has been established to effectively prevent, manage, or reverse ICU-AW (Latronico et al., 2017). Possible interventions to prevent ICU-AW are insulin therapy and early rehabilitation (Zorowitz, 2016) and prevention of bed rest and increased mobilisation during the ICU admission are advocated (Kress & Hall, 2014; Zorowitz, 2016). Further research is needed however, aimed at preventing ICU-AW and targeting rehabilitation in ICU patients (Hermans et al., 2014; Sidiras et al., 2019; Zorowitz, 2016).

## 1.3 Poor long-term physical outcome in survivors

Patients surviving critical illness often experience profound physical (Desai et al., 2011; Fan, Dowdy, et al., 2014; Hermans et al., 2019; Herridge et al., 2011; Pfoh et al., 2016) and mental (Desai et al., 2011; Herridge et al., 2011;

Jonasdottir et al., 2018) health consequences and associated poor quality of life for years after their ICU stays. Herridge and colleagues (2003) reported marked functional limitations in survivors of ARDS, one, two and five years after ICU discharge (Cheung et al., 2006; Herridge et al., 2003; Herridge et al., 2011). The median distance the patients walked in the six-minute walk (6MW) test, one year after discharge from the ICU, was 66% of the predicted value, and only 49% had returned to work at that time (Herridge et al., 2003). Furthermore, their physical health-related quality of life assessed with the physical component score (PCS) of the Short-Form 36 version 2® Health Survey (SF-36v2) was 1.5 standard deviations (SDs) lower than the mean score for an age- and gender-matched control group, one year after ICU discharge (Herridge et al., 2011). The same participants, five years after ICU discharge, walked 76% of the predicted walking distance in the 6MW test and their PCS scores of SF-36v2 were approximately 1 SD lower than mean score of the control population (Herridge et al., 2011). A recent propensity score matched cohort study reported increased mortality and morbidity five years after the ICU stay in patients with stays of at least eight days (Hermans et al., 2019). Given that in survivors of critical illness, physical health impairments can remain prominent five years afterwards (Hermans et al., 2019; Herridge et al., 2011), research needs to focus on long-term rehabilitation following hospital discharge, i.e., well beyond the immediate hospital stay.

## 1.4 Recovery of physical function after critical illness

The factors that influence the recovery of physical function after critical illness warrant elucidation (Gandotra et al., 2019; Parotto et al., 2018). Critically ill patients constitute a heterogeneous group, and their physical recovery trajectories are diverse (Gandotra et al., 2019). Older age and comorbidities before ICU admission, in survivors of ARDS, were associated with a decline in physical function five years after ICU stay (Pfoh et al., 2016). Prolonged duration of bed rest in the ICU was associated with muscle weakness in survivors of acute lung injury throughout a two year follow-up (Fan, Dowdy, et al., 2014). Length of ICU stay and mean daily dose of corticosteroids were associated with physical impairment for up to a year in survivors of acute lung injury (Needham et al., 2014). An ICU stay of at least eight days has been associated with impairments in handgrip strength, shorter walking distance (6MW test) and worse self-reported physical function (Physical Function (PF) domain of the SF-36 Health Survey) five years after the ICU stay (Hermans et al., 2019). This poor functional status was associated with medications during ICU stay (i.e., benzodiazepines, vasopressors and opioids) and if the patient had an earlier ICU stay before the current one. Older age was observed to be

a risk factor for physical limitations in survivors of acute respiratory failure who required MV for at least four days (Neumeier et al., 2017), as well as in ARDS survivors (Pfoh et al., 2016). A study of ICU survivors aged 70 years or older revealed that higher body mass index (BMI) and greater functional self-efficacy (measured with a Modified Self Efficacy Scale that assesses confidence in performing various activities) was associated with better functional recovery, and hearing and vision impairments were associated with worse recovery (Ferrante et al., 2016). Furthermore, an association has been reported between male gender and greater functional recovery in survivors of acute respiratory failure (Neumeier et al., 2017). However, a recent study reported that young women, with fewer continuous sedation days and shorter ICU length of stay (LOS), had the most complete trajectory of physical recovery after acute respiratory failure compared with three other trajectory groups (Gandotra et al., 2019). Older patients with longer sedation and ICU LOS demonstrated the worst physical recovery of those four groups.

## 1.5 Physiotherapy and mobilisation in the ICU

As members of the interdisciplinary healthcare team, physiotherapists participate in the management of critically ill patients (Gosselink et al., 2008). Physiotherapists use physiological principles and an understanding of pathophysiology along with clinical practice to lay the foundation for exercise prescriptions for patients in the ICU (Denehy & Berney, 2006). Current physiotherapy practices in ICUs in Iceland follow the established guidelines of the European Respiratory Society and European Society of Intensive Care Medicine Task Force on Physiotherapy for Critically Ill Patients (Gosselink et al., 2008). These best practice guidelines identified several important focuses for physiotherapy practice in managing critical illness: ‘Physical deconditioning, neuromuscular and musculoskeletal complications, prevention and treatment of respiratory conditions, and emotional problems and communication’. The guidelines recommended physiotherapists to evaluate the patient before treatment to identify problems amenable to physiotherapy and decide on an appropriate intervention. Additionally, vital functions should be monitored and acted upon for safe and effective intervention.

### 1.5.1 Definition of mobilisation

In the literature, the terminology for mobilisation tends to be variable, and mobilisation has been called (early) mobilisation, physiotherapy, physical rehabilitation or exercise to name a few. Physiotherapists use the term ‘mobilisation’ with respect to exploiting the acute effects of low levels of exercise and upright positioning in the management of acute patients to

prevent or address the multisystem deficits in the oxygen transport system (Dean, 2008). However, 'mobilisation' is a widely used term subsuming a complex phenomenon with wide variation in application, components and timing (Amidei, 2012). A recent review that evaluated how physical rehabilitation interventions in the ICU were measured and reported in 117 studies reported a heterogeneous litterature with poor reporting of physical rehabilitation interventions (Reid et al., 2018). An integrative review reported the absence of an agreed definition for what constitutes early mobilisation for patients who are mechanically ventilated (Laurent et al., 2016). When to begin mobilisation after initiation of MV in our patients, and what type of mobilisation we should choose are questions that need to be addressed (Clarissa et al., 2019).

A concept analysis of the term 'mobilisation' within the critical care setting has established that it is "an interdisciplinary, goal-directed therapy to facilitate movement and improve patient outcomes" (Amidei, 2012). Mobilisation in the ICU has been defined as moving actively or turning in bed, active limb exercises, sitting on the edge of the bed, passive or active transfer to a chair, standing and walking (Stiller, 2000). Mobilisation is used as an intervention for patients with a range of disorders, including critically ill patients in the ICU, with the purpose of improving respiratory function and cardiorespiratory fitness; reducing the harmful effects of bed rest and immobility; increasing functional independence and improving alertness and wellbeing (Stiller, 2007). Mobilisation that is administered with the patient upright, elicits both an exercise stimulus and a gravitational one (Dean & Butcher, 2012), thus upright mobilisation augments oxygen transport and offsets the negative effects of bed rest in immobilised patients in the ICU (Dean, 2008). Mobilisation starting early, or within the first two to five days after the initiation of MV, is a physiologically justifiable intervention to attenuate muscle weakness in ICU patients, and also has multiple other organ system benefits (Hodgson et al., 2013).

### 1.5.2 Safety and feasibility of mobilisation in the ICU

The safety of mobilising patients in the ICU has been established (Adler & Malone, 2012; Bailey et al., 2007; Dunn et al., 2017; Hashem, Nelliot, et al., 2016; Laurent et al., 2016; Nydahl et al., 2017). Several years ago, descriptive studies reported the success and safety of early mobilisation of ICU patients where 88% of ICU patients ambulated a median of 200 feet at ICU discharge (Thomsen et al., 2008) and 69% ambulated more than 100 feet at ICU discharge with less than 1% activity-related adverse events (Bailey et al., 2007). The activity-related events were falling to the knees without injury,

feeding tube removal, systolic blood pressure higher than 200 mm Hg or lower than 90 mm Hg, and oxygen desaturation lower than 80%. A recent systematic review and meta-analysis evaluated 22,351 mobilisation or rehabilitation sessions in 7,546 patients (Nydahl et al., 2017). In those sessions, 583 (2.6%) safety events occurred, including four cardiac arrests, two endotracheal tube (ETT) removals, 11 falls, 50 catheter events or removals, 126 episodes of haemodynamic changes, 78 desaturation episodes and 312 events described as 'other'. The investigators concluded that early mobilisation and physical rehabilitation have a low risk of safety events when implemented as a routine practice in an ICU. Safety criteria have been published for mobilisation practices in the ICU, to be used as guidance to minimise the risk of adverse effects (Hodgson, C. L. et al., 2014; Ross & Morris, 2010; Stiller, 2007).

The feasibility of intensive physiotherapy and mobilisation early in the course of critical illness has been established (Adler & Malone, 2012; Bailey et al., 2007; Cameron et al., 2015; Griffiths & Hall, 2010; Hashem, Parker, et al., 2016; Hodgson et al., 2016; Laurent et al., 2016; Perme & Chandrashekar, 2009; Pohlman et al., 2010; Thomsen et al., 2008; Truong et al., 2009). Mobilisation may be effective in preventing the muscle weakness and functional impairment commonly seen after critical illness (Hashem, Nelliot, et al., 2016; Hodgson et al., 2013).

### 1.5.3 RCTs studying mobilisation

A systematic review of randomised controlled trials (RCTs), published in 2013 identified early exercise/physiotherapy as the only effective intervention to improve long-term physical function in patients who are critically ill (Calvo-Ayala et al., 2013). However, varied outcomes have been published from RCTs designed to examine the effects of enhanced physical rehabilitation and mobilisation in the ICU (Burtin et al., 2009; Denehy et al., 2013; Kayambu et al., 2015; Morris et al., 2016; Moss et al., 2016; Schaller et al., 2016; Schweickert et al., 2009; Wright et al., 2017). Positive effects include reduced ICU LOS (Schaller et al., 2016), reduced duration of MV and reduced occurrence of delirium (Schweickert et al., 2009), improved physical function (Burtin et al., 2009; Schweickert et al., 2009), improved functional mobility (Schaller et al., 2016) and improved physical health-related quality of life (Burtin et al., 2009; Kayambu et al., 2015; Morris et al., 2016). However, three RCTs did not report any benefit of enhanced physical rehabilitation during the ICU stay (Denehy et al., 2013; Moss et al., 2016; Wright et al., 2017). It is interesting that two RCTs with positive outcomes had sedation withdrawal as a part of their protocol for the research group (Schaller et al., 2016; Schweickert et al., 2009). Furthermore, according to a recent meta-analysis, rehabilitation

and active mobilisation in the ICU did not have an effect on patient mortality (Tipping et al., 2017). However, the evidence for the effectiveness of early mobilisation on physical function outcomes in critically ill patients who are mechanically ventilated is of low quality, due to small sample sizes, lack of blinding, and variation in both interventions and outcome measures (Doiron et al., 2018).

### 1.5.4 Early mobilisation of patients on mechanical ventilation

How early mobilisation should begin after initiation of MV in order to be called early mobilisation has not been defined (Taito et al., 2016). An international survey of practices in 951 ICUs in France, Germany, the United Kingdom, and the United States reported 48% of sites used early mobilisation practices; however, the delivery was highly variable (Bakhru et al., 2016). The number of patients who are mobilised with an ETT in situ and who are mechanically ventilated has been reported to be low (Berney et al., 2013; Brock et al., 2018; Harrold et al., 2015; Jolley et al., 2017; Nydahl et al., 2014). A point prevalence study in 38 ICUs in Australia and New Zealand reported, that 3% of mechanically ventilated patients with an ICU LOS over 48 hours sat on the edge of the bed and no patient on MV had higher level of mobilisation (Berney et al., 2013). In 116 ICUs in Europe, over a 24-hour period, 8% of all mechanically ventilated patients with an ETT in situ sat on the edge of the bed or had a higher level of mobilisation (Nydahl et al., 2014). Mobilisation practices in patients with ETT and on MV in 19 ICUs in Australia and Scotland were studied (Harrold et al., 2015). They reported sitting on the edge of the bed or a higher level of upright mobilisation in 2.1% of patients in the Australian cohort and in 2.7% in the Scottish cohort. Mobilising patients to a sitting position on the edge of the bed or higher level of upright mobilisation occured on 16% of total patient days in mechanically ventilated patients in 42 ICUs in the United States, however, the investigators defined mechancial ventilation as any ventilation with ETT, non-invasive positive pressure ventilation and tracheostomy (Jolley et al., 2017). An audit in one ICU in Australia of 202 patients over 742 ICU days revealed that patients who were invasively mechanically ventilated received active mobilisation (marching on the spot or walking) on 2% of patient days or active transfer (transfer from bed to chair with weight bearing) on 13% of patient days (Brock et al., 2018). Motion sensors have been used for objective evaluation of physical activity levels during the first five days in mechanically ventilated patients in the ICU (Beach et al., 2017). The participants performed a median of 16.8 minutes of physical activity over 1.0 MET (one MET is equivalent to the energy expended at rest) per day. According to the treating physiotherapists, the main barriers were sedation at baseline, and sedation and fatigue on day five. A feasibility study on exercise testing in adult patients who had been in the ICU for a median of 14.5 days was performed recently (Sommers et al., 2019). Thirty-

seven patients (18 were mechanically ventilated) who were physiologically stable underwent the test, in a semi-recumbent position on a bed-based cycle ergometer. Of these, 28 could cycle actively (11 were mechanically ventilated). The exercise testing was found to be safe and feasible for patients who were mechanically ventilated and physiologically stable. The patients in this study were able to perform a maximum work load of a median (IQR) of five watts (2.5-9.5) at a median (IQR) level of exertion of 13 (11-14) on a Borg scale. The investigators concluded that the patients in the study had a very low ability to tolerate exercise.

### 1.5.5 Barriers to early mobilisation in the ICU

Mobilising a patient who is critically ill is not without risk, because the patient is normally attached to intravascular lines, catheters, and life-support systems which limit his or her body positioning and mobilising options (Adler & Malone, 2012). Additionally, complications that include fluctuating haemodynamic status and potential muscle weakness are often present. Thus, many barriers have been reported that hinder mobilisation to an upright position. Sedation has been reported as a common barrier, as well as the health professional´s perception of physiological instability (Harrold et al., 2015; Nydahl et al., 2014). A recently published systematic review of both quantitative and qualitative studies evaluated factors that can influence physical activity in survivors of critical illness, both in the ICU setting (93% of studies) and after ICU discharge (7% of studies) (Parry et al., 2017). The investigators reported five major themes and several sub themes, including both barriers to and enablers of physical activity. The themes are: patient physical and psychological capability to perform physical activity (including delirium, sedation, illness severity, comorbidities, weakness, anxiety, confidence and motivation), safety influences (including physiological stability and concern for lines), culture and team influences (including leadership, interprofessional communication, administrative buy-in, clinical expertise and knowledge), motivation and beliefs about physical activity from patients, family and health care professionals regarding the benefits/risks and environmental influences (including funding, access to rehabilitation programs, staffing and equipment). They reported that the barriers and enablers to physical activity span diverse factors and the majority are modifiable. Dubb and colleagues (2016) synthesised data from 40 studies and identified 28 multifaceted obstacles to early mobilisation including 14 related to patients, five structural, five cultural and four process-related barriers (Dubb et al., 2016). They proposed over 70 solutions to overcome the identified barriers.

### 1.5.6 Physiotherapists' clinical reasoning and decision-making in the ICU

The benefits of mobilising adult patients who are mechanically ventilated in the ICU have substantial evidential support, but the practice remains underused (Nydahl et al., 2014). Physiotherapists need to overcome barriers to early mobilisation and facilitate its implementation into ICU practice (Cameron et al., 2015). When the physiotherapist begins to mobilise a patient, she or he needs to consider and decide on the optimal type of mobilisation, its type, intensity, duration, and frequency (Cameron et al., 2015; Dean, 2008), comparable to the FITT principle (frequency, intensity, type and time) (ACSM, 2010), and then, during the mobilisation session, the physiotherapist modifies these parameters (Dean, 2008). However, the processes of physiotherapists´ clinical reasoning and decision-making during upright mobilisation of a critically ill patient are not well known.

Qualitative research methods have been used to examine the factors that influence physiotherapists' clinical reasoning and decision-making in acute care (Chipchase & Prentice, 2006; Holdar et al., 2013; Holdsworth et al., 2015; Masley et al., 2011; Smith et al., 2007). Physiotherapists have an important role in acute care and provide skilled care distinct from that of other health professionals (Masley et al., 2011). Their clinical reasoning includes integration of medical information including data concerning the impact of all physiological systems, leading to constant assessment with rapid decision-making in a crowded, complex, fast paced environment. They focus on the patient as a whole, with their main concern being the patient's safety and functional mobility. Smith and colleagues (2007), identified that experience, unique knowledge base, professional identity, and preferred practice model influenced acute care cardiorespiratory physiotherapists (Smith et al., 2007). Furthermore, indicators that experienced acute care physiotherapists used to establish whether a patient had the capacity to tolerate mobilisation have been reported (Chipchase & Prentice, 2006). They were indicators related to the patient's history and background, physiological parameters, observational indicators and physical indicators. Together these indicators informed the physiotherapist during an individualised, task-specific and dynamic assessment and treatment process.

## 1.6 Summary and rationale

The number of patients surviving critical illness is growing and we need to rethink our approach to care to improve their long-term function and quality of life (Iwashyna & Netzer, 2012). Mobilisation is advocated in ICU physiotherapy

practice (Cameron et al., 2015) to attenuate muscle weakness in ICU patients (Hodgson et al., 2013), but mobilisation is poorly defined and its practice is inconsistent and underused (Hodgson et al., 2013; Investigators. et al., 2015; Nydahl et al., 2014). Several studies have shown that spontaneous awakening and breathing trials, delirium monitoring and early mobilisation during the ICU stay improve patient outcomes (Balas et al., 2014; Hsieh et al., 2019). It is recommended that these should be implemented within general practice, and sedation treatment should be interrupted each day paired with a spontaneous breathing trial and mobilisation (Hsieh et al., 2019). Understanding the factors that influence the trajectory of physical recovery may help survivors in their recovery after critical illness (Gandotra et al., 2019). Furthermore, identifying underlying risk factors, both modifiable and non-modifiable, that can affect the trajectory of physical recovery, is essential for health professionals for effective ICU and post ICU interventions to be designed (Desai et al., 2011).

The diversity of patients who are critically ill and inadequate knowledge on when to initiate physiotherapy, specifically upright mobilisation, and regarding the optimal dose of therapy for each individual patient makes early mobilisation of critically ill patients challenging. What may be tolerated by one patient may not be by another, or for the same patient with treatments just hours apart. Clarification of when to initiate upright mobilisation, how to choose the optimal type, the appropriate intensity, duration and frequency is key to progressing upright mobilisation with the aim of speedy and effective physical recovery. Identifying factors related to the patient´s health status before the onset of critical illness, factors related to the acuity of illness, and factors connected with the ICU stay can assist physiotherapists in tailoring interventions appropriately to improve physical recovery during the ICU stay, on the hospital ward after ICU discharge and after hospital discharge.

This thesis is intended to augment evidence-based knowledge about the effects of increased volume of individualised and response-driven upright mobilisation starting early after initiation of MV on the short- and long-term physical recovery of critically ill patients, and to identify predictors of poor long-term physical recovery. Additionally, we wanted to shed light on the physiotherapists' clinical reasoning and decision-making during their initiation and progression of upright mobilisation in their patients. Knowledge about practitioner clinical reasoning and decision making would help elucidate its current status and establish how this may be improved.

# 2 Aims

The aims of this thesis were threefold. First, to elucidate factors in physiotherapists' clinical reasoning and decision-making processes when initiating and progressing mobilisation in patients who were critically ill in the ICU. Second, to investigate the short- and long-term outcomes of intensive twice-daily upright mobilisation starting early after the initiation of MV in ICU patients, and third, to identify predictors of poor long-term physical recovery in survivors of critical illness.

## 2.1 Specific aims and hypotheses

**Study I**

To investigate what specific parameters or factors influence and guide physiotherapists´ in their clinical reasoning and decision-making processes when they initiate and progress mobilisation to an upright position in a particular patient in the ICU, and to elucidate the barriers or facilitators that the physiotherapists identify regarding their treatment of patients in the ICU, especially with upright mobilisation.

**Study II**

To evaluate the effects of intensive twice-daily upright mobilisation administered by physiotherapists and to examine its effects on outcomes of mechanically ventilated patients in the ICU, in the short and long terms (one year).

We hypothesised that intensive twice-daily upright mobilisation, starting on day three after initiation of MV compared with once-daily mobilisation starting on day five, reduce the duration of MV, ICU and hospital LOS, and improve physical health-related quality of life and physical function long-term in patients who are mechanically ventilated for over 48 hours.

**Study III**

To identify predictors of poor long-term physical recovery one year after ICU stay.

We hypothesised that patients´ baseline characteristics (including age and gender), variables related to the severity of illness, ICU-related variables, and LOS, increase the risk of poor physical recovery for at least one year after ICU discharge.

# 3 Materials and methods

The studies were performed at Landspitali – The National University Hospital of Iceland, a 620-bed tertiary care university hospital, located in Reykjavik. The acute care service of the hospital is located in two buildings, Landspitali Fossvogur and Landspitali Hringbraut, 3.5 km apart. Each building has a 10 bed ICU and a physiotherapy department, with an experienced physiotherapist covering each ICU department.

The doctoral student, i.e., the author of this dissertation, prepared a research protocol for two studies, an RCT from the spring of 2010 until the autumn of 2011, and a qualitative study, from the autumn of 2012 until February 2014. The RCT began in both ICUs of the hospital in late October 2011 and the recruiting of patients ended on October 31st 2014. Follow-up data collection ended in November 2015, with data analysis completed in 2018. The data collection for the qualitative study started in February 2014 and ended in February 2015, with data analysis completed in 2017. A description of the studies is given in Table 1.

Table 1. Overview of the designs of studies I, II and III

| | Study I | Study II | Study III |
|---|---|---|---|
| Aim | Investigate what specific parameters or factors influence and guide physiotherapists´ in their clinical reasoning and decision-making processes when they initiate and progress upright mobilisation in a particular patient who is critically ill in the ICU | To evaluate the effects of intensive twice-daily upright mobilisation administered by physiotherapists and to examine its effects on outcomes of mechanically ventilated patients in the ICU, in the short and long terms (one year) | Identify predictors of poor long-term physical recovery one year after ICU discharge |
| Design | Qualitative research design | Randomised, controlled, assessor blinded, longitudinal, parallel-group, intervention trial | Regression analysis |
| Participants | 12 physiotherapists, working at the inpatient service at Landspitali – The National University Hospital in Iceland | 50 adult ICU patients, requiring MV more than 48 hours. They were ambulating and independent in activities of daily life before critical illness | A cohort of 50 patients from study II |
| Intervention | - | Two sessions of progressive upright mobilisation daily (n=29), to coincide with daily arousal protocol, compared with once-daily mobilisation (n=21) | - |
| Data collection and Instruments | Clinical observation and observation notes<br>Semi-structured interview transcripts<br>The investigators reflective notes | Duration of mechanical ventilation<br>ICU and hospital LOS<br>Short-form 36 version 2 ® Health Survey<br>Six-minute walk test<br>Medical Research Council – sum score<br>Modified Barthel Index<br>Baseline charateristics<br>Illness severity variables<br>ICU-related variables<br>Variables on the intervention components | Physical recovery variables:<br>Medical Research Council – sum score<br>Six minute walk test<br>Short-form 36 v2 ® Health Survey, Physical Function domain<br>Exposure variables:<br>Baseline characteristics<br>Severity of illness variables<br>ICU-related variables<br>LOS |
| Data analysis | Conventional content analysis | Wilcoxon rank sum test<br>Chi-Squared test<br>Independent t-test<br>Linear mixed effect model | Regression analysis<br>Wilcoxon rank sum test<br>Chi-Squared test<br>Independent t-test |

## 3.1 Study I

The study had a qualitative research design with a two-phase data collection. The results were reported according to the Standards for Reporting Qualitative Research (O´Brien et al., 2014).

### 3.1.1 Setting and participants

The participants in the study were physiotherapists working in the acute care services of Landspitali - The National University Hospital of Iceland. Twenty-six physiotherapists who were working in the adult inpatient service at the time of the study and who either covered patients in the ICUs and/or provided after-hours on-call services in the ICU, were considered eligible. The primary investigator introduced the study and its data collection methods to the physiotherapists at a staff meeting in each physiotherapy unit and volunteers were asked to contact the primary investigator to be included in the study. Twelve physical therapists volunteered and participated.

### 3.1.2 Data collection

The data collection was conducted from February 2014 to February 2015. The first phase of the study consisted of an observation (Yin, 2011), where the primary investigator observed each physiotherapist participant with a critically ill adult patient, preferably on MV, in the ICU. The focus of the observation was to describe each participant's preparation for and implementation of one physiotherapy session with the patient, including mobilisation to an upright position sitting on the edge of the bed. Additionally, the observation focused on the participant's communication with the ICU nurses and other health professionals, the handling of the patient's tubes, lines and drains, the communication between the participant and the patient, and the participant's reactions to the patient's responses throughout the session. There was no interaction between the participant and the observing investigator positioned several metres away to record observations (See observation scheme in Appendix 1). After the observation, the investigator sat down in a quiet place and reflected on her observations and noted down the main points (Yin, 2011). The second phase of the study which was scheduled later the same day consisted of a semi-structured interview (Jónsdóttir, 2013; Yin, 2011). The interview was held in a private room situated in the physiotherapy department. It was semi-structured to facilitate dialogue, and included rich descriptions from the participants, focusing on the factors that the participants contemplated during their clinical reasoning and decision-making processes before, during, and after the observed mobilisation session. The participants' reflections about

mobilisation of critically ill patients in general were also scrutinised. The participants' demographics were collected at the end of the interviews. The interviews were audio-recorded and were later transcribed verbatim by the investigator (See interview guide in Appendix 1). The 12 patients (one for each physiotherapist participant observed) in the observation phase were mechanically ventilated or had recently been extubated. All 12 of them were alert and seven were mechanically ventilated through an ETT. Six of the seven patients had undergone a tracheostomy and five were changed to a speaking valve before being mobilised to the edge of the bed. Four patients were receiving oxygen through a face mask or through a nasal cannula, and one patient was being ventilated with a Bilevel Positive Airway Pressure machine. No data were documented about individual patients. A pilot study had been performed to establish the data collection framework before the formal data collection was launched. The pilot study consisted of an observation and interview with one physiotherapist who met the recruitment criteria but who was not included in the formal study.

### 3.1.3 Analysis

The data analysis (including observation notes, reflective notes, interview transcripts) was conducted manually with conventional content analysis, which is a qualitative research method designed to interpret meaning from text content (Graneheim & Lundman, 2004; Hsiu-Fang & Shannon, 2005). First, the primary investigator immersed herself in the text by reading each transcript multiple times. Then, she read each transcript systematically to search for patterns that could describe and elucidate factors in the participants' clinical reasoning and decision-making processes when mobilising and progressing mobilisation of their patients. Keywords or short phrases that captured the essence of the physiotherapists' thoughts and reflections were highlighted. After four randomly selected transcripts had been examined, codes began to emerge, which were identified and written in the text margins. Then the primary investigator, overseen by other investigators, sorted the codes based on their interrelationships, and preliminary categories were determined and translated into English from Icelandic. These categories were organised accordingly and entered into an Excel® spreadsheet. Each category was entered into a row in the first column, followed by (in the following columns but in the same row) each participant's own words describing the category. The remaining eight transcripts were coded guided by these categories, one spreadsheet for each participant. Because no new categories came to light from the last two transcripts coded, this comparative process established data saturation. After coding all 12 transcripts, the data within each category were examined and cross-referenced

with the data from the primary investigator's observation and reflective notes. During this process, some categories were merged and others were separated. These were sorted based on their interrelationships and entered in a separate Excel® spreadsheet. This final Excel® spreadsheet included all of the participant data to facilitate transparent data analysis. From these data the final categories, subcategories and encompassing factors were discussed and determined by the investigators.

To enhance the probability of our study findings being credible, a persistent and rigorous field observation and prolonged engagement was conducted by the primary investigator, who was an experienced ICU physiotherapist, familiar with the context of the ICU in which the data collection took place (Lincoln & Guba, 1985). Furthermore, the primary investigator´s follow-up with the interview phase after the observation phase, and the research team´s deep probing of the factors that informed the mobilisation session of each of the 12 participants´ ensured triangulation of both the sources and the data collection methods. Negative case analysis was employed where a search for disconfirming data was performed and its results discussed amongst the research team to further refine the findings of the study.

## 3.2 Study II

This study design was prospective, longitudinal, parallel-group, assessor-blinded, RCT. The study was reported according to the Consort 2010 guidelines (Moher et al., 2010).

### 3.2.1 Setting and participants

The study was conducted in two mixed-patient population ICUs in a 620-bed tertiary care university hospital, situated in Reykjavik, Iceland. Both ICUs have physiotherapist coverage five days a week during regular hours with on-call service evenings, weekends and holidays. The ICUs have a 1:1 nurse:patient ratio and 24-hour intensivist coverage. Eligible patients were 18-80 years of age, admitted to the ICU because of a critical illness, and requiring MV for over 48 hours. They were able to ambulate independently before the onset of acute illness and able to cooperate during assessment and intervention for follow-up measurements up to one year after ICU discharge. Patients were excluded from the study by the attending medical team (not directly involved in the study) if they had poor survival prognoses. Also, patients were excluded if they had been admitted to the hospital more than two weeks prior to the ICU admission or if progressive upright mobilisation could not be performed (e.g., patients with prolonged haemodynamic instability, patients with severe head injuries or substantial unstable fractures). Randomisation to one of two groups was as follows. After a patient who met the inclusion criteria was identified by the research team, the team asked the ICU clerk to draw a paper slip from a bag, randomly allocating patients to the intensive twice-daily mobilisation group or the once-daily mobilisation group.

### 3.2.2 Intervention

Two experienced ICU physiotherapists implemented the intervention for each group on weekdays and 26 on-call physiotherapists on weekends and holidays. Beforehand, they were oriented to the patient safety parameters that the chief intensivists in both ICUs had defined (Table 2), and to the different physiotherapy and mobilisation interventions applied for the two study groups (Table 3). For mechanically ventilated patients in the ICUs, a daily arousal and spontaneous breathing protocol was typically initiated for both groups at 9 am. Both groups had access to respiratory physiotherapy including airway clearance, which was added as indicated, potentially increasing the number of upright mobilisation sessions. Following ICU discharge, both groups received standard physiotherapy according to clinical practice guidelines.

To discriminate between upright active mobilisation and more passive mobilisation without upright positioning, the investigators defined upright mobilisation and passive mobilisation for both groups. Upright mobilisation was defined as an intervention with progressive stages, sitting on the edge of bed, standing or walking with or without assistance, which represents mobilisation levels 3 to 10 on the ICU Mobility Scale (Hodgson, C. et al., 2014). The upright mobilisation intervention in the study included active assisted and active exercises, and strength, balance, functional and transfer training. Passive mobilisation was defined as a passive range of motion exercises and active assisted and active exercises performed in a supine position as well as passive transfer to a chair, which represents mobilisation levels 0 to 2 on the ICU Mobility Scale (Hodgson, C. et al., 2014). International clinical practice guidelines state that mobilising patients upright should be progressed in accordance with their responses (Gosselink et al., 2008). Thus, the participating physiotherapists progressed patients' mobilisation based on their clinical judgement.

Table 2. Patient safety during upright mobilisation

| |
|---|
| Cardiovascular instability |
| Tachycardia (>130 beats/min)<br>Bradycardia (<40 beats/min)<br>Heart rhythm disturbances<br>Low blood pressure (SBP<90 mmHg)<br>Patient receiving >2 vasoactive drugs<br>Intra-aortic ballon pump<br>Extra Corporal Membrane Oxygenation (ECMO) |
| Open abdomen |
| Severe respiratory failure |
| $FiO_2$ >0.6<br>PEEP >10 cm $H_2O$ Respiratory rate >35/min<br>High-frequency oscillatory ventilation |
| High risk for hemorrhage or active bleeding |
| Active thrombotic disease |
| Other diseases that require heavy sedation or muscle relaxants |
| July 27th. 2011. Alma D Möller, Kristinn Sigvaldason |

#### *3.2.2.1 Once-daily mobilisation group*

Intervention started when the patient had been intubated and on MV longer than 96 hours. Mobilisation was based on international clinical practice guidelines for ICU patients (Gosselink et al., 2008), and was performed once-daily until ICU discharge. For patients who were mechanically ventilated, the usual practice was that the physiotherapy was scheduled for approximately 9 am. At this time, the patients were not always awake, thus passive range of motion exercises were performed in such cases, progressing to active assisted and active exercises commensurate with increased patient arousal, unless upright positioning was contraindicated (Table 2). When considered appropriate by the physiotherapist, passive transfer to a reclining chair or sitting on the edge of the bed was initiated, followed by functional transfer training (Table 3).

#### *3.2.2.2 Intensive twice-daily mobilisation group*

The intervention was comparable to that for the daily mobilisation group. Differences included the intervention being initiated after 48 hours from the start of MV and consisting of two sessions of progressive upright mobilisation (mobilisation levels 3 to 10 on the ICU Mobility Scale (Hodgson, C. et al., 2014)) daily, until ICU discharge unless upright mobilisation was contraindicated (Table 2). The first physiotherapy session of the day that was to include a mobilisation session was scheduled for late morning, to coincide with the patient being awake due to the daily arousal protocol. This maximised patients' capacities to cooperate and participate in their interventions. The focus of each intervention was on individualised and response-driven progressive upright mobilisation, including sitting on the edge of the bed or a higher level of mobilisation. Components of the intervention were functional, strength, balance and transfer training, with the specific aim of progressing patients to standing and walking (Table 3).

Table 3. The components of the physiotherapy intervention for both groups

| | Intensive twice-daily mobilisation group | Once-daily mobilisation group |
|---|---|---|
| Onset | Commenced after 48 hours of mechanical ventilation | Commenced after 96 hours of mechanical ventilation |
| Frequency, duration | Two sessions daily, ≥20 minutes each | One session daily, ≥20 minutes |
| Timing | First session timed later in the morning, after sedation stop, to coincide with the patient being awake. Second session in the afternoon | Session timed at 09-10 am (usual practice) |
| Type, repetitions intensity | Type focused on a progressive upright mobilisation* with sitting over the edge of the bed or higher level of mobilisation starting as early as the patient´s condition permitted.<br>Repetitions and intensity were based on patient´s responses and enhanced with increased patient´s arousal and participation in the activity | Type, repetitions and intensity as considered appropriate by the physiotherapist |
| Content | Patient who was sedated or unresponsive, or if a mobilisation to an upright position was contraindicated: Passive range of motion exercises and body positioning. Consider upright position, sitting over the edge of the bed if patient was medically stable, even though not completely aroused.<br>Patient who was medically stable and could participate: upright mobilisation with sitting over the edge of the bed, including assisted-active to active exercises. Transfer training from supine to turning in bed to sitting over the edge of the bed. Exercises in upright position included assisted-active to active exercises, functional, strength, balance and transfer training progressing to an active transfer to a chair towards standing and walking. Passive transfer to a reclining chair in cooperation with nurses | Passive range of motion exercises and body positioning. Progressing to active assisted and active exercises with increased arousal.<br>When considered appropriate, usually after removal of the endotracheal tube, passive transfer to a reclining chair or sitting over the edge of the bed, followed by functional transfer training, standing up, transfer to a chair, standing up and walking |
| After removal of endotracheal tube | Respiratory physiotherapy, including airway clearance and mobilisation added to research protocol as needed | |
| After ICU discharge | Standard physiotherapy | |

* The investigators defined upright mobilisation as an intervention with progressive stages, i.e., sitting over the edge of bed, standing or walking with or without assistance, which constitutes mobilisation level 3 to 10 on the ICU Mobility Scale by Hodgson C. et al. Feasibility and inter-rater reliability of the ICU Mobility Scale. Heart Lung. 2014;43:19-24.

### 3.2.3 Outcomes

The primary outcomes, measured in days, were duration of MV, ICU- and hospital LOS. The secondary outcomes were health-related quality of life and physical function assessed at three to six time-points, at baseline (four weeks before ICU admission), at ICU discharge, at hospital discharge, and at three, six and 12 months after ICU discharge (Table 4). The physical function outcomes were exercise capacity, muscle strength and functional independence. Additionally, descriptive outcomes were baseline characteristics, clinical data from and after the ICU stay, and data on the components of the intervention.

#### *3.2.3.1 Health-related quality of life*

Health-related quality of life was assessed with the Short-Form 36 Health Survey version 2® (SF-36v2) (Saris-Baglama et al., 2010). SF-36 was constructed to measure health status in the general population, clinical practice and in research, as well as in health policy evaluations (Ware & Sherbourne, 1992). The SF-36v2 questionnaire is the second version of the SF-36 and contains 36 questions on the participant's health and wellbeing for the last four weeks (Ware et al., 2007). Its outcomes are reported within eight health domains: 1) physical function, 2) role physical, 3) bodily pain, 4) general health, 5) vitality, 6) social function, 7) role emotional and, 8) mental health. From the domains, a PCS and a mental component score (MCS) are computed, and these are reported in the study as norm-based scores, with a mean score of 50 and SD of 10. The SF-36v2 scale has been translated into Icelandic. Psychometric testing of the Icelandic version has been performed on Icelandic university students and on patients in rehabilitation due to chronic pain (Eiríksdóttir, 2011). The results have revealed good internal consistency. The scale is widely used for measuring patient-reported health-related quality of life, including that of ICU patients (Burtin et al., 2009; Denehy et al., 2013; Herridge et al., 2003; McWilliams et al., 2018; Wright et al., 2017).

#### *3.2.3.2 Exercise capacity*

Exercise capacity was measured with the distance walked in six minutes, based on the established six-minute walk (6MW) test (ATS, 2002). The 6MW test is a widely used, simple, self-paced, standardised test that measures submaximal level of functional capacity. The 6MW test is recommended, both in the clinical setting and for research purposes, as a functional walk test that is reflective of activities of daily living (Solway et al., 2001). The test evaluates the responses of all body systems during exercise and the outcome of the test reflects the person's functional exercise level for physical activities, as most of the activities

of daily life are performed at a submaximal level of exertion (ATS, 2002). The measurement properties of the 6MW test have been thoroughly researched (Solway et al., 2001), and the test has been found to be a valid and responsive functional capacity measurement in patients surviving acute respiratory failure (Chan et al., 2015). The 6MW test has been used in both RCTs and in cohort studies as an outcome measure on physical function after critical illness (Denehy et al., 2013; Herridge et al., 2003; Needham et al., 2014; Wright et al., 2017). The American Thoracic Society´s guidelines state that one walk test is sufficient in most clinical settings, but a practice test should be considered with at least a one-hour interval between tests (ATS, 2002).

#### *3.2.3.3 Muscle strength*

Muscle strength was measured with the Medical Research Council sum score (MRC-SS) (Kleyweg et al., 1991). The MRC-SS is based on the Medical Research Council (MRC) scale for muscle strength with the following grade system: “0 = No visible contraction, 1 = Visible contraction without movement of the limb (non-existent for hip flexion), 2 = Movement of the limb but not against gravity, 3 = Movement against gravity over (almost) the full range, 4 = Movement against gravity and resistance, 5 = Normal”. The MRC scale is widely used in clinical practice and has shown excellent inter-rater reliability in ICU survivors when trained research staff performed the measurements (Fan et al., 2010).

The MRC-SS is a common tool in the ICU setting and was initially developed for and validated for patients with Guillian-Barre syndrome (Kleyweg et al., 1991). The MRC-SS measures muscle strength in six muscle groups, performing the following movements bilaterally: abduction of the arm, flexion of the elbow, extension of the wrist, flexion of the hip, extension of the knee and dorsiflexion of the ankle, with a score ranging from 0 (paralysis) to 60 (normal strength). The MRC-SS has high inter-observer agreement (Connolly et al., 2013; Hermans et al., 2012; Hough et al., 2011; Kleyweg et al., 1991), and is sensitive to change (Kleyweg et al., 1991). The patient needs to be awake, understand the procedure, and be cooperative with manual muscle testing, thus, injury, coma and/or delirium often prohibited evaluation (Hough et al., 2011). The MRC-SS is used as a clinical screening tool in the ICU, with scores equal or lower than 48 suggesting ICU-acquired weakness (ICU-AW) (De Jonghe et al., 2002). Inter-observer agreement for diagnosing ICU-AW in patients in the ICU, using the cut-off point of MRC-SS<48 points, has varied from good agreement (Hermans et al., 2012), to moderate agreement (Connolly et al., 2013) , towards fair agreement (Hough et al., 2011). Limitations in using the MRC-SS to diagnose ICU-AW early in the course of critical illness have been reported

(Connolly et al., 2013; Hough et al., 2011). Often patients cannot perform the test, or their changeable clinical status reduces the reliability of the test results (Connolly et al., 2013). Additionally, despite high inter-observer agreement, the MRC-SS has been reported not to be a sufficiently robust tool to diagnose ICU-AW and lacked the discrimination to identify weak patients with rehabilitation potential after critical illness (Connolly et al., 2015). Additionally, the MRC-SS has a ceiling effect and for the tester to differentiate between the score of 4 and 5 may be subjective (Hermans et al., 2012).

#### *3.2.3.4 Functional independence*

Functional independence was measured with the Modified Barthel Index (MBI), that assesses an individual's functional independence (Shah et al., 1989). The original Barthel Index (BI), which was published in 1965, is a sensitive, valid and reliable instrument (Mahoney & Barthel, 1965). It measures an individual's functional independence in ten functions of activities of daily life (ADL). It is simple and easy to use, and covers feeding, bathing, grooming, dressing, bowel and bladder function, toilet use, transfers from bed to chair, mobility and stairs. The score ranges from 0 (totally dependent) to 100 (completely independent). The BI was modified in1989 (Shah et al., 1989). In the original BI, each item is scored in three steps (Mahoney & Barthel, 1965), but in the modified version of Shah and colleagues (1989) the MBI, each item is scored in five steps (Shah et al., 1989). The reliability of MBI (Cronbach´s alpha 0.90) is greater compared with the original BI version (Shah et al., 1989). The score given to each item in the MBI is based on the amount of physical assistance required to perform the task. The total possible score in both the BI and the MBI ranges from 0 (total dependence) to 100 (total independence). The MBI has been translated into Icelandic but has not been psychometrically tested. It is used extensively by occupational therapists in Iceland. Both the MBI and BI have been widely used in studies of rehabilitation of stroke patients (West et al., 2010), the elderly (Brooks et al., 2006) and in an outcome study of physical therapy interventions on ventilator-dependent patients at a respiratory care centre (Yang et al., 2010). The BI has been used in ICU rehabilitation trials (Schweickert et al., 2009; Yang et al., 2010).

#### *3.2.3.5 Descriptive variables*

Descriptive variables were patient baseline characteristics, clinical data from the ICU stay and follow-up data after ICU discharge. Pre-existing morbidities were assessed with the Charlson Comorbidity Index (CCI) (Charlson et al., 1987), and the Functional Comorbidity Index (FCI) (Groll et al., 2005). The severity of illness at ICU admission was assessed with the APACHE II (Acute Physiology and

Chronic Health Evaluation II). The Richmond Agitation Sedation Scale (RASS) was used to assess the patient´s sedation level (Sessler et al., 2002). Descriptive variables were collected daily on the components of each intervention.

### 3.2.4 Data collection

The patients´ baseline characteristics and clinical data were collected by the primary investigator. When the patients had been discharged from the ICU and transferred to a general ward, she approached the patients, whose next of kin had given consent to participate in the study, in order to confirm their consents. If they confirmed informed consent, the SF-36v2 and MBI questionnaires were administered. Patients were asked to base their responses to the questions retrospectively, with respect to their health status four weeks prior to ICU admission. Assistance from next of kin was permitted.

Physiotherapists, who practised at the hospital and agreed to participate in performing the performance-based physical function measurements during the course of the study, were trained in a standardised manner. They were blinded to the patients´ group allocation and performed all physical function measurements at ICU discharge, hospital discharge and at three, six and 12 months after ICU discharge. They examined each patient in the ICU and the hospital ward on the day of discharge and recorded the MRC-SS, and completed the MBI in cooperation with each patient´s nurse or nurse assistant. At three, six and 12 months after ICU discharge, the patients returned to the hospital for a follow-up assessment. The primary investigator first sought descriptive data from the participants, and then she administered the SF-36v2 and MBI questionnaires, which the patients completed with assistance from relatives as needed. Then, the trained and blinded physiotherapists performed the physical function measurements of the MRC-SS and the 6MW test. Patients who had never performed the 6MW test before, performed two tests with a one-hour interval. If a patient was unable to return to the hospital for follow-up assessment, the MBI form and SF-36v2 were mailed or completed by telephone. Three patients who lived some distance from the hospital were able to perform the 6MW test in a standardised manner under the supervision of experienced physiotherapists in their communities.

The ICU physiotherapists who performed the intervention recorded the following data on a research sheet daily: patients' current medical conditions and sedation levels (in cooperation with the bedside nurses), the results of their assessments, the intervention parameters and the patient's responses to the intervention and any reasons for missed sessions (see Appendix 2).

Furthermore, all upright mobilisation sessions recorded by the nurses on the 24-hour ICU documentation sheet were documented in detail by the primary investigator and compared with those recorded by the physiotherapists. This enabled comparison of all upright mobilisation interventions received by the patients in both groups during their ICU stays, thus served as a validation check.

Table 4. Timeline of the outcome measurements

| | Baseline | ICU stay | ICU discharge | Hospital discharge | 3, 6 and 12 months after ICU discharge |
|---|---|---|---|---|---|
| Baseline and clinical data | x | x | | | |
| Safety monitoring | | x | | | |
| Intervention components | | x | | | |
| SF-36v2 | x | | | | x |
| MBI | x | | x | x | x |
| MRC-SS | | | x | x | x |
| 6MWT | | | | | x |

MBI, Modified Barthel Index; MRC-SS, Medical Research Council - sum score; SF-36v2, Short Form-36 Health Survey version 2; 6MWT, Six-minute walk test

### 3.2.5 Analysis

The sample size was based on the work of Burtin and colleagues (Burtin et al., 2009), due to the fact that no objective data were available to guide the power calculation for optimal sample size when the study was designed. Their calculations showed that a sample size of 36 participants was required for each group to detect a validated minimally clinically important difference of 50 metres walking distance in the 6MW test with a statistical power of 80% and an α level of 0.05. We aimed to include 120 participants in the study over a period of three years, 60 in each group. Given the ICU setting, aiming for 60 patients in each group allowed for considerable drop out.

The primary outcomes were analysed with the Wilcoxon rank sum test. Parametric secondary outcomes for repeated measures were analysed between groups, over time with a linear mixed effect model, and with the Wilcoxon rank sum test if their distribution was non-parametric. Descriptive outcomes were compared with use of the chi-squared test, independent t-test and Wilcoxon´s rank sum test. Data were analysed with SAS software, version 9.4 (SAS Institute, Cary, NC, USA) and Microsoft Office Excel 2007 programme. Alpha was set at <0.05.

## 3.3 Study III

Study III was based on secondary analysis of the data from the cohort in study II. A regression analysis was conducted to better elucidate factors that were associated with poor physical recovery one year after ICU discharge.

### 3.3.1 Participants

A cohort of 50 critically ill patients from study II were analysed, 17 women and 33 men. They were functionally independent and able to ambulate independently before the onset of critical illness that required an ICU admission with MV for more than 48 hours.

### 3.3.2 Outcome variables

In this regression analysis, three dependent variables from study II were selected as outcome measures that characterised the patients' physical recovery one year after they were discharged from the ICU. These three dependent variables represent three principle levels of the World Health Organisation´s International Classification of Functioning, Disability and Health (ICF) framework (World Health Organization, 2001). The first variable was muscle strength, representing limitation of body functions and structures. The MRC-SS was used to measure global muscle strength. The second level was limitation of activities representing exercise capacity. Exercise capacity was assessed with the distance walked in the six-minute walk test (6MW test) (metres). The third level was limitation of participation representing self-reported physical function, which was evaluated with the SF-36v2, using the Physical Function domain raw score (SF-36v2 PF domain).

The exposure variables were the patient's baseline characteristics, variables related to illness severity, ICU-related variables, and ICU and hospital LOS. The patient's functional independence before the onset of critical illness was assessed with the MBI scale. The CCI and the FCI were used to assess if the patient had any the comorbidity when they were admitted to the ICU. The patient's severity of illness at admission to the ICU was assessed with the APACHE II scale. For a more detailed description of the variables, refer to section 3.2.3.

### 3.3.3 Analysis

Descriptive analysis was performed on the patient's exposure variables, which were the patient's baseline characteristics, severity of illness at ICU admission, variables related to the ICU stay, and ICU and hospital LOS. Additionally, the patient's trajectory of physical recovery was analysed at three, six and 12

months after ICU discharge with the outcomes of MRC-SS, 6MW distance, and SF-36v2 PF domain. Continuous variables were described by means and SD if they were normally distributed, but otherwise by median and interquartile range (IQR). Categorical variables were described by counts (n) and percentages (%). The descriptive variables were tested for differences between genders using the independent t-test, Wilcoxon rank sum test or chi-squared test.

Regression analysis was performed in three steps. First a bivariate association was examined between each of the three physical recovery variables, muscle strength (MRC-SS), exercise capacity (6MW distance), and self-reported physical function (SF-36v2 PF domain), and the exposure variables, baseline characteristics, severity of illness, ICU-related variables, and LOS. A Pearson correlation coefficient was calculated for continuous and ordinal variables that were normally distributed and a Spearman correlation coefficient was calculated for continuous variables with skewed distribution. Second, a linear regression model was used, adjusting for gender and age, to evaluate the associations of the exposure variables, one at a time, with each of the three physical recovery variables. Third, the same model was used to evaluate the associations of two baseline characteristics, gender and age, with each of the three physical recovery variables at 12 months after ICU discharge. The association of gender and age with each physical recovery variable was tested by reciprocally adjusting only for these two variables. Then the association was again tested by additionally adjusting for each exposure variable separately. The semi-partial squared correlation (type II) and semi-partial eta-square were calculated, respectively. Data were analysed with SAS software, version 9.4 (SAS Institute, Cary, NC, USA) and the Microsoft Office Excel® 2007 program was used for data handling. The significance level was set at <0.05.

## 3.4 Ethical consent and approval for the studies

The studies were approved by Landspitali – The National University Hospital of Iceland´s Ethical Committee (16/2011 and 48/2013). The Chief Medical Director of the hospital approved the studies (23.02.2011 and 05.12.2013), as well as the directors of the ICUs and the physiotherapy departments of the hospital. The Icelandic Data Protection Authority was notified (2011020259ÞS/- and 18.12.2013). The Chief of Human Resources of the hospital approved study I (08.01.2014).

For study I, the participating physiotherapists signed informed consent and the patients gave verbal consent or nodded yes with their head for the observation of a typical mobilisation session. For study II, informed consent was obtained from the patients or their next of kin. If an informed consent was obtained from a patient´s next of kin, the patient personally confirmed the consent later when and if well enough to do so. Study II was registered at ClinicalTrials.gov: NCT02301273.

# 4 Results

A summary of the main results from studies I, II and III is presented in this chapter, corresponding to the aims of the thesis (Figure 1). For detailed results refer to the publications at the end of this thesis.

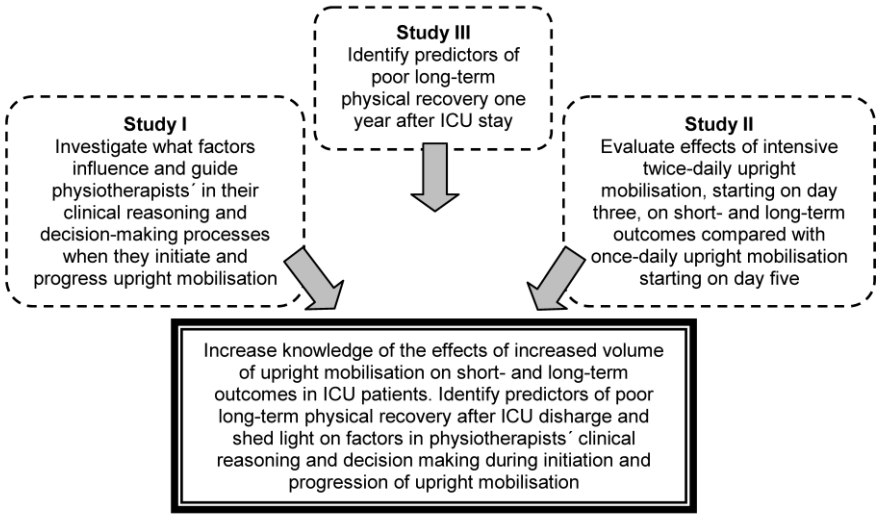


Figure 1. Overview of study aims

## 4.1 Study I

The data analysis revealed six categories and four encompassing factors as being important in the physiotherapists´ clinical reasoning and decision-making processes when they initiated and progressed the mobilisation of a patient who was critically ill. The six categories were: 1) Patient, 2) ICU context, 3) Physiotherapist, 4) Transfer, 5) FITT parameters (frequency, intensity, type, time or duration), and 6) Expected outcome. Each category included several subcategories. Overarching these six categories were four encompassing factors: i) Safety & wellbeing, ii) Continuous assessment & intervention intertwined, iii) Individualised & response-driven intervention, and iv) Barriers & solutions. The six categories and four encompassing factors were intertwined, and guided participants' clinical reasoning and decision-making processes when initiating and progressing the mobilisation of patients who were critically ill. These are shown in Figure 2.

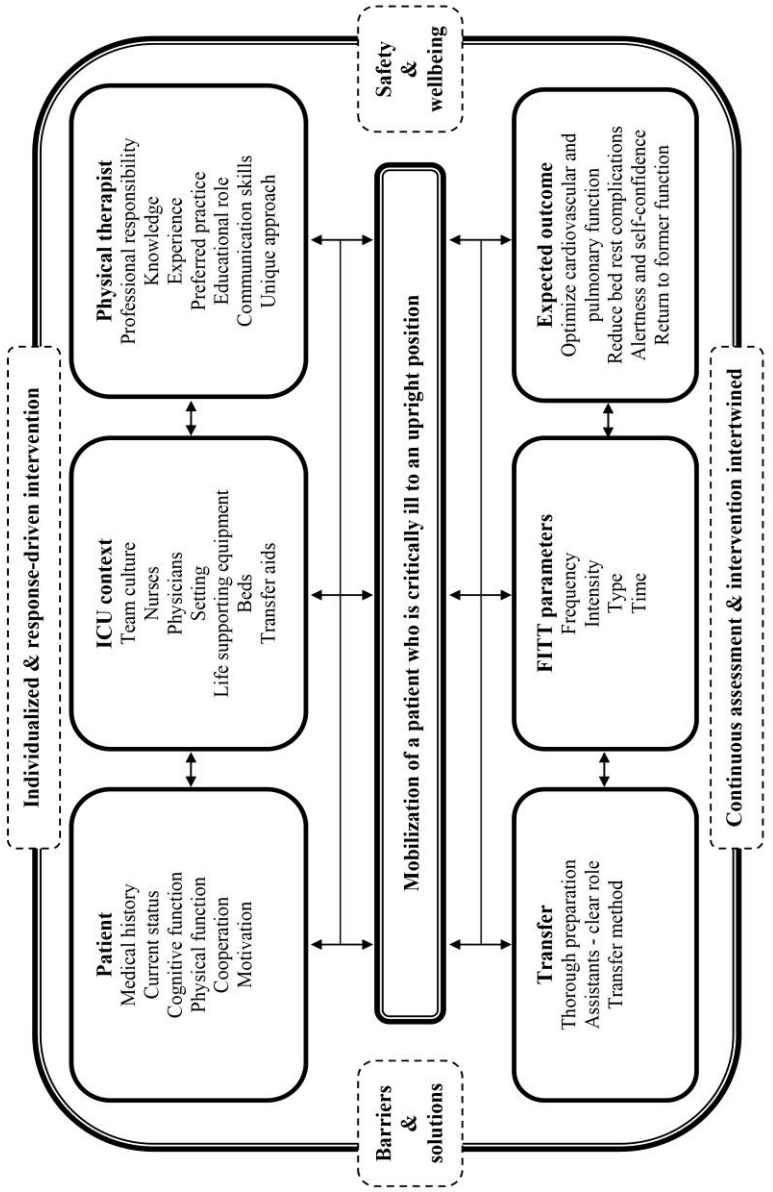


Figure 2. The six categories and four encompassing factors, illustrating physiotherapists' clinical reasoning and decision-making processes when initiating and progressing mobilisation in patients who are critically ill

## 4.2 Study II

The two study groups were largely comparable in baseline characteristics and admission disease severity (Table 5). Clinical data from the ICU stay and descriptive outcomes after ICU discharge were not different between the two groups (Table 6). A difference was not detected between the groups in any of the three primary outcomes, duration of MV, ICU or hospital LOS (Table 7). There was no difference between groups in any of the secondary outcomes of self-reported health-related quality of life or performance-based physical function at any time point measured (Table 8).

The content of the physiotherapy intervention is reported in Table 9. Participants in the twice-daily mobilisation group received their first upright mobilisation session that included sitting on the edge of the bed or a higher level of upright mobilisation on a median (IQR) of day seven (5-13) from initiation of MV, and the once-daily mobilisation group on day eight (6-15). Fifteen patients (52%) in the twice-daily mobilisation group and 13 patients (65%) in the once-daily mobilisation group remained on bed rest and did not mobilise to an upright position for seven days or longer after the initiation of MV. Twelve of these 15 patients (80%) in the twice-daily mobilisation group were deeply sedated at that time and 12 patients (92%) of the 13 in the once-daily mobilisation group. These 24 patients had continuous intravenous sedation, and their sedation level according to RASS was from -4 to -5 during physiotherapy. The twice-daily mobilisation group received upright mobilisation (mobilisation levels 3 to 10 on the ICU Mobility Scale) during physiotherapy on a significantly higher percentage of ICU days, compared with the once-daily mobilisation group: 31% of ICU days compared with 22% ($p<0.03$), respectively. Furthermore, the twice-daily mobilisation group received upright mobilisation with any health care provider in the ICU on an average of 35% of ICU days compared with 24% in the once-daily mobilisation group ($p<0.02$).

Table 5. Baseline characteristics and admission disease severity

| | Intensive twice-daily mobilisation n=29 | Once-daily mobilisation n=21 | P value |
|---|---|---|---|
| Sex, male | 19 (65.5%) | 14 (66.7%) | .93 |
| Age (y), median (IQR) | 62 (50-70) | 64 (58-74) | .26 |
| Prior residence, home | 28 (96.6%) | 21 (100%) | .40 |
| Married / cohabitation | 19 (65.5%) | 14 (66.7%) | .93 |
| BMI (kg/m$^2$), mean (95% CI) | 33.0 (28.5-37.4) | 32.1 (29.1-35.1) | .74 |
| % Obese (BMI (kg/m$^2$) $\geq$ 30) | 14 (48.3%) | 12 (57.1%) | .54 |
| MBI, baseline, median (IQR) | 100 (100-100) | 100 (100-100) | .48 |
| Education, elementary (ISCED 1.2) | 14 (48.3%) | 13 (61.9%) | .34 |
| Regular exercise ($\geq$150 min/w) | 6 (20.7%) | 5 (26.3%) | .75 |
| Current smoker | 10 (34.5%) | 4 (19.1%) | .23 |
| Former smoker | 9 (31.3%) | 14 (66.7%) | .01 |
| Never smoked | 10 (34.5%) | 3 (14.3%) | .11 |
| ***Employment status before ICU*** | | | .23 |
| Employed | 10 (34.5%) | 10 (47.6%) | |
| Retired | 9 (31.0%) | 9 (42.9%) | |
| Unemployed | 3 (10.3%) | 1 (4.8%) | |
| Disability | 7 (24.1%) | 1 (4.8%) | |
| ***ICU admission diagnosis*** | | | .28 |
| Severe sepsis / septic shock | 11 (37.9%) | 12 (57.1%) | |
| Pneumonia | 5 (17.2%) | 3 (14.3%) | |
| Acute respiratory failure | 3 (10.3%) | 1 (4.8%) | |
| Heart disease (medical) | 2 (6.9%) | 1 (4.8%) | |
| Multi-trauma | 2 (6.9%) | 4 (19.1%) | |
| Major elective surgery | 3 (10.3%) | 0 | |
| Other | 3 (10.3%) | 0 | |
| ***Disease severity and comorbidities*** | | | |
| APACHE II - mean (95% CI) | 23.5 (19.7-27.2) | 22.0 (18.2-25.8) | .59 |
| CCI - median (IQR) | 2 (1 to 5) | 2 (1 to 5) | .80 |
| 0 comorbidities | 6 (20.7%) | 4 (19.1%) | .89 |
| 1-2 comorbidities | 9 (31.0%) | 8 (38.1%) | .60 |
| $\geq$3 comorbidities | 14 (48.3%) | 9 (42.9%) | .70 |
| FCI - median (IQR) | 2 (2 to 4) | 2 (1 to 4) | .50 |
| 0 comorbidities | 3 (10.3%) | 2 (9.5%) | .92 |
| 1-2 comorbidities | 15 (51.7%) | 12 (57.1%) | .70 |
| $\geq$3 comorbidities | 11 (37.9%) | 7 (33.3%) | .74 |

Data is presented as mean (95% CI), median (IQR) or n (%). Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II score; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; FCI, Functional comorbidity index; ICU, intensive care unit; ISCED, The International Standard Classification of Education; IQR, inter-quartile range; MBI, Modified Barthel Index.

Table 6. Patient outcomes

| | Intensive twice-daily mobilisation n=29 | Once-daily mobilisation n=21 | p value |
|---|---|---|---|
| Developed ARDS during ICU stay | 9 (31.0%) | 6 (28.6%) | 0.85 |
| Renal replacement therapy in ICU | 6 (20.7%) | 6 (28.6%) | 0.52 |
| ICU-AW indication at ICU discharge* | 13/20 (65.0%) | 8/13 (61.5%) | 0.84 |
| **Discharge location from hospital** | | | 0.23 |
| Home | 10 (34.5%) | 7 (33.3%) | |
| Nursing home | 3 (10.3%) | 0 | |
| Other hospital | 7 (24.1%) | 2 (9.5%) | |
| Rehabilitation centre | 6 (20.7%) | 8 (38.1%) | |
| Other | 1 (3.5%) | 3 (14.3%) | |
| Deceased | 2 (6.9%) | 1 (4.8%) | |
| **Mortality** | | | |
| 30 days mortality | 1 (3.4%) | 1 (4.8%) | 0.82 |
| 90 days mortality | 2 (6.9%) | 2 (9.5%) | 0.74 |
| 12 months mortality | 3 (10.3%) | 2 (9.5%) | 0.92 |
| **Residence at 12 months after ICU discharge** | | | 0.20 |
| Home | 22 (84.6%) | 19 (100%) | |
| Nursing home | 3 (11.5%) | 0 | |
| Rehabilitation centre | 1 (3.8%) | 0 | |
| **Employment 12 months after ICU discharge** | | | 0.65 |
| Employed and returned to work | 5 (19.2%) | 5 (26.3%) | |
| Employed and not returned to work | 4 (15.4%) | 3 (15.8%) | |
| Retired | 9 (34.6%) | 7 (36.8%) | |
| Unemployed | 1 (3.8%) | 2 (10.5%) | |
| Disability | 7 (26.9%) | 2 (10.5%) | |

Data is presented as n (%). Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit; ICU-AW, intensive care unit acquired weakness; MRC-SS, Medical Research Council sum-score. Definition of ICU-AW indication: MRC-SS less than 48 at ICU discharge. *20 participants in the intensive twice-daily mobilisation group and 13 in the daily mobilisation group could be measured at ICU discharge.

Table 7. Primary outcomes

| | Intensive twice-daily mobilisation n=29 | Once-daily mobilisation n=21 | Median difference | Z / p value |
|---|---|---|---|---|
| Duration of MV (days) | 8.8 (6.4 to 19.3) | 7.8 (5.4 to 17.7) | -0.8 (-4.3 to 3.0) | -0.14 / 0.89 |
| ICU LOS (days) | 12.4 (8.4 to 19.6) | 11.0 (7.3 to 22.8) | -0.5 (-5.3 to 4.6) | -0.18 / 0.86 |
| Hospital LOS (days) | 36.9 (21.5 to 55.7) | 24.6 (15.5 to 56.6) | -5.1 (-19.8 to 6.0) | -1.10 / 0.29 |

Outcomes are presented as days. Data is presented as median (IQR) and median difference (95% CI). Abbreviations: CI, confidence interval; ICU, intensive care unit; IQR, inter-quartile range; LOS, length of stay; MV, mechanical ventilation.

Table 8. Secondary outcomes

| | | Baseline | n | ICU discharge | n | Hospital discharge | n | 3 months after ICU discharge | n | 6 months after ICU discharge | n | 12 months after ICU discharge | n |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SF-36v2 PCS | Twice-daily mobilisation | 44.1 (40.1 to 48.0) | 26 | | | | | 36.3 (32.3 to 40.3) | 25 | 38.5 (34.4 to 42.6) | 24 | 38.3 (34.2 to 42.4) | 23 |
| | Once-daily mobilisation | 46.1 (41.4 to 50.9) | 18 | | | | | 37.4 (32.6 to 42.3) | 18 | 37.3 (32.3 to 42.2) | 18 | 40.2 (35.5 to 45.0) | 18 |
| | Mean difference | -2.1 (-11.7 to 7.6) | | | | | | -1.1 (-10.9 to 8.7) | | 1.2 (-8.8 to 11.3) | | -1.9 (-11.7 to 7.9) | |
| | t Value / p | -0.66 / 1.0 | | | | | | -0.34 / 1.0 | | 0.37 / 1.0 | | -0.60 / 1.0 | |
| SF-36v2 MCS | Twice-daily mobilisation | 46.8 (42.5 to 51.1) | 26 | | | | | 44.4 (40.1 to 48.8) | 25 | 47.5 (43.0 to 51.9) | 24 | 47.3 (42.9 to 51.8) | 23 |
| | Once-daily mobilisation | 52.9 (47.7 to 58.1) | 18 | | | | | 47.9 (42.7 to 53.2) | 18 | 48.9 (43.6 to 54.3) | 18 | 50.3 (45.1 to 55.4) | 18 |
| | Mean Difference | -6.1 (-16.5 to 4.4) | | | | | | -3.5 (-14.1 to 7.2) | | -1.5 (-12.3 to 9.4) | | -3.0 (-13.6 to 7.6) | |
| | t Value / p | -1.79 / 0.63 | | | | | | -1.01 / 0.97 | | -0.42 / 1.0 | | -0.86 / 0.99 | |
| Six minute walk distance | Twice-daily mobilisation | | | | | | | 419.3 (346.8 to 491.8) | 22 | 451.1 (378.3 to 523.9) | 21 | 477.6 (404.1 to 551.1) | 18 |
| | Once-daily mobilisation | | | | | | | 415.4 (331.9 to 498.9) | 16 | 467.9 (384.4 to 551.4) | 16 | 480.0 (395.9 to 564.2) | 14 |
| | Mean Difference | | | | | | | 3.9 (-158.9 to 166.8) | | -16.9 (-179.9 to 146.2) | | -2.5 (-166.9 to 162.0) | |
| | t Value / p | | | | | | | 0.07 / 1.0 | | -0.3 / 1.0 | | -0.04 / 1.0 | |
| MRC-SS | Twice-daily mobilisation | | | 40.2 (37.1 to 43.4) | 20 | 48.8 (45.7 to 52.0) | 20 | 52.9 (50.0 to 55.8) | 26 | 55.0 (52.1 to 58.0) | 24 | 56.9 (53.8 to 59.9) | 23 |
| | Once-daily mobilisation | | | 42.4 (38.5 to 46.2) | 13 | 52.3 (48.8 to 55.8) | 18 | 54.6 (50.8 to 58.4) | 14 | 54.4 (50.8 to 58.1) | 15 | 55.9 (52.2 to 59.6) | 15 |
| | Mean difference | | | -2.2 (-10.2 to 5.9) | | -3.5 (-11.1 to 4.1) | | -1.7 (-9.5 to 6.0) | | 0.6 (-7.1 to 8.3) | | 0.9 (-6.8 to 8.7) | |
| | t Value / p | | | -0.86 / 0.99 | | -1.47 / 0.90 | | -0.71 / 1.0 | | 0.25 / 1.0 | | 0.39 / 1.0 | |
| | | Median (IQR) | n | Median (IQR) | n | Median (IQR) | n | Median (IQR) | n | Median (IQR) | n | Median (IQR) | n |
| MBI | Twice-daily mobilisation | 100 (100 to 100) | 27 | 3 (0 to 15) | 29 | 88.5 (44 to 98) | 26 | 99 (81 to 100) | 26 | 100 (93 to 100) | 24 | 100 (91.5 to 100) | 24 |
| | Once-daily mobilisation | 100 (100 to 100) | 19 | 4 (0 to 14) | 19 | 86 (60.5 to 98) | 20 | 100 (95 to 100) | 17 | 100 (90 to 100) | 18 | 100 (98 to 100) | 17 |
| | Median difference | 0.0 (0.0 to 0.0) | | -4.0 (0.0 to 4.0) | | -9.0 (0.0 to 18.0) | | 0.0 (0.0 to 4.0) | | 0.0 (0.0 to 0.0) | | 0.0 (0.0 to 4.0) | |
| | Z / p | 0.71 / 0.48 | | -0.34 / 0.74 | | 0.29 / 0.77 | | 0.82 / 0.41 | | -0.19 / 0.85 | | 0.85 / 0.40 | |

Data is presented as Least Squares Means (95% CI), median (IQR), mean difference (95%CI) and median difference (95% CI) Abbreviations: CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; MBI, Modified Barthel Index; MRC-SS, Medical Research Council - sum score; SF-36v2, Short Form-36 Health Survey version 2; PCS, Physical Component Score; MCS, Mental Component Score.

Table 9. Implementation and components of the intervention for both groups

| | Intensive twice-daily mobilisation n=29 | Once-daily mobilisation n=21 | Z / p value |
|---|---|---|---|
| ***Days in the ICU (median (IQR))*** | | | |
| ICU LOS (days) | 12.4 (8.4 to 19.6) | 11.0 (7.3 to 22.8) | -0.18 / 0.86 |
| ICU days before initiation of MV | 0.1 (0-1.1) | 0.0 (0-0.5) | -0.98 / 0.33 |
| ICU days from initiation of MV until ICU discharge (protocol days) | 11 (8.1-19) | 11 (7.2-22.1) | -0.18 / 0.86 |
| ***Implementation and content of intervention (median (IQR))*** | | | |
| ICU days including physiotherapy (intervention days) | 9 (5-17) | 7 (3-16) | -1.29 / 0.20 |
| Intervention days, with adequate sedation level (RASS level -1 to +1) | 4 (3-9) | 3 (2-5) | -1.35 / 0.18 |
| Intervention days with upright mobilisation | 4 (2-6) | 2 (1-5) | -1.98 / <0.05 |
| Intervention days with passive mobilisation | 5 (3-11) | 4 (2-14) | -0.76 / 0.45 |
| Intervention sessions | 16 (8-32) | 8 (4-16) | -2.27 / 0.02 |
| Intervention sessions with upright mobilisation | 5 (3-9) | 3 (1-6) | -2.35 / 0.02 |
| ***Milestones achieved on day of protocol (median (IQR))*** | | | |
| First intervention on day | 3 (3-3) | 5 (4-6) | 5.00 / <0.0001 |
| First upright mobilisation session on day | 7.5 (5-13) | 8.5 (6-15) | 0.62 / 0.53 |
| First ambulation session on day | 8 (5-11) | 12 (8-23) | 1.77 / 0.08 |
| | | | **t Value / p** |
| ***Amount of upright mobilisation during ICU stay (mean (SD))*** | | | |
| Proportion of ICU days that included intervention with upright mobilisation | 31% (13.4%) | 22% (17.2%) | 2.23 / 0.03 |
| Proportion of ICU days that included upright mobilisation with any health provider | 35% (16.8%) | 24% (18.4%) | 2.33 / 0.02 |
| ***Main reasons for delay in upright mobilisation for one week or longer (n (%))*** | | | |
| No upright mobilisation for one week or longer after initiation of MV | 15/29 (51.7%) | 13/20* (65%) | |
| Deep sedation | 12/15 (80%) | 12/13 (92.3%) | |
| Vasopressors | 9/15 (60%) | 7/13(53.8%) | |
| Continuous renal replacement therapy | 3/15 (20%) | 4/13 (30.8%) | |

* One missing value

## 4.3 Study III

The cohort consisted of 33 men and 17 women with similar baseline characteristics, severity of illness, ICU-related variables and LOS. The only difference was employment status, in that more women were unemployed and receiving disability benefits ($p<0.01$) (Table 10). The trajectory of physical recovery over the follow-up period over one year after ICU discharge was significantly worse for women than men (Table 11). Multivariate linear regression models, after adjusting for gender and age, showed associations between six exposure variables and the outcome in one or two physical recovery variables measured at 12 months after ICU discharge (Tables 12-14). The baseline exposure variables and their associations with physical recovery variables were: 1) Higher BMI (lower exercise capacity ($p=0.03$)). 2) Higher comorbidity measured with the FCI (lower exercise capacity ($p=0.01$)). 3) Lower self-reported physical function (lower exercise capacity ($p=0.01$) and lower self-reported physical function ($p<0.02$)). 4) Lower functional independence measured with the MBI (lower self-reported physical function ($p=0.04$)). The ICU-related variable was: 5) Lower muscle strength measured at ICU discharge (muscle weakness ($p=0.01$) and lower self-reported physical function ($p=0.03$)). The LOS variable was: 6) Longer hospital stay (muscle weakness ($p<0.02$) and lower exercise capacity ($p<0.03$)).

The results of the multivariate regression models when adjusted only for age showed that the female gender had an association all three physical recovery variables at 12 months after ICU discharge, i.e.: with muscle weakness (Eta-Square 0.21, CI (-0.75 to -0.17), $p=0.003$), with lower exercise capacity (Eta-Square 0.40, CI (-0.87 to -0.40), $p<0.0001$), and with lower self-reported physical function, (Eta-Square 0.14, CI (-0.68 to -0.09), $p=0.01$). The same models, after adjusting for age and each exposure variable at a time, showed that the female gender had an association with muscle weakness at 12 months after ICU discharge for all exposure variables, except for one ICU-related exposure variable (Table 12). Gender did not have an association with muscle strength at 12 months after ICU discharge, when adjusted for age and muscle strength (MRC-SS) at ICU discharge. The same models showed that the female gender had an association with lower exercise capacity at 12 months after ICU discharge adjusted for age and all exposure variables (Table 13). And the same models showed that the female gender had an association with lower self-reported physical function at 12 months after ICU discharge, when adjusted for age and all exposure variables except for four exposure variables (Table 14). Gender did not have an association with self-reported physical function at 12

months after ICU discharge when adjusted for age and employment status, age and self-reported physical function at baseline, age and muscle strength at ICU discharge or age and ICU-AW at ICU discharge.

The results from the multivariate regression models, when adjusted for gender only, showed that age was associated with lower exercise capacity at 12 months after ICU discharge (Eta-Square 0.20, CI (-0.68 to -0.21), $p<0.001$). The same models, after adjusting for gender and each exposure variable at a time, showed that age was associated with lower exercise capacity at 12 months after ICU discharge for all exposure variables except for two exposure variables. Age did not have an association with exercise capacity at 12 months after ICU discharge when adjusted for gender and employment status, nor when adjusted for gender and ICU-AW at ICU discharge (Table 13).

Table 10. Comparison between women and men

| | Women n=17 | | Men n=33 | | p value |
|---|---|---|---|---|---|
| ***Baseline characteristics*** | | | | | |
| Age | 63 | (60-71) | 62 | (54-73) | .52 |
| Residence, home | 17 | 100% | 32 | 97% | .47 |
| Married or cohabiting | 12 | 71% | 21 | 64% | .62 |
| Elementary school education (ISCED 1,2) | 11 | 65% | 16 | 48% | .28 |
| Employment status: | | | | | <0.01 |
| Employed | 3 | 18% | 17 | 52% | |
| Retired | 5 | 29% | 13 | 39% | |
| Unemployment | 3 | 18% | 1 | 3% | |
| Disability | 6 | 35% | 2 | 6% | |
| Regular exercise (≥ 150 min/week) | 1 | 7% | 10 | 30% | .06 |
| BMI (kg/m$^2$) | 36.0 | (28.4-43.7) | 30.8 | (28.9-32.7) | .07 |
| Modified Barthel Index (MBI) | 100 | (100-100) | 100 | (100-100) | .06 |
| SF-36v2 PF domain (raw score) | 60.0 | (41.3-78.7) | 72.5 | (63.6-81.4) | .16 |
| Charlson Comorbidity Index (CCI) | 3 | (2-5) | 2 | (0-4) | .09 |
| Functional Comorbidity Index (FCI) | 2 | (2-4) | 2 | (1-4) | .08 |
| ***Severity of illness*** | | | | | |
| ICU admission diagnosis: | | | | | .39 |
| Severe sepsis / septic shock | 9 | 53% | 14 | 42% | |
| Pneumonia | 4 | 24% | 4 | 12% | |
| Acute respiratory failure | 2 | 12% | 2 | 6% | |
| Multi-trauma | 0 | 0% | 6 | 18% | |
| Major elective surgery | 0 | 0% | 3 | 9% | |
| Cardiac | 1 | 6% | 2 | 6% | |
| Other | 1 | 6% | 2 | 6% | |
| APACHE II score | 23.8 | (18.6-29.0) | 22.4 | (19.2-25.5) | .61 |
| Sepsis during ICU stay | 11 | 65% | 15 | 45% | .20 |
| ARDS during ICU stay | 6 | 35% | 9 | 27% | .56 |
| Renal replacement therapy in ICU | 5 | 29% | 7 | 21% | .52 |
| ***ICU variables*** | | | | | |
| No upright mobilisation ≥ first 7 days | 10 | 59% | 18 | 56% | .86 |
| Upright mobilisation started on day | 8 | (5-22) | 8 | (5-13) | .43 |
| Duration of MV (days) | 15 | (6-22) | 7.5 | (5-11) | .07 |
| MRC-SS at ICU discharge | 36.9 | (28.3-45.5) | 43.1 | (37.7-48.6) | .20 |
| MRC-SS at ICU discharge, % of full score | 61.5 | (47.2-75.8) | 71.9 | (62.8-81.0) | .20 |
| ICU-AW indication (MRC-SS < 48) | 8 | 80% | 13 | 57% | .20 |
| MBI at ICU discharge | 2 | (0-5) | 7 | (0-16) | .21 |
| ***Length of stay (LOS)*** | | | | | |
| ICU LOS (days) | 19.2 | (8-24) | 10.7 | (7-19) | .12 |
| Hospital LOS (days) | 40.6 | (24–57) | 28 | (16-50) | .16 |

Data is presented as mean (95%CI), median (IQR) or number (%). Abbreviations: APACHE II score, Acute Physiology and Chronic Health Evaluation II score; ARDS, acute respiratory distress syndrome; BMI, body mass index; CI, confidence interval; ICU, intensive care unit; ICU-AW, intensive care unit acquired weakness; ISCED, International Standard Classification of Education; IQR, inter-quartile range; MBI, Modified Barthel Index; MRC-SS, Medical Research Council sum-score; SF-36v2 PF domain, Short-Form 36 Health Survey version 2 Physical Function domain. ICU-AW indication is defined: MRC-SS < 48 points; Upright mobilisation is defined: Sitting on edge of bed, or standing up or walking with or without assistance consistent with level 3-10 on the ICU Mobility Scale, including assisted active, active exercises, functional, balance and transfer training in those positions.

Table 11. Trajectory of physical recovery 3, 6 and 12 months after ICU discharge

| | Women n=17 | | Men n=33 | | p value |
|---|---|---|---|---|---|
| ***3 months after ICU discharge*** | | | | | |
| MRC-SS | 48.7 | (45.4-51.9) | 56.0 | (54.2-57.8) | <0.001 |
| MRC-SS, % of full score | 81.1 | (75.7-86.6) | 93.3 | (90.4-96.3) | <0.001 |
| 6MW distance | 380.6 | (306.0-455.2) | 480.3 | (414.8-545.7) | 0.09 |
| 6MW distance, % predicted value | 61.8 | (51.1-72.6) | 68.9 | (60.1-77.8) | 0.37 |
| SF-36v2 PF domain (raw score) | 30.8 | (14.9-46.6) | 57.9 | (46.5-69.3) | <0.01 |
| SF-36v2 PF domain (norm-based score) | 31.0 | (25.0-37.1) | 41.4 | (37.1-45.8) | <0.01 |
| ***6 months after ICU discharge*** | | | | | |
| MRC-SS | 50.1 | (48.5-51.7) | 57.3 | (56.1-58.6) | <0.001 |
| MRC-SS, % of full score | 83.5 | (80.8-86.2) | 95.6 | (93.5-97.7) | <0.001 |
| 6MW distance | 346.0 | (230.3-461.7) | 539.8 | (480.6-599.0) | <0.001 |
| 6MW distance, % predicted value | 55.9 | (38.3-73.6) | 77.9 | (70.1-85.7) | <0.01 |
| SF-36v2 PF domain (raw score) | 28.2 | (15.8-40.6) | 65.2 | (52.9-77.5) | <0.001 |
| SF-36v2 PF domain (norm-based score) | 30.1 | (25.3-34.8) | 44.2 | (39.5-48.9) | <0.001 |
| **12 months after ICU discharge** | | | | | |
| MRC-SS | 54.2 | (51.6-56.7) | 57.8 | (56.7-59.0) | <0.001 |
| MRC-SS, % of full score | 90.3 | (86.0-94.6) | 96.4 | (94.5-98.3) | <0.001 |
| 6MW distance | 281.9 | (132.5-431.3) | 557.3 | (500.5-614.1) | <0.001 |
| 6MW distance, % predicted value | 45.9 | (22.6-69.1) | 81.2 | (73.8-88.5) | <0.001 |
| SF-36v2 PF domain (raw score) | 43.2 | (30.3-56.1) | 66.0 | (55.3-76.7) | 0.01 |
| SF-36v2 PF domain (norm-based score) | 35.8 | (30.9-40.7) | 44.5 | (40.4-48.6) | 0.01 |

Data is presented as mean (95%CI). Abbreviations: CI, confidence interval; ICU, intensive care unit; MRC-SS, Medical Research Council Sum-Score; SF-36v2 PF, Short-Form 36 Health Survey version 2 Physical Function domain; 6MW distance, six-minute walk distance. MRC-SS measures manual muscle strength in six muscle groups bilaterally (shoulder abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, ankle dorsiflexors) with a MRC-SS range from 0 to 60. Reference value for % predicted value in 6MW distance for gender and age: Gibbons WJ. et al. 2001. SF-36v2 PF domain raw score,range from 0-100, higher score indicating better physical function; SF-26v2 PF norm-based score has a mean of 50 with a SD = 10.

Table 12. Exposure variables and the physical recovery variable muscle strength at 12 months after ICU discharge

| Model: Linear Regression Model<br>Dependent Variable: MRC-SS at 12 months after ICU discharge<br>Parameter Estimates | | | | |
|---|---|---|---|---|
| Variable | Standardised Estimate | Squared Semipartial r / Eta-Square | 95% CI | p Value |
| Gender | -0.46 | 0.21 | -0.75 to -0.17 | 0.003 |
| Age | -0.27 | 0.07 | -0.56 to 0.02 | 0.065 |
| Married or cohabiting | 0.05 | 0.00 | -0.25 to 0.35 | 0.745 |
| Gender | -0.46 | 0.21 | -0.76 to -0.17 | 0.003 |
| Age | -0.28 | 0.08 | -0.58 to 0.02 | 0.065 |
| Elementary school education (ISCED 1.2) | 0.04 | 0.00 | -0.26 to 0.34 | 0.789 |
| Gender | -0.47 | 0.22 | -0.77 to -0.17 | 0.003 |
| Age | -0.27 | 0.07 | -0.56 to 0.02 | 0.068 |
| Employment status | | 0.01 | | 0.955 |
| Gender | | 0.17 | | 0.008 |
| Age | | 0.01 | | 0.557 |
| Regular exercise (>150 min/week) | 0.11 | 0.01 | -0.20 to 0.41 | 0.473 |
| Gender | -0.43 | 0.18 | -0.73 to -0.13 | 0.006 |
| Age | -0.29 | 0.08 | -0.58 to 0.01 | 0.055 |
| BMI at baseline | -0.13 | 0.02 | -0.44 to 0.19 | 0.420 |
| Gender | -0.41 | 0.17 | -0.72 to -0.10 | 0.012 |
| Age | -0.29 | 0.08 | -0.58 to 0.00 | 0.053 |
| Modified Barthel Index at baseline | -0.02 | 0.00 | -0.31 to 0.28 | 0.913 |
| Gender | -0.46 | 0.21 | -0.75 to -0.17 | 0.003 |
| Age | -0.27 | 0.07 | -0.57 to 0.02 | 0.071 |
| SF-36v2 PF domain | -0.09 | 0.01 | -0.44 to 0.26 | 0.593 |
| Gender | -0.45 | 0.20 | -0.77 to -0.12 | 0.008 |
| Age | -0.32 | 0.10 | -0.65 to 0.01 | 0.054 |
| Charlson Comorbidity Index | 0.22 | 0.05 | -0.10 to 0.53 | 0.169 |
| Gender | -0.48 | 0.23 | -0.77 to -0.19 | 0.002 |
| Age | -0.36 | 0.13 | -0.67 to -0.05 | 0.025 |
| Functional Comorbidity Index | -0.15 | 0.02 | -0.47 to 0.16 | 0.325 |
| Gender | -0.43 | 0.18 | -0.72 to -0.14 | 0.005 |
| Age | -0.22 | 0.05 | -0.53 to 0.09 | 0.152 |
| ICU admission diagnosis | | 0.11 | | 0.521 |
| Gender | | 0.15 | | 0.011 |
| Age | | 0.10 | | 0.034 |
| APACHE II | 0.10 | 0.01 | -0.21 to 0.41 | 0.524 |
| Gender | -0.46 | 0.21 | -0.75 to -0.17 | 0.003 |
| Age | -0.30 | 0.09 | -0.61 to 0.01 | 0.054 |

| | | | | |
|---|---|---|---|---|
| Sepsis during ICU stay | -0.07 | 0.00 | -0.38 to 0.24 | 0.665 |
| Gender | -0.44 | 0.19 | -0.74 to -0.14 | 0.005 |
| Age | -0.26 | 0.07 | -0.56 to 0.04 | 0.089 |
| ARDS during ICU stay | -0.04 | 0.00 | -0.35 to 0.27 | 0.799 |
| Gender | -0.46 | 0.21 | -0.75 to -0.17 | 0.003 |
| Age | -0.28 | 0.08 | -0.60 to 0.03 | 0.073 |
| Renal replacement therapy in ICU | 0.21 | 0.04 | -0.07 to 0.50 | 0.137 |
| Gender | -0.48 | 0.23 | -0.77 to -0.20 | 0.002 |
| Age | -0.29 | 0.08 | -0.57 to 0.00 | 0.048 |
| No upright mobilisation ≥ 1 week | -0.18 | 0.03 | -0.48 to 0.12 | 0.236 |
| Gender | -0.42 | 0.18 | -0.72 to -0.13 | 0.006 |
| Age | -0.24 | 0.06 | -0.54 to 0.06 | 0.108 |
| Upright mobilisation started on day | -0.01 | 0.00 | -0.32 to 0.30 | 0.946 |
| Gender | -0.43 | 0.18 | -0.74 to -0.12 | 0.008 |
| Age | -0.30 | 0.09 | -0.60 to 0.01 | 0.056 |
| Duration of MV | 0.03 | 0.00 | -0.28 to 0.35 | 0.824 |
| Gender | -0.47 | 0.22 | -0.77 to -0.16 | 0.004 |
| Age | -0.28 | 0.08 | -0.58 to 0.02 | 0.069 |
| MRC-SS at ICU discharge | 0.45 | 0.20 | 0.11 to 0.80 | 0.012 |
| Gender | -0.29 | 0.08 | -0.61 to 0.04 | 0.082 |
| Age | -0.15 | 0.02 | -0.48 to 0.19 | 0.375 |
| ICU-AW indication (MRC-SS < 48) | -0.33 | 0.11 | -0.72 to 0.06 | 0.098 |
| Gender | -0.35 | 0.12 | -0.69 to -0.01 | 0.045 |
| Age | -0.13 | 0.02 | -0.52 to 0.26 | 0.488 |
| MBI at ICU discharge | 0.17 | 0.03 | -0.24 to 0.58 | 0.412 |
| Gender | -0.42 | 0.18 | -0.72 to -0.11 | 0.009 |
| Age | -0.16 | 0.03 | -0.56 to 0.23 | 0.412 |
| ICU LOS | 0.04 | 0.00 | -0.28 to 0.35 | 0.813 |
| Gender | -0.47 | 0.22 | -0.78 to -0.16 | 0.004 |
| Age | -0.28 | 0.08 | -0.58 to 0.02 | 0.068 |
| Hospital LOS | -0.35 | 0.12 | -0.64 to -0.07 | 0.017 |
| Gender | -0.34 | 0.12 | -0.63 to -0.06 | 0.020 |
| Age | -0.24 | 0.06 | -0.51 to 0.03 | 0.078 |

Missed data for MRC-SS at 12 months. Female: 3 diseased; 2 telephone/mail contact. Male: 2 diseased; 2 trauma; 3 lost to follow up.

Table 13. Exposure variables and the physical recovery variable exercise capacity at 12 months after ICU discharge

| Model: Linear Regression Model<br>Dependent Variable: 6MW distance at 12months after ICU discharge | | | | |
|---|---|---|---|---|
| **Parameter Estimates** | | | | |
| Variable | Standardised Estimate | Squared Semipartial r / Eta-Square | 95% CI | p Value |
| Age | -0.45 | 0.20 | -0.68 to -0.21 | <.001 |
| Gender | -0.63 | 0.40 | -0.87 to -0.40 | <.0001 |
| Married or cohabiting | 0.04 | 0.00 | -0.22 to 0.30 | 0.756 |
| Gender | -0.64 | 0.41 | -0.88 to -0.39 | <.0001 |
| Age | -0.46 | 0.21 | -0.72 to -0.20 | 0.001 |
| Elementary school education (ISCED 1.2) | -0.11 | 0.01 | -0.35 to 0.13 | 0.365 |
| Gender | -0.61 | 0.37 | -0.85 to -0.37 | <.001 |
| Age | -0.44 | 0.19 | -0.67 to -0.20 | 0.001 |
| Employment status | | 0.03 | | 0.581 |
| Gender | | 0.21 | | <.001 |
| Age | | 0.03 | | 0.137 |
| Regular exercise (> 150 min/week) | 0.23 | 0.05 | 0.00 to 0.46 | 0.055 |
| Gender | -0.58 | 0.34 | -0.81 to -0.36 | <.0001 |
| Age | -0.48 | 0.23 | -0.71 to -0.26 | 0.000 |
| BMI at baseline | -0.27 | 0.07 | -0.52 to -0.03 | 0.030 |
| Gender | -0.52 | 0.27 | -0.76 to -0.28 | <.0001 |
| Age | -0.51 | 0.26 | -0.73 to -0.28 | <.000 |
| Modified Barthel Index at baseline | 0.14 | 0.02 | -0.11 to 0.40 | 0.254 |
| Gender | -0.59 | 0.35 | -0.83 to -0.34 | <.0001 |
| Age | -0.42 | 0.18 | -0.11 to 0.40 | 0.001 |
| SF-36v2 PF domain at baseline | 0.35 | 0.12 | 0.08 to 0.63 | 0.014 |
| Gender | -0.50 | 0.25 | -0.74 to -0.27 | <.0001 |
| Age | -0.29 | 0.08 | -0.55 to -0.02 | 0.035 |
| Charlson Comorbidity Index | -0.04 | 0.00 | -0.32 to 0.24 | 0.795 |
| Gender | -0.62 | 0.38 | -0.87 to -0.38 | <.000 |
| Age | -0.43 | 0.18 | -0.71 to -0.16 | 0.003 |
| Functional Comorbidity Index | -0.30 | 0.09 | -0.53 to -0.07 | 0.014 |
| Gender | -0.54 | 0.29 | -0.77 to -0.32 | <.0001 |
| Age | -0.38 | 0.14 | -0.60 to -0.16 | <.002 |
| ICU admission diagnosis | | 0.16 | | 0.458 |
| Gender | | 0.28 | | <.0001 |
| Age | | 0.08 | | 0.002 |
| APACHE II | -0.11 | 0.01 | -0.36 to 0.15 | 0.400 |
| Gender | -0.62 | 0.38 | -0.86 to -0.38 | <.0001 |
| Age | -0.41 | 0.17 | -0.66 to -0.16 | 0.003 |

| | | | | |
|---|---|---|---|---|
| Sepsis during ICU stay | -0.13 | 0.02 | -0.39 to 0.12 | 0.293 |
| Gender | -0.59 | 0.35 | -0.84 to -0.35 | <.0001 |
| Age | -0.42 | 0.18 | -0.66 to -0.17 | <.002 |
| ARDS during ICU stay | 0.06 | 0.00 | -0.21 to 0.33 | 0.646 |
| Gender | -0.62 | 0.38 | -0.86 to -0.38 | <.0001 |
| Age | -0.42 | 0.18 | -0.69 to -0.16 | <.003 |
| Renal replacement therapy in ICU | 0.21 | 0.04 | -0.02 to 0.43 | 0.072 |
| Gender | -0.65 | 0.42 | -0.88 to -0.42 | <.0001 |
| Age | -0.45 | 0.20 | -0.68 to -0.23 | <.0001 |
| No upright mobilisation ≥ 1 week | 0.06 | 0.00 | -0.19 to 0.31 | 0.620 |
| Gender | -0.64 | 0.41 | -0.89 to -0.39 | <.0001 |
| Age | -0.44 | 0.19 | -0.69 to -0.20 | 0.001 |
| Upright mobilisation started on day | -0.02 | 0.00 | -0.28 to 0.25 | 0.885 |
| Gender | -0.61 | 0.37 | -0.88 to -0.35 | <.0001 |
| Age | -0.44 | 0.19 | -0.69 to -0.18 | 0.001 |
| Duration of MV | -0.11 | 0.01 | -0.37 to 0.15 | 0.392 |
| Gender | -0.59 | 0.35 | -0.85 to -0.34 | <.0001 |
| Age | -0.43 | 0.18 | -0.67 to -0.18 | 0.001 |
| MRC-SS at ICU discharge | 0.25 | 0.06 | -0.16 to 0.65 | 0.219 |
| Gender | -0.42 | 0.18 | -0.80 to -0.03 | 0.035 |
| Age | -0.38 | 0.14 | -0.73 to -0.04 | 0.033 |
| ICU-AW indication (MRC-SS <48) | -0.20 | 0.04 | -0.61 to 0.21 | 0.329 |
| Gender | -0.47 | 0.22 | -0.83 to -0.11 | 0.013 |
| Age | -0.36 | 0.13 | -0.75 to 0.02 | 0.063 |
| MBI at ICU discharge | -0.05 | 0.00 | -0.39 to 0.29 | 0.774 |
| Gender | -0.65 | 0.42 | -0.91 to -0.38 | <.0001 |
| Age | -0.48 | 0.23 | -0.80 to -0.16 | <.005 |
| ICU LOS | -0.08 | 0.01 | -0.33 to 0.18 | 0.551 |
| Gender | -0.61 | 0.37 | -0.86 to -0.35 | <.0001 |
| Age | -0.44 | 0.19 | -0.68 to -0.19 | <.001 |
| Hospital LOS | -0.27 | 0.07 | -0.52 to -0.03 | 0.028 |
| Gender | -0.51 | 0.26 | -0.76 to -0.27 | <.0001 |
| Age | -0.45 | 0.20 | -0.67 to -0.23 | 0.000 |

Missed data for 6MW test at 12 months. Female: 3 diseased; 1 trauma; 3 declined outcome measure; 2 telephone/mail contact. Male: 2 diseased; 3 lost to follow up; 4 declined outcome measure.

Table 14. Exposure variables and the physical recovery variable self-reported physical function at 12 months after ICU discharge

| Model: Linear Regression Model<br>Dependent Variable: SF-36v2 Physical Function domain at 12 months after ICU discharge | | | | |
|---|---|---|---|---|
| **Parameter Estimates** | | | | |
| Variable | Standardised Estimate | Squared Semipartial r / Eta-Square | 95% CI | p Value |
| Gender | -0.38 | 0.14 | -0.68 to -0.09 | 0.013 |
| Age | -0.18 | 0.03 | -0.47 to 0.12 | 0.236 |
| Married or cohabiting | -0.20 | 0.04 | -0.50 to 0.10 | 0.188 |
| Gender | -0.39 | 0.15 | -0.68 to -0.09 | 0.012 |
| Age | -0.13 | 0.02 | -0.43 to 0.18 | 0.404 |
| Elementary school education (ISCED 1.2) | -0.22 | 0.05 | -0.51 to 0.08 | 0.145 |
| Gender | -0.36 | 0.13 | -0.65 to -0.06 | 0.018 |
| Age | -0.17 | 0.03 | -0.46 to 0.13 | 0.256 |
| Employment status | | 0.04 | | 0.622 |
| Gender | | 0.07 | | 0.076 |
| Age | | 0.00 | | 0.641 |
| Regular exercise (>150 min/week) | 0.17 | 0.03 | -0.14 to 0.49 | 0.262 |
| Gender | -0.33 | 0.11 | -0.64 to -0.02 | 0.037 |
| Age | -0.20 | 0.04 | -0.50 to 0.10 | 0.186 |
| BMI at baseline | -0.15 | 0.02 | -0.47 to 0.17 | 0.352 |
| Gender | -0.33 | 0.11 | -0.65 to -0.01 | 0.041 |
| Age | -0.20 | 0.04 | -0.50 to 0.10 | 0.186 |
| Modified Barthel Index at baseline | 0.30 | 0.09 | 0.01 to 0.59 | 0.041 |
| Gender | -0.37 | 0.14 | -0.65 to -0.08 | 0.013 |
| Age | -0.12 | 0.01 | -0.41 to 0.17 | 0.402 |
| SF-36v2 PF domain at baseline | 0.39 | 0.15 | 0.07 to 0.70 | 0.018 |
| Gender | -0.29 | 0.08 | -0.58 to 0.00 | 0.054 |
| Age | -0.03 | 0.00 | -0.34 to 0.28 | 0.834 |
| Charlson Comorbidity Index | -0.15 | 0.02 | -0.48 to 0.18 | 0.362 |
| Gender | -0.38 | 0.14 | -0.68 to -0.08 | 0.014 |
| Age | -0.11 | 0.01 | -0.44 to 0.22 | 0.501 |
| Functional Comorbidity Index | -0.24 | 0.06 | -0.54 to 0.07 | 0.127 |
| Gender | -0.35 | 0.12 | -0.64 to -0.05 | 0.022 |
| Age | -0.11 | 0.01 | -0.41 to 0.19 | 0.461 |
| ICU admission diagnosis | | 0.13 | | 0.459 |
| Gender | | 0.09 | | 0.048 |
| Age | | 0.04 | | 0.183 |
| APACHE II | -0.12 | 0.01 | -0.44 to 0.19 | 0.435 |
| Gender | -0.38 | 0.14 | -0.68 to -0.08 | 0.014 |
| Age | -0.14 | 0.02 | -0.45 to 0.18 | 0.389 |

| | | | | |
|---|---|---|---|---|
| Sepsis during ICU stay | -0.04 | 0.00 | -0.36 to 0.28 | 0.809 |
| Gender | -0.37 | 0.14 | -0.69 to -0.05 | 0.023 |
| Age | -0.17 | 0.03 | -0.48 to 0.14 | 0.268 |
| ARDS during ICU stay | 0.17 | 0,03 | -0.15 to 0.48 | 0.293 |
| Gender | -0.39 | 0,15 | -0.68 to -0.09 | 0.012 |
| Age | -0.12 | 0,01 | -0.44 to 0.19 | 0.443 |
| Renal replacement therapy in ICU | 0.07 | 0.00 | -0.24 to 0.37 | 0.660 |
| Gender | -0.39 | 0.15 | -0.70 to -0.09 | 0.012 |
| Age | -0.18 | 0.03 | -0.48 to 0.12 | 0.231 |
| No upright mobilisation ≥ 1 week | 0.04 | 0.00 | -0.28 to 0.35 | 0.820 |
| Gender | -0.37 | 0.14 | -0.68 to -0.06 | 0.020 |
| Age | -0.22 | 0.05 | -0.53 to 0.09 | 0.160 |
| Upright mobilisation started on day | 0.00 | 0.00 | -0.32 to 0.32 | 0.978 |
| Gender | -0.40 | 0.16 | -0.72 to -0.09 | 0.015 |
| Age | -0.17 | 0.03 | -0.49 to 0.14 | 0.265 |
| Duration of MV | -0.17 | 0.03 | -0.48 to 0.15 | 0.284 |
| Gender | -0.34 | 0.12 | -0.65 to -0.04 | 0.030 |
| Age | -0.14 | 0.02 | -0.44 to 0.16 | 0.350 |
| MRC-SS at ICU discharge | 0.42 | 0.18 | 0.04 to 0.80 | 0.033 |
| Gender | -0.23 | 0.05 | -0.59 to 0.15 | 0.215 |
| Age | -0.00 | 0.00 | -0.37 to 0.36 | 0.99 |
| ICU-AW indication (MRC-SS <48) | -0.38 | 0.14 | -0.79 to 0.04 | 0.075 |
| Gender | -0.29 | 0.08 | -0.66 to 0.07 | 0.112 |
| Age | 0.06 | 0.00 | -0.35 to 0.47 | 0.755 |
| MBI at ICU discharge | 0.14 | 0.02 | -0.27 to 0.56 | 0.487 |
| Gender | -0.37 | 0.14 | -0.68 to -0.05 | 0.024 |
| Age | -0.08 | 0.01 | -0.48 to 0.32 | 0.690 |
| ICU LOS | -0.09 | 0.01 | -0.41 to 0.22 | 0.548 |
| Gender | -0.36 | 0.13 | -0.67 to -0.05 | 0.024 |
| Age | -0.16 | 0.03 | -0.46 to 0.15 | 0.300 |
| Hospital LOS | -0.22 | 0.05 | -0.52 to 0.09 | 0.167 |
| Gender | -0.32 | 0.10 | -0.62 to -0.01 | 0.045 |
| Age | -0.17 | 0.03 | -0.46 to 0.13 | 0.261 |

Missed data for SF-36v2 at 12 months. Female: 3 diseased. Male: 2 diseased; 3 lost to follow up; 1 declined outcome measure.

# 5 Discussion

The results of this thesis extend the findings of previously published intervention studies, guidelines, and mobilisation protocols. First, our findings enhance the knowledge base and understanding of the clinical decision-making processes used by physiotherapists when they position ICU patients upright and progressively mobilise them, particularly when patients are mechanically ventilated. The physiotherapists´ approach to upright mobilisation was unique due to their professional background in exercise physiology, movement mechanics and mobility, and movement dysfunction. This knowledge enabled them to extend mobilisation beyond patient transfers, from supine to an upright position sitting on the edge of the bed, towards individualised and response-driven interventions that included mobilising upright and eliciting effective and safe patient responses. Second, the clinical RCT resulted in being statistically underpowered due to its pre-set three-year timeframe. Thus, the intensive twice-daily mobilisation group was not shown to exhibit superior primary or secondary outcomes, compared with the once-daily mobilisation group, as hypothesised. The twice-daily group did not start upright mobilisation early as planned, apparently due to their deep sedation for days after initiation of MV. Both study groups showed poor long-term physical recovery. This finding led to the last study that examined associations between the exposure variables (baseline characteristics, severity of illness variables, ICU-related variables and LOS), and three physical recovery variables, (muscle strength, exercise capacity, and self-reported physical function), measured at one year after ICU discharge. We observed that women tended to have worse physical recovery than men in all three physical recovery variables. Furthermore, an association was observed, independent of gender and age, with having more functional comorbidities (FCI), higher BMI, lower functional independence (MBI), and lower self-reported physical function at baseline, lower muscle strength at ICU discharge, longer hospital stays, and poorer physical recovery at one year after ICU discharge. Below the results are discussed in more detail, followed by a reflection on the clinical implications of this programme of research, and finally recommendations for future research are described.

## 5.1 Physiothrapists clinical reasoning during upright mobilisation in the ICU

To the best of our knowledge this is the first study that has investigated the clinical reasoning and decision-making processes of physiotherapists during the specific task of initiating and progressing mobilisation to an upright position in patients who are critically ill. A qualitative methodology was used, consisting of an observation phase of 12 physiotherapists, each initiating and progressing an upright mobilisation session with a single patient, followed by a semi-structured interview about the mobilisation session and mobilisation of critically ill patients who are critically ill and mechanically ventilated in general.

The first category that was identified in study I was called Patient. Three out of six subcategories in category Patient are somewhat similar to the results of a qualitative study using an in-depth interview with 12 acute care physiotherapists (Chipchase & Prentice, 2006). They examined how physiotherapists assessed a patient´s capacity for mobilisation and identified the following indicators: 1) History or background indicator representing the patient's mobility status and comorbidities. 2) Physiological parameters of stability or function within a body system. 3) Observational indicators, such as skin colour and the patient´s position in bed and, 4) Physical indicators representing an assessment of the patient's movement capability. These indicators are somewhat comparable to the subcategories of Medical history, Current status and Physical function, identified in study I. However, the results of study I extend the findings of Chipchase and Prentice (Chipchase & Prentice, 2006), by including the physiotherapists´ evaluation of the patient's cognitive function, and the importance of ensuring motivation and cooperation from the patient during the mobilisation. Involving the patient in the decision-making process is consistent with findings reporting the importance of sharing the clinical decision-making with patients to enhance their cooperation (Holdar et al., 2013). Critically ill patients who have the ability, usually wish to be involved in care decision-making (Lindberg et al., 2015).

The second category identified in study I, ICU context, described multiple influences on a physiotherapist's clinical reasoning and decision-making process during upright mobilisation of a patient who is critically ill. The subcategories are: Team culture, Nurses, Physicians, Setting, Life supporting equipment, Beds and Transfer aids. Similar findings have been reported before (Chipchase & Prentice, 2006; Smith et al., 2007). Smith and

colleagues (2007) identified physical factors such as furniture and equipment, organisational factors such as communication, and socio-professional factors such as the actions and decisions of other health professionals, as being influential in the decision-making of physiotherapists in acute care (Smith et al., 2007). Additionally, studies have reported that factors such as technology and the physical environment also influence physiotherapists' mobilisation strategies (Chipchase & Prentice, 2006; Smith et al., 2007).

In study 1, the physiotherapists assumed a high level of professional responsibility, demonstrating leadership when it came to initiating and directing the mobilisation of critically ill patients, especially those with complications. Correspondingly, this influenced the team culture in the participating ICUs which was favourable towards moving and positioning patients upright. This augmented teamwork culture has been reflected in mobilisation quality assurance planning when front-line staff are engaged (Hopkins et al., 2007). Unit culture has also been reported as a major barrier to mobilising patients in the ICU (Barber et al., 2015); however, this was not consistent with our findings. The findings of study I identified categories that related uniquely to the physiotherapists themselves. Smith and colleagues (2007), identified factors that influenced acute care cardiorespiratory physiotherapists' decision-making, such as their experience, unique knowledge base, professional identity, and preferred practice model (Smith et al., 2007) which is consistent with our findings. In addition, in study I, the physiotherapists´ communication skills and educational role, in relation to both patients and ICU staff, were identified as important factors in their decision-making, which is consistent with the findings of other studies (Masley et al., 2011; Smith et al., 2008). Lack of confidence in handling life-support equipment such as ETTs has been reported in other team contexts (Holdsworth et al., 2015). A recent study conducted in four metropolitan hospitals reported that physiotherapists, nurses, and physicians identified sedation and the presence of an ETT to be the most important factors in the decision not to commence out of bed mobilisation (defined as targeted exercise with patient participation to a sitting position on the edge of the bed or out of bed) (Berney et al., 2019). The experienced physiotherapists in study I did not consider the ETT to be a barrier, but preferred that the nurse handle the ETT during upright mobilisation while the physiotherapist was responsible for the security of the patient in the mobilisation. However, less experienced physiotherapists experienced some lack of confidence in mobilising patients who were mechanically ventilated with an ETT. They were inclined to rely on advice from the ICU nurse regarding whether a patient was

ready to be mobilised to an upright position. Recommendations for safety criteria during active mobilisation of adult patients who are mechanically ventilated with an ETT have been published based on an expert consensus, to minimise the risk of adverse events (Hodgson, C. L. et al., 2014). The physiotherapists participating in study I discussed the importance of educating and supporting ICU nurses to ensure effective upright patient mobilisation.

Our findings highlighted the physiotherapists' unique approach when mobilising patients who are critically ill, beyond the transfer itself, from a supine position to sitting on the edge of the bed, through the intervention towards the expected outcome. This process requires specialised knowledge in exercise physiology, movement mechanics and mobility, and movement dysfunction. This is also supported by previous findings that physiotherapists in acute settings have knowledge and expertise about movement and function, distinguishing them from nurses, for example, who also mobilise patients (Masley et al., 2011), but not prescriptively, i.e., with a view to enhancing the trajectory towards functional independence. The health professional´s background affects how he or she defines and implements early mobilisation (Clarissa et al., 2019). Physiotherapists have been reported to achieve a higher level of mobilisation resulting in a higher number of patients sitting in a chair, standing and ambulating, than nurses (Garzon-Serrano et al., 2011).

Study I reports on the physiotherapists' ongoing assessment and evaluation of the critically ill patients during the mobilisation session, which was the foundation for predicting patients' capacity to effectively and safely tolerate the treatment intervention, and at the same time elicit the optimal response; thus mobilisation was individualised and response-driven. Similar moment-to-moment evaluation and modification of the mobilisation parameters was based on the patient's responses as the session proceeded, as has been described previously (Masley et al., 2011), and constitutes the foundation for effective and safe patient mobilisation. The physiotherapists' clinical reasoning regarding the mobilisation intervention was similar to the principle of FITT, which stands for frequency, intensity, time or duration, and type; these are established components of exercise training (ACSM, 2010). In study 1, the physiotherapists structured the mobilisation intervention by choosing a type of mobilisation, the appropriate exercise intensity for the patient, the duration of the intervention, connecting these factors with how often during the day a particular patient was expected to be mobilised. This intervention was individualised and based on constant assessment of the

patient's responses to mobilisation moment-to-moment. This supports the view that physiotherapists in acute care make decisions about exercise intensity and duration within one session based on patient assessment, as well as deciding the frequency of mobilisation over the day (Masley et al., 2011).

Possible barriers to upright mobilisation of critically ill patients and their solutions were discussed in the semi-structured interviews. In study I, the physiotherapists did not consider morbid obesity to hinder upright mobilisation. The solution was to engage more staff, use transfer aids and be aware of one's own ergonomics. Life supporting equipment and the ventilator were discussed and how to adjust these before mobilising the patient. If a patient was intubated with an ETT, how to secure the tubes was discussed in the interviews. Many physiotherapists preferred that the nurse secure the ETT during mobilisation while the physiotherapist ensured the safety of the patient during upright mobilisation. ICU beds that were not possible to lower sufficiently for the patient's feet to touch the floor while sitting on the edge of the bed were considered a barrier, but the solution was to use an aerobic stepper platform for standing up because there was space for the patient and the physiotherapist and one assistant to stand on the platform. The importance of appropriate transfer aids was discussed as a facilitator of upright mobilisation in patients who were overweight. Barriers to mobilisation of critically ill patients in general have been reported in other studies. One study that included physiotherapists, nurses and physicians, considered that barriers included the presence of an ETT, sedation and lines, communication factors including identification of appropriate staff for mobilising patients, and lack of resources such as staff, equipment and training (Barber et al., 2015). Those factors, however, were not identified as barriers in study I. In another study, physiotherapists and nurses reported risk of self-injury and excess work stress as barriers (Jolley et al., 2014). A third study has reported increased workload and concerns that a patient was haemodynamically unstable, or nervousness about losing lines or tubes as barriers for implementation of an early rehabilitation programme (Eakin et al., 2015). In study I, lack of resources or increased work load was not mentioned by the physiotherapists. A multi-component package of the evidence-based practice of Awakening and Breathing Coordination, Delirium management and Early mobility has improved outcomes for mechanically ventilated adults (Balas et al., 2014). However, the implementation is complex and challenging (Costa et al., 2017), and a thematic content analysis identified 107 barriers to its implementation, divided into four classes:1) Patient-related: Lack of

cooperation and instability and safety concerns. 2) Clinician-related: Concerns about staff and patient safety, safety of tubes, catheters and wires, to name a few. 3) Protocol-related barriers, and 4) ICU contextual barriers: Safety culture, physical environment such as equipment and resources. The barriers identified by Costa and colleagues (2017) are somewhat similar to the three categories and two factors the physiotherapists in study I contemplated when they were initiating and progressing the mobilisation of a critically ill patient to an upright position. The categories are: Patient, ICU context, and Physiotherapist, and the encompassing factors are: Safety & wellbeing and Barriers & solutions. In fact, those similarities relate to the general aspects of the results of study I, but the categories: Transfer, FITT parameters and Expected outcome as well as the encompassing factors: Continuous assessment & intervention intertwined and Individualised & response-driven intervention are purely physiotherapeutic in nature and reflect the physiotherapists' unique approach to upright mobilisation built on their knowledge base as physiotherapists, namely their knowledge of exercise physiology, movement mechanics and mobility, and movement dysfunction.

The emphasis of the physiotherapists on progressive upright mobilisation being individualised and response-driven vs. protocol-driven was apparent in our findings. This is somewhat distinct from reports of guidelines that provide specific protocols with well-defined progressions (Gosselink et al., 2011; Hodgson et al., 2016; Morris et al., 2008; Sommers et al., 2015). Our findings suggested the principles for prescribing individualised and response-driven upright mobilisation warrant elucidation. Such principles, consistent with the FITT components, warrant elucidation, specifically, to refine the clinical reasoning and the decision-making processes involved in mobilising patients in the ICU. In turn, this will result in refinement of the assessments and treatment protocols outlined in established guidelines to date.

## 5.2 Intensive twice-daily upright mobilisation compared with once-daily mobilisation

The hypothesis was not supported that intensive twice-daily upright mobilisation, compared with once-daily mobilisation, reduces the duration of MV, ICU and hospital LOS, and improves self-reported health-related quality of life and performance-based physical function in patients who are mechanically ventilated for over 48 hours. Although the study was underpowered, both study groups showed poor physical health-related quality of life and low exercise capacity one year after ICU discharge.

Baseline characteristics, comorbidities, admission diagnoses and disease severity were similar amongst the two groups. All but one participant in the study lived at home, and all 50 were ambulating and independent functionally before the critical illness that led to the ICU admission. They had a high disease severity score at admission and high comorbidity. Close to 30% developed ARDS during the ICU stay and over 60% had an indication of ICU-AW at ICU discharge, with muscle strength (measured with the MRC-SS) lower than 48 (De Jonghe et al., 2002). The mortality rate was low despite high APACHE II score: one in each group died within 30 days, and three in the twice-daily group and two in the once-daily group died within a year.

The twice-daily mobilisation group started upright mobilisation later than expected, on day seven after initiation of MV, and the once-daily mobilisation group on day eight. Fifteen patients in the twice-daily group did not mobilise to an upright position (ICU Mobility Scale, level 3 or higher) (Hodgson, C. et al., 2014) for one week or longer after initiation of MV. Out of the 15 patients that did not mobilise to an upright position for one week or longer, 12 patients were deeply sedated during that time and nine were on continuous infusion of one to three potent vasoactive drugs (vasopressors and inotropes). The deep sedation for days after initiation is likely to have reduced the frequency of upright mobilisation sessions in this group, together with cardiovascular instability as manifested by the use of vasoactive support. Sedation has been reported to hinder physical activity measured objectively in an ICU (Beach et al., 2017), and a recent publication suggested that ICU practitioners may be reluctant to reduce sedation in ventilated patients (Berney et al., 2019). However, a study performed in a cardiothoracic setting reported a minimal risk of performing active in-bed or out of bed exercises for mechanically ventilated patients on vasoactive support, as long as a holistic clinical assessment had been performed prior to initiation of the exercise rehabilitation (Boyd et al., 2018).

Interestingly, even though the twice-daily group started upright mobilisation later than planned, they received one or more sessions of upright mobilisation sitting on the edge of the bed or higher level of mobilisation (ICU Mobility Scale, level 3 or higher) on 35% of ICU days. This is a greater or similar volume of upright mobilisation during the ICU stay than has been reported previously. In United States, 27% of total patient days included mobilisation to a sitting position on the edge of the bed or higher level of mobilisation (Jolley et al., 2017). In Germany, 24% of patients were mobilised to a sitting position on the edge of the bed or higher level of mobilisation in one day point prevalence study in 116 ICUs (Nydahl et al.,

2014). In Australia, 38% of all patient days included active mobilisation or active transfer (ICU Mobility Scale, level 4 or higher) (Brock et al., 2018). And finally, 60.2% of patients were mobilised during their ICU stay in 10 ICUs in Australia and 40.1% in nine ICUs in Scotland (Harrold et al., 2015). The question remains, how harmful is a delay in initiating upright mobilisation for critically ill patients? Critically ill patients have displayed muscle wasting after only one week of an ICU stay (Parry & Puthucheary, 2015). The greatest muscle mass loss seems to occur within the first 2-3 weeks of the ICU stay (Gruther et al., 2008). A study of the impact of 10 days of bed rest on healthy individuals, mean age 67 years, showed detrimental effects on lower extremity muscle function and aerobic capacity, with a mean loss of 12% in $VO_2$max (Kortebein et al., 2008). The authors speculated that a more pronounced loss of lower extremity muscle strength and aerobic capacity would occur in ICU patients.

Six RCTs studying physiotherapy interventions in the ICU, including mobilisation, had similar primary outcomes as study II (Burtin et al., 2009; Denehy et al., 2013; Hodgson et al., 2016; Morris et al., 2016; Moss et al., 2016; Wright et al., 2017). Two RCTs however, where the protocol was started within 72 hours from initiation of MV, and included sedation interruption, reported different findings (Schaller et al., 2016; Schweickert et al., 2009). A multi-centre, international RCT in surgical ICUs, which studied goal-directed mobilisation, initiated within 72 hours from initiation of MV, including daily awakening, reported a median (IQR) ICU LOS of seven days (5-12) versus 10 days (6-15) in the control group (p=.005) that received the institutional standard mobilisation including daily awakening trial (Schaller et al., 2016). Another RCT studied early physical therapy and occupational therapy coordinated with daily interruption of sedation in patients on MV in two medical centres (Schweickert et al., 2009). The investigators reported a shorter time on MV, a median (IQR) of 3.4 days (2.3-7.7), compared with 6.1 days (4.0-9.6) in the standard group, where no physiotherapy was routinely provided for the first two weeks of the ICU stay. Those two RCTs included participants with less severe acute illness on ICU admission than was the case in study II, as judged by lower APACHE II scores. The ICU LOS in study II was longer than that of Schaller and colleagues (Schaller et al., 2016), and the duration of MV in study II was longer than that reported by Schweickert and colleagues (Schweickert et al., 2009). This difference may be explained by the higher median age and higher severity of illness scores (APACHE II) in study II.

The secondary outcome of self-reported health-related quality of life in study II reported no difference between groups, which agrees with three other RCTs (Denehy et al., 2013; Moss et al., 2016; Wright et al., 2017). The secondary outcome of 6MW distance in study II reported no difference between groups, which agrees with two RCT trials (Denehy et al., 2013; Wright et al., 2017). However, the mean distance walked in the present study remained below that of the age-matched controls (Gibbons et al., 2001) at 12 months after ICU discharge. Exercise limitation measured with the 6MW distance has been reported up to five years after prolonged ICU stay due to ARDS (Herridge et al., 2011). Muscle strength measured with the MRC-SS in study II showed no difference between the two study groups, similar to the results of other RCTs (Kayambu et al., 2015; McWilliams et al., 2018; Schweickert et al., 2009).

Study II, although underpowered, has increased the knowledge related to several aspects of mobilising patients upright in the ICU. We studied a group of adults who were independent in ADL and who had one or more comorbidities before the onset of severe critical illness that required MV for over 48 hours. No difference was observed in either the primary or secondary outcomes between the intensive twice-daily mobilisation group and the once-daily mobilisation group. The twice-daily group did not start upright mobilisation on day three after initiation of MV as planned. Fifteen patients out of 29 remained on complete bed rest for a week or more after initiation of MV, and 12 of those were on continuous intravenous sedation with sedation levels on the RASS scale from -4 to -5. Despite that, both groups were mobilised upright on similar or more ICU days than previously reported in other studies. It is possible that the volume of upright mobilisation was too similar in the two groups to detect a difference between them and, furthermore, an even greater volume, e.g., three mobilisation sessions or more daily may be needed. If so, then, future studies need to establish potential differential effects of intensity vs. duration of mobilisation. From study I, participating physiotherapists reported guiding interventions based on ongoing assessment of each patient's responses in study I; however, the degree to which they reported being confident in doing so was questionable at times. Thus, it is conceivable that response-driven upright mobilisation was below the therapeutic threshold necessary to show objective short- and long-term benefits in our trial.

## 5.3 Exposure variables that are associated with poor physical recovery one year after ICU discharge

The results from study III, a secondary regression analysis of the cohort of 50 patients in study II, shed light on the trajectory of patients' physical recovery and the factors that are associated with limited recovery. The female gender was found to have an association with poor self-reported and performance-based physical recovery at one year after ICU discharge. The only difference observed between genders in baseline characteristics, severity of illness at admission, in ICU-related variables and LOS, was that more women were unemployed or receiving disability benefit than men. Women have been reported to have worse outcomes after critical illness than men (Brown et al., 2017; Neumeier et al., 2017). Younger women with short sedation time and short ICU LOS had better outcomes than older patients with longer sedation and longer ICU LOS (Gandotra et al., 2019). Brown and colleagues (2017) identified four groups of ARDS patients based on their recovery six months after ICU discharge (Brown et al., 2017). In these four groups, gender, ethnicity, smoking status before ARDS, and other baseline factors predicted recovery, where women of Hispanic origin who smoked had the poorest recovery, but men who did not smoke and were not of Hispanic origin had the best recovery. Better understanding of the factors that mediate the difference in physical recovery between genders is needed (Gandotra et al., 2019; Neumeier et al., 2017).

Other exposure factors identified in study III that were associated with poor long-term physical recovery after adjustment for gender and age were: high BMI at baseline, low functional independence (MBI) at baseline, high comorbidity count (FCI) at baseline, low self-reported physical function (SF-36v2 PF domain) at baseline, muscle weakness (MRC-SS) at ICU discharge, and longer hospital stay. A study of ICU survivors aged 70 years or older reported that high BMI was associated with better functional recovery (Ferrante et al., 2016). Griffith and colleagues (2018) reported that a higher comorbidity count (FCI) was strongly associated with lower health-related quality of life in the year following ICU discharge (Griffith et al., 2018). Patients with ICU stays of at least eight days had worse five-year morbidity and mortality after critical illness, compared with patients with shorter stays (Hermans et al., 2019). Exposure factors were identified explaining the association between long ICU stay and morbidity five years after the ICU stay. They included the use of benzodiazepine drugs, vasopressors and opioids during the ICU stay. A recent study reported that neither the APACHE II score nor the duration of MV were associated with health-related quality of

life in ICU survivors who required more than 48 hours of MV, 12 months after ICU discharge (Griffith et al., 2018). This agrees with the results of study III in that neither the APACHE II score nor the duration of MV was associated with self-reported physical function. Survivors of critical illness have identified their main health challenges as weakness, fatigue, and decreased walking capacity in the year following ICU discharge (Nedergaard et al., 2018). These reports emphasise the need for core physical outcomes consistent with patients' priorities and preferences. Identifying those patients who would benefit most from rehabilitation in the ICU warrant elucidation (Berney et al., 2019).

The present study identified several exposure factors that are associated with poor long-term physical recovery. Physiotherapists can document these exposure factors in patients who are mechanically ventilated for longer than 48 hours to identify those who are at risk of poor long-term physical recovery and provide them with more tailored physiotherapy interventions in the ICU and after ICU discharge. Additionally, physiotherapists need deeper understanding of the physical recovery process in ICU survivors to enable appropriate interventions for long-term physical recovery and quality of life in ICU survivors to be designed and implemented.

## 5.4 Methodological strengths and limitations

The findings from study I are based on a qualitative methodology, therefore they are representative of the study sample and cannot be generalised to other populations of physiotherapists. Several means were used to ensure the trustworkthiness and transferability of the results. The credibility of the findings was assured through prolonged engagement and persistent observation, where the primary investigator, who was responsible for the analysis, knew the site of the observation of the physiotherapists‘ mobilisation practices (Lincoln & Guba, 1985). The primary investigator followed up with an interview after each observation phase, and 12 physiotherapists with diverse experience assured multiple sources of information which ensured triangulation of the data collection methods. And finally, outcomes that were different (negative cases) were analysed especially.

In study II, repeated self-reported and performance-based outcome measures during the course of one year highlight the trajectory of recovery in survivors of critical illness. This was a single centre trial, which is both a methodological strength and a limitation. The trial was underpowered due to study termination after three years. The physiotherapists who implemented

the intervention were highly experienced, but they were not blinded to the patient group assignment. The physiotherapists who performed the physical function measurements were trained in a standardised way and blinded to the patient group assignments. The patients answered the SF-36v2 health survey after discharge from the ICU to evaluate their baseline health-related quality of life retrospectively, which may have resulted in a recall bias. The ICU protocol of daily arousal and spontaneous breathing trials had not been fully implemented at the time of the initial data collection and intervention from November 2011 to the end of October 2014. Thus, the participants in the twice-daily group had an optimal sedation level on less than half of the intervention days. This may have delayed the first upright mobilisation session which was planned to start on day three after the initiation of MV, but actually started on day seven. Additionally, the once-daily mobilisation group received a considerable amount of upright mobilisation due to the standard physiotherapy practice in the ICUs. This may have led to a small separation between the study groups. Two of the measurement tools that were used have been recommended by an expert consensus statement on physical rehabilitation for survivors of critical illness after hospital discharge, the SF-36 Health Survey and the 6MW test. (Major et al., 2016). The MRC-SS, however was not recommended as a core outcome tool after critical illness.

The strengths of study III are the three physical recovery outcomes selected to describe the patients´ physical recovery one year after ICU discharge: one self-reported and two performance-based outcomes, consistent with the ICF framework (World Health Organization, 2001). Using performance-based and self-reported outcomes is important for evaluating distinct constructs of physical recovery in ICU survivors (Berry et al., 2019). Study III is an observational study which rules out any assumptions about the causality of the associations reported. No adjustment was made for cumulative type I error rate as a result of the large number of the statistical models presented. The study had fewer women than men, and the women had higher percentage of unemployment and disability and may not have been a representative sample of the typical female ICU patient. The clinical diagnosis of ICU-AW at ICU discharge was performed with MRC-SS <48 points (Ali et al., 2008; De Jonghe et al., 2002). Despite high inter-observer agreement, the MRC-SS has been reported not to be a robust tool to diagnose ICU-AW (Connolly et al., 2015).

## 5.5 Future perspectives

Based on this thesis, several recommendations for further detailed studies emerged, aimed at refining the implementation and progression of early upright mobilisation for patients who are admitted to an ICU and require prolonged MV. Consistent with international practice standards, physiotherapists systematically mobilise patients and position them upright during their critical illness and ensure long-term rehabilitation is instituted. The aims are to reduce bed rest and its complications, and prevent the well-established, poor long-term physical and mental recovery. Based on this research, the following observations for clinical practice and related research are presented.

- Physiotherapists play a crucial role in implementing and progressing mobilisation and reducing bed rest in patients who are critically ill. There are abundant opportunities for physiotherapists to promote physical recovery in and after ICU and hospital discharge by working closely with the ICU and hospital team and educating its members accordingly.
- For physiotherapists to prescribe therapeutic upright mobilisation with maximum patient cooperation and effect, they need to work closely with intensivists and nurses to use the periods of lightening of sedation for implementation of upright mobilisation in patients who are mechanically ventilated.
- Physiotherapists need to work with intensivists to define the earliest opportunity for mobilisation to be initiated in each patient individually; arbitrarily setting ‘early’ by a set day of mechanically ventilation initiation was not supported.
- Structured mobilisation protocols in the literature are questionable as they lack attention to patient responses as a guide for progression through the stages of mobilisation. Elucidation of the optimal assessment of the ICU patient is needed and how the outcome can be used to establish the timing, the intensity and duration of positioning patients upright and mobilising them. Additionally, prescribing the parameters of the mobilisation session and how to modify the parameters as needed within a treatment session is warranted.

- ICU clinicians need to be aware of the fact that women who were independent functionally and ambulating before an onset of critical illness that included MV for longer than 48 hours, need to be identified and provided with interventions to expedite maximal physical recovery.
- Consistent with mobilisation that is response-driven rather than protocol-driven is the need for novel research designs that include the principles of response-driven interventions.
- Currently the type, the timing, the duration, the intensity of physiotherapy including upright mobilisation (supported by the FITT parameters) for optimization of functional outcomes in critically ill patients in and after ICU discharge warrant elucidation.
- Understanding the physical recovery trajectory in survivors in and after ICU discharge is essential for ICU clinicians and researchers to design and implement appropriate interventions to improve the long-term physical recovery and quality of life of ICU survivors.
- Further studies are needed to design a core set of patient-centred physical recovery outcomes measured at the ICU and hospital discharge. These core outcome measures can be used in the ICU setting and in a multidisciplinary ICU-follow-up clinic where physiotherapists can identify patients who are at risk of poor physical recovery and can provide tailored and targeted rehabilitation interventions.
- The clinical reasoning processes of physiotherapists with respect to upright mobilisation with the goal of walking need elucidating; specifically, how they establish the therapeutic parameters for a given patient, within and throughout each mobilisation session, within their margins of safety. A response-driven intervention is advocated, but it is important to establish how a physiotherapist can best interpret each individual patients response in the context of prescribing a given mobilisation session, for optimal outcomes and safety.

# 6 Conclusions

The findings from this thesis add new and novel knowledge to several aspects of early upright mobilisation in the ICU. We studied a group of adult patients, who had been independent in ADL, had one or more comorbidities, before the onset of severe critical illness that required MV for longer than 48 hours.

The physiotherapists in this study individualised mobilising and positioning their ICU patients to an upright position and titrated the progression of the session based on constant assessment of the patients' responses to the mobilisation. This supports the need for principles that guide the physiotherapists in moving and positioning their patients upright, rather than adhering strictly to structured protocols. Moving and actively positioning patients upright as much as possible was supported as an intervention of choice, but the distinctions between one or two daily sessions remain to be established along with the optimal session parameters (i.e., type, duration and intensity) for a given patient. The ICU survivors displayed poor long-term physical recovery, where women appeared to be at greater risk of delayed physical recovery, compared with men. Knowledge of the risk factors for poor physical recovery will enable physiotherapists to better target and tailor their mobilisation interventions for ICU patients, where time and cost are of the essence. This work also sheds light on the need for research designs that elucidate principles to guide when to initiate mobilisation at the earliest opportunity for each patient, and principles for guiding the mobilisation prescription based primarily on each patients' response to being positioned upright and passively or actively mobilised.

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# Original publications

# Paper I

# Physical Therapists' Clinical Reasoning and Decision-Making Processes When Mobilizing Patients Who Are Critically Ill: A Qualitative Study

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***The study was approved by the institutional Ethics Review Committee (48/2013), the Chief Medical Director (December 5, 2013) and the Chief of Human Resources (January 8, 2014). The Icelandic Data Protection Authority was notified (December 18, 2013). The participants provided informed signed consent. The patients gave verbal consent or nodded, for the observation of a typical mobilization session, which was a part of their daily physiotherapy in the Intensive Care Unit.***

**Purpose:** Although mobilization is a widely practiced intervention for patients who are critically ill, the clinical reasoning and decision-making processes used by physical therapists to maximize its effectiveness warrants elucidation. This study's purpose was to investigate factors guiding physical therapists' clinical reasoning and decision-making processes when initiating and progressing mobilization in patients who are critically ill. **Methods:** In a 2-phased qualitative research design, 12 physical therapists working in a tertiary care university hospital were observed before, during, and after a mobilization session with 1 patient, followed by a semistructured interview. **Results:** Six categories (patient; intensive care unit-context; physical therapist; transfer; FITT parameters [frequency, intensity, type, and time]; and expected outcome) and 4 encompassing factors (safety and well-being; continuous assessment and intervention intertwined; individualized and response-driven intervention; and barriers and solutions) emerged as important in guiding participants' clinical reasoning when mobilizing their patients. **Conclusions:** The categories and encompassing factors identified, influenced, and guided participants in their clinical reasoning and decision-making when they initiated mobilization and progressed its parameters. The approach was goal-oriented and tailored to each patient's needs based on moment-to-moment evaluation of responses. The categories and factors that emerged favored a response-driven rather than a protocol-driven approach to mobilizing patients who are critically ill. **(Cardiopulm Phys Ther J. 2018;29:13–25)** *Key Words: early mobilization, clinical decision making, clinical reasoning, intensive care, critical care, physical therapy*



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## INTRODUCTION AND PURPOSE

Mobilization of patients in the intensive care unit (ICU) is a feasible and safe intervention[1-5] to reduce muscle weakness and functional impairment.[4,5] Mobilization constitutes both a gravitational and an exercise stimulus to the patient[6] and elicits acute physiological effects that augment circulation, perfusion, ventilation, muscle metabolism, and alertness.[7] Although mobilizing patients in the ICU has substantial evidence that informs clinical practice guidelines,[7] the practice remains underused.[8,9] This may reflect the diversity of patients who are critically ill, as well as lack of knowledge regarding clinical reasoning and decision making about when and how to mobilize by ICU team members including physical therapists.

Mobilizing patients who are critically ill is challenging and not without risk.[1] Patients typically are attached to lines, catheters, and life supports which limit body positioning and mobilizing options. Complications include fluctuating hemodynamic status and potential muscle weakness. To begin mobilizing a patient, the physical therapist needs to establish its optimal mode, intensity, duration, and frequency[10,11]; (not unlike the prescription of the FITT principle for patients who are medically stable or in the chronic stage of their conditions, ie, frequency, intensity, type, and time), and then, during the session, the physical therapist often needs to modify these parameters.[11]

Several investigators have examined factors influencing physical therapists' clinical reasoning and decision making in acute care using qualitative research methods.[12-15] In one study, investigators examined indicators used by experienced acute care physical therapists to establish a patient's capacity to tolerate being mobilized.[15] Indicators reported were history/background, physiological parameters, observational, and physical indicators (muscular/limb and functional indicators). Collectively, these informed an individualized, task-specific, and dynamic process for assessment and treatment intervention.

Although mobilization is advocated in established ICU physical therapist practice,[2] it remains poorly defined and inconsistently practiced.[4,8,9] The question remains as to how health professionals can overcome barriers to patient mobilization and facilitate the translation of the unequivocal physiologic knowledge supporting it, into practice.[2] In addition, mobilization strategies need to be elucidated so that patient outcomes are maximized.[4] Although mobilization in the ICU has been elucidated,[1,2] how physical therapists reason and make decisions for each patient is unclear. Therefore, our research question was as follows: What factors guide clinical reasoning and decision-making processes of physical therapists when they initiate and progress mobilization in a particular patient who is critically ill?

## METHODS

### Study Design

A qualitative research design was implemented, with a 2-phase data collection consisting of an observation[16] and a semistructured interview,[16,17] conducted from February 2014 to February 2015. The data were analyzed with conventional content analysis, a qualitative research method designed to interpret meaning from text content.[18,19]

### Participants and Recruitment

Participants were recruited from the acute care services of a tertiary care university hospital with 2 ICUs. Twenty-six physical therapists working in the inpatient service and either covered patients in the ICUs and/or provided after-hours on-call services, were eligible. They were oriented to the study and its data collection methods at a staff meeting and volunteers were asked to contact the primary investigator to be included in the study. Twelve physical therapists participated.

### Ethical Consent

The study was approved by the institutional Ethics Review Committee (48/2013), the Chief Medical Director (December 5, 2013), and the Chief of Human Resources (January 8, 2014). The Icelandic Data Protection Authority was notified (December 18, 2013). The participants provided informed signed consent. The patients gave verbal consent or nodded, for the observation of a typical mobilization session, which was a part of their daily physical therapy in the ICU. No data about individual patients were documented.

### Data Collection

In the first phase of the study, the primary investigator observed each participant with an adult patient in the ICU, before, during, and after a single mobilization session. This observation focused on describing each participant's preparation for and implementation of mobilization. Other key components observed were the participant's communication with the ICU nurses and other health professionals; the handling of the patient's tubes, lines, and drains; and the communication between patient and participant; and the patient's responses throughout the session. There was no interaction between the participant and the observing investigator positioned several meters away to record observations (Table 1 for observation scheme). After the observation session, the investigator reflected on her observations and noted main points.[16] The second phase of the study, scheduled later the same day, consisted of a semistructured interview by the investigator with the participant about the factors she or he contemplated

**TABLE 1**

Format for the Observation Scheme Used by the Investigator When Observing Each Physical Therapist

| Observation Scheme | |
|---|---|
| Notice nonverbal behavior | |
| People present | Verbal agreement from patient |
| Date | Starts and finishes (time) |
| | Location |
| Has this physical therapist mobilized this patient before? | |
| Patient (observation from primary investigator) | |
| Well-being | |
| Alert, RASS scale | Can patient communicate? |
| Disabilities, morbid obesity, main problem | |
| Equipment | |
| Ventilator? | Lines, drains |
| Bed | Hoist system used? |
| | Stepstool |
| Physical therapist's preparation before mobilization | |
| Interaction with ICU team | |
| Interaction with patient | |
| Assessment of readiness to be mobilized | |
| Contraindication to be mobilized, reason | |
| The mobilization: type, method, to sit on edge of bed | |
| Does the patient participate, and how much? | |
| Interaction with patient during the mobilization | |
| Interaction with ICU team during mobilization, staff participation | |
| Patient's reaction to mobilization | |
| Physical therapist's reaction to the patient's reaction | |
| Mobilization stopped, reason | |
| | Time of mobilization |
| Interaction with patient after mobilization | |
| Interaction with ICU team after mobilization | |
| Primary investigators notes after mobilization | |

ICU, intensive care unit; RASS scale, Richmond Agitation Sedation Scale.

before, during, and after the observed mobilization session, and about mobilization of patients who are critically ill in general. The interview was semistructured to facilitate dialog and rich descriptions focusing on the clinical reasoning and decision-making processes and the factors that participants considered during the mobilization session. Information on participants' demographics was collected at the end of the interviews that lasted from 35 to 90 minutes. The interviews were audio recorded and transcribed verbatim by the investigator (Appendix 1 for interview guide). A pilot observation and interview had been conducted on 1 physical therapist, who met the recruitment criteria but was not included in the study, before the formal data collection to establish the data collection framework. The patients were mechanically ventilated or had recently been extubated. All 12 of them (1 for each participant) were alert, 7 were mechanically ventilated through an endotracheal tube, 4 patients received oxygen through a face mask or through nasal cannulae, and 1 patient was ventilated with a bilevel positive airway pressure machine. No data about individual patients were documented.

## Data Analysis

The manual data analysis (observation notes, reflective notes, interview transcripts) was conducted using conventional content analysis.[18] The primary investigator began by reading each transcript systematically multiple times to immerse herself in the text. Then she read the transcript, searching for patterns and commonalities that described and could elucidate participants' clinical reasoning and decision-making processes when mobilizing their patients. Essential keywords or short phrases capturing the essence of the physical therapists' thoughts were highlighted. After scrutinizing 4 randomly selected transcripts, labels for codes were identified and written in the text margins. Then the investigator, with checks from the other investigators, sorted

the codes based on their interrelationships and decided on preliminary categories that were then translated into English from Icelandic. These categories were entered into an Excel spreadsheet and organized accordingly. Each category was entered into a row in the first column, followed by each participant's own words explaining the category in the following columns, but the same row. The remaining transcripts were coded guided by these categories, 1 spreadsheet for each participant. This comparative process ensured data saturation, as no new categories emerged from the last 2 transcripts. Then, the data within each category were examined and cross-referenced with those from the investigator's observation and reflective notes. During this process, some categories merged and others diverged, which identified final categories. These were sorted based on their interrelationships and recorded in a separate Excel spreadsheet of all participant data to facilitate transparent data analysis. From these the final categories, subcategories and encompassing factors were discussed and determined by the investigators.

## Strategies to Ensure Trustworthiness of the Findings

We sought to enhance the probability of achieving credible findings in our study by conducting persistent and rigorous field observation and prolonged engagement by the primary investigator who is an experienced ICU physical therapist, familiar with the context in which the data collection took place.[20] Furthermore, triangulation of both sources and data collection methods was achieved, in which the investigator followed up on the observation phase with the interview phase, in addition to probing each of the 12 participant's clinical reasoning and decision-making processes that informed each mobilization session. Negative case analysis was used where search for disconfirming data was conducted and discussed among the research team to refine the findings of the study.

## RESULTS

Twelve eligible physical therapists participated in the study. They included practitioners with diverse experience, 10 women and 2 men. Their demographics appear in Table 2.

Six categories emerged from the data, each including several subcategories. The categories were patient; ICU context; physical therapist; transfer; FITT (frequency, intensity, type, time, or duration) parameters; and expected outcome. Overarching these categories were 4 encompassing factors, safety, and well-being; continuous assessment and intervention intertwined; individualized and response-driven intervention; and barriers and solutions. The 6 categories and 4 encompassing factors were intertwined, and guided participants' clinical reasoning and decision-making processes when initiating and progressing mobilization in patients who are critically ill. These are shown in Figure 1. Tables 3 and 4 also show these 6 categories and the 4 encompassing factors, respectively, but with representative samplings of participants' comments.

**TABLE 2**
Characteristics of Physical Therapists (n = 12)

| | n |
|---|---|
| Sex | |
| Female | 10 |
| Male | 2 |
| Highest qualification | |
| Bachelor's degree | 11 |
| Master's degree | 1 |
| Years of clinical experience | |
| 0–2 | 4 |
| 2–10 | 3 |
| 10–20 | 2 |
| >20 | 3 |
| Years of acute care experience | |
| 0–2 | 5 |
| 2–10 | 3 |
| 10–20 | 1 |
| >20 | 3 |

## Categories

***Patient.*** Relevant information on each patient's medical/surgical histories was collected and evaluated by the participants. Contraindications, limitations, or precautions were noted. Each patient's nurse was approached by the participant to seek further information on the patient's status and how the patient had been responding to nursing/medical care immediately before. At bedside after introducing herself or himself to the patient, the physical therapist observed and assessed vital signs from the monitors. Also, cognitive ability was evaluated to determine the patient's potential understanding and willingness to participate with the planned mobilization. Attention was paid to the patient's size and muscle bulk, and brief clinical assessment was performed when the patient was recumbent to determine his or her mobility status. Engaging the patient in the mobilization process, if sufficiently awake and alert, was a priority.

***ICU Context.*** The cultures of both participating ICUs in this study were positive toward mobilization. This was illustrated by the teams' attitudes and cooperation with the investigators and participants. Typically, each participant worked closely with the patient's ICU nurse during mobilization. Frequent discussions occurred about precautions based on medical history or contraindications regarding safety of mobilization. Also, participants conferred with nurses about the role of each team member during mobilization, and they usually assumed responsibility for directing the session. Physicians were available

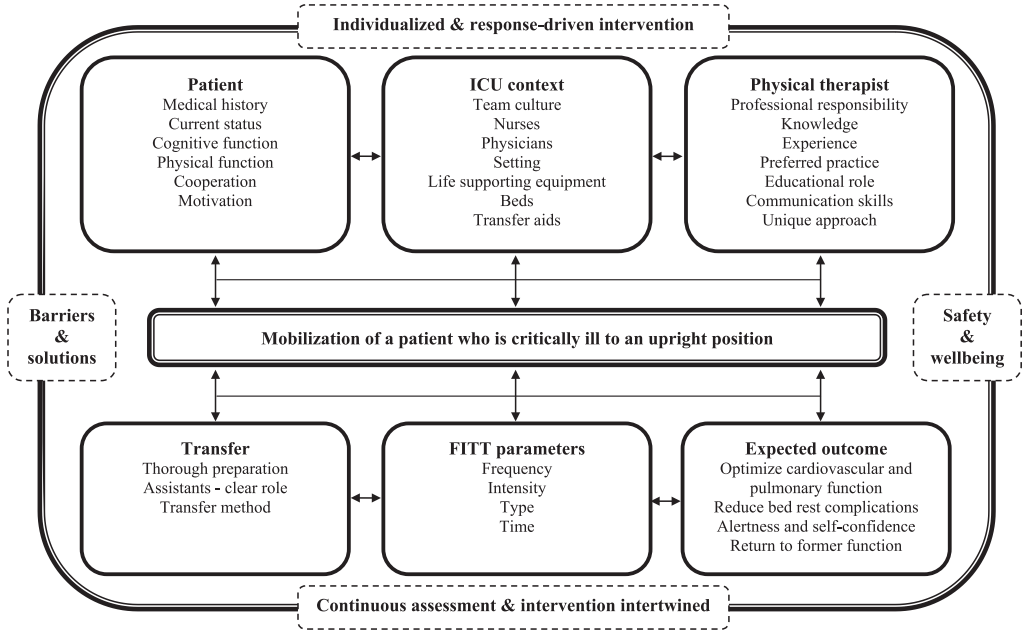


**Fig. 1.** The 6 categories and 4 encompassing factors illustrating physical therapists' clinical reasoning and decision-making process when initiating and progressing mobilization in patients who are critically ill.

and could be consulted. The ICU setting influenced mobilization, eg, limited space around the bed and extent of life-supporting technology. The nurse was usually requested by the participant to handle the endotracheal tube. Some ICU beds could not be lowered sufficiently for the patient's feet to reach the floor when sitting over the edge of the bed, which could hinder standing. Participants emphasized the need for judicious use of transfer aids such as electronic hoist systems, walkers, and belts.

*Physical Therapist.* Physical therapists' professional responsibility for mobilizing patients who are critically ill was reflected in this study by participants assuming a leading role in directing mobilization of patients, particularly those whose status was complicated. Statements by participants, that physical therapists were experts in mobility and mobilization, highlighted their unique knowledge base that guided their clinical reasoning and decision making when mobilizing patients. Differences among some participants however were noted. These were more related to the insecurity observed in and verbalized by some newly graduated participants about the ICU environment and the life-supporting equipment, rather than the mobilization intervention itself. These participants were inclined to rely on the ICU nurse to advise them about a patient's readiness to be mobilized. The physical therapists preferred active mobilization with patient participation whenever possible. Enabling the patient to sit up over the edge of the bed was chosen over passive transfer to a chair. In addition, a professional education role emerged. The participants described the benefits of mobilization in terms of both motivating patients and the ICU nurses.

*Transfer.* The importance of thorough preparation before mobilizing a patient, even to a sitting position over the edge of the bed was highlighted. Assessments of patients' functional and mental abilities typically guided decisions about need for assistants and technical aids. Also, each team member's role with respect to providing assistance was clarified beforehand. The physical therapists chose and directed the hands-on method used to transfer the patient to a sitting position over the edge of the bed and engaged the patient functionally in the transfer as much as possible.

*FITT Parameters.* Although the participants based their mobilization prescriptions somewhat analogous to the FITT principle,[21] this was more qualitatively than quantitatively, in that no structured intensities, durations, repetitions, or frequencies were prescribed. The frequency of mobilization sessions anticipated over the day was used to inform the duration and intensity of individual mobilization sessions. Participants wanted to ensure that their patients would have sufficient strength and endurance for several mobilization sessions throughout the day to ensure frequent regular gravitational and exercise stress for maximal therapeutic benefit. Intensity was increased gradually by progressively making upright positions more erect. As well, more participation from the patient was promoted by having the patient maintain a position with minimal support, as tolerated, and by progressing the exercise stimulation, eg, intensity, duration, repetitions. Progressing the duration a patient was in a given body position, including upright, was based typically on the patient's responses. Initially, the participant's aim was to enable the patient assume an upright position such as

**TABLE 3**

Summary of Findings: A Sample of the Physical Therapists' Comments Underpinning the Development of the Categories and Subcategories

| Category | Subcategory | A Sample of the Participants' Comments |
|---|---|---|
| Patient | Medical history | "Regarding the patient's medical history and the long recumbence, I knew that I was going to do assisted-active exercises and then help him to sit up on the edge of the bed" (HOLLY) |
| | | "I would like to know if the patient is not allowed to go over or under some limit in vital signs, then I can say this is enough, now we help him to lie down because he is reaching this limit. I mobilize the patient, I want to know" (FLORA) |
| | Current status | "I ask if he has been unstable, how is his respiratory status, has his arterial saturation been falling" (HOLLY) |
| | | "Does he seem to be in pain, you see it often on the patient's face" (HATTIE) |
| | Cognitive function | "First you look at the patient, is he awake, can he speak, can he understand me, has he done this before so that he knows what to expect" (HAZEL) |
| | Physical function | "You assess the strength in the patient's legs by asking him to press the leg into your hands from flexion in hip and knee. On the scale of 0–10, I would say that she has 5" (HARPER) |
| | | "I wanted to see how much he could move himself around in the bed, if he was active in bed… could he move against gravity" (HOLLY) |
| | Cooperation | "The physical therapist wants to know the patients opinion on the planned mobilization and get his consent. You cannot force people to do something that they do not want to do" (HEIDI) |
| | Motivation | "How do you motivate someone so that he wants to get out of bed? you have to remember that there is a person behind the patient…. You may have a plan, a routine and you want to finish this task, but you have to do it in a way to ensure that the patient is satisfied, that he feels good and has agreed to participate to ensure that he will cooperate next time" (HATTIE) |
| ICU context | Team culture | "The culture is for mobilization, nobody is allowed to lie in bed if he can be mobilized actively" (FLORA) |
| | | "They lined up, this is like a well-oiled machine" (HOPE) |
| | Nurses, consultation cooperation | "Consult with the nurses, they know the patient well" (HAZEL) |
| | | "A situation when physical therapist and nurse must be extra careful, for example unstable vital signs" (FLORA) |
| | | "The physical therapist is often responsible for the security during the movement… that the patient doesn't fall, his well-being and deciding when to stop. I at least take that responsibility during mobilization to the edge of the bed. The nurse however is maybe more thinking about the lines and the ventilator" (HATTIE) |
| | Physicians | "The contact with the orthopedic surgeons is not as good as for example with the lung physicians or the plastic surgeons. I can pick up the phone and call them" (FELICITY) |
| | Setting | "The bedside environment was too narrow, we were stuck in the corner of the room. There was just a table and WC chair, and we could hardly fit in, even though the patient was not big" (FREYA) |
| | Life-supporting equipment | "The ventilator is not a problem, I have often mobilized ventilated patients, but you need help from the nurse to hold the tube and guard that nothing will disconnect, you need at least one person for that" (HATTIE) |
| | | "You have to adjust the lines before the mobilization" (FLORA) |
| | Beds | "The air mattress is good for the patient to lie on, but it is not good to mobilize the patient. You cannot lower the bed down enough" (FELICITY) |
| | Transfer aids | "We are always getting heavier and heavier patients, unfortunately we are short of equipment for big patients. We are short of WC chairs, wheelchairs, walkers, mobile hoist and sling systems to lessen the load on the hospital staff. Those tools do not exist for overweight patients" (FLORA) |
| | | "Sometimes there are newly graduated nurses who have not used the hoist and sling system… you have to educate them without being dominating" (FAY) |

(*continued on next page*)

**TABLE 3 (*continued*)**

| Category | Subcategory | A Sample of the Participants' Comments |
|---|---|---|
| Physical therapist | Professional responsibility | "The physical therapist should direct if there is a difficult mobilization… Use equipment of cause and someone who directs it, and the bed in the right height, appropriate equipment on the patient or under him or to stand on, who is doing what, who is supporting his back, who is directing the equipment, who is handling the patient" (FREYA) |
| | | "They called from recovery and asked me to help mobilize a patient who is 190 kg after a small operation. Their idea was that they could not do it. I said on the phone the patient is used to those 190 kg and he might sit up easily. The recovery nurses asked me to come anyway, and I did. Of cause you are worried about her system and everybody focused on that the patient needed to get out of bed as soon as possible. I asked the patient to sit up and she sat up with little help, I and the nurse, we helped the patient sit up" (FLORA) |
| | Knowledge | "You can foresee the best way for the person to transfer… how you can mobilize easier… our skills as physical therapists" (FAY) |
| | | "Of cause it is a complicated intervention to mobilize a patient with severe burn injury. You have to bandage his legs (Cotton Elastic Crepe Bandage) if he has fresh skin grafts, you have to be self confident to immobilize that joint with bandage" (FELICITY) |
| | Experience | "I trust the nurses and what they say. If they evaluate and say he is not ready, he is feeling bad, he is labile, then I think ok, they know him better, they know how the system works here and I listen to them" (FRANK [8 months acute care experience]) |
| | | "You need guts to say no, I am not going to mobilize this patient, which is important… to trust your clinical assessment. Even though the on-call card says mobilization, it is not always realistic" (HEIDI [8 years acute care experience]) |
| | Preferred practice | "Physically you do not get a lot out of a passive transfer to a chair… You get so much more out of sitting to the edge of the bed. You are working with your trunk muscles, holding your head up. It is much harder than sitting in a chair… You do not participate in the transfer to a chair… I would always choose the edge of the bed over a chair" (HEIDI) |
| | Educational role | "There are many nurses in the ICU and you can't expect that they are all used to mobilize patients who are on a ventilator… the nurse says shall we wait until tomorrow, the patient is a bit… and you know that she doesn't trust herself to do this. Then we have to spot this and be able to educate and support" (HARPER) |
| | | "If the patient is reluctant, you educate the patient on the importance of mobilization. The physical therapist tries to motivate and engage patient in the mobilization" (HAZEL) |
| | Communication skills | "Listen to the patient and try to let them control some part of the mobilization too, but you can't let them control totally, sometimes you have to do something because it cannot wait, but try to negotiate with the patient in a way that he feels good and I feel good" (HATTIE) |
| | Unique approach | "We are made for being upright and moving, not lie in bed so the thought is to get the patient into that natural position" (FLORA) |
| | | "I want him to use as much as possible the function that he has" (HOLLY) |
| Transfer | Thorough preparation | "The assessment in supine tells me that the patient needs the assistance of 3 during the mobilization intervention" (HOLLY) |
| | Each assistant has a clear role | "I find it useful in the beginning to decide the role of each person, then everybody knows his responsibility" (HATTIE) |
| | | "That everybody is in synchrony… that each one has a distinct role… if the patient has a poor balance that the nurse does not leave to fetch a towel or something without telling me" (HEIDI) |
| | The transfer method to a sitting position over the edge of bed | "If the patent is poorly, then I use this method (*one hand under the patient's knee and the other hand under the patient's back, with the headrest of the bed high*), but if the patient is stronger I use a thumb-grip. You take the patient's right hand with your right hand and your thumbs cross and your palms touch, and I take the patient's legs with my left hand or right depending on which side you are on… If this patient had been 150 kg I would have asked for |

(*continued on next page*)

**TABLE 3 (*continued*)**

| Category | Subcategory | A Sample of the Participants' Comments |
|---|---|---|
| | | 2 assistants, one for the legs and another supporting the back and I would also support the back from the other side" (FLORA) |
| FITT parameters | Frequency | "Maybe it is ideal to sit for shorter time now and go again tonight or into a chair" (FELICITY) |
| | | "I try to distribute the exercises over the day, I ask the ICU team to help the patient into a chair during the evening and I try to help the patient sit to the edge of the bed 3× during the day, then we can work on the endurance that way" (HATTIE) |
| | Intensity: position, participation and exercise repetitions | "First I want to see if he can hold the sitting position without support, it tells me a lot about how strong he is and how secure I am with the next step that I want to take with him" (FINN) |
| | | "Give him minimal support for the exercises, but still enough support for him to have the energy for the training. It is just a feeling" (HOLLY) |
| | | "You are assessing the patient and treating him at the same time, you look for what he can do, ok this works, then I will repeat it several times to increase the patients strength" (HATTIE) |
| | Type: choice of position and different exercises | *Position*: "I thought that I was not going to mobilize the patient to the edge of bed. But when I did passive ROM I felt that he was awake. It is very different from do passive ROM on a patient who is awake compared with a patient who is asleep" (HEIDI) |
| | | "It is important to start as soon as possible, with exercises, sit on the edge of the bed, or stand up or just transfer into a chair" (FLORA) |
| | | *Passive exercises*: "She has been very passive, we must move the joints, get the circulation running" (FAY) |
| | | *Active exercises with assistance*: "Bend the hip and knee… to see what the patient could do, how much help she would need and it indicates how hard she is willing to work" (HAZEL) |
| | | *Active exercises*: "She could easily do 3 repetitions against gravity so I added 2 more" (FLORA) |
| | | *Functional exercises*: "You try to work with the balance and activate the legs and all that, and put weight on the hands" (*while sitting*) (HARPER) |
| | | "I help him with the movement that I think will be useful for him to gain functional independence… just a small activation now to encourage functional activation in the limbs" (HOLLY) |
| | Time | "I was wondering if he was tired because he needed more support, but I felt him relaxing and his breathing slowed down … and I thought that he must be feeling good… It was too good for him to lie down, let him to enjoy it a little longer" (HEIDI) |
| Expected outcome | Optimize cardiovascular and pulmonary function | "The upright position, the activation, the breathing and circulation and digestion and everything" (FREYA) |
| | | "The lungs… The blood pressure the heart is pumping against gravity" (HEIDI) |
| | Reduce bed rest complications | "I am always thinking about the harmful effects of bed rest, if the patient can be exercised, he gets exercise" (FLORA) |
| | Alertness and self-confidence | "The patient woke up when sitting on the edge of bed and spoke with us" (HOLLY) |
| | | "That the patient feels that he is doing something, not lying in bed, that is why I do not only want him to sit on the edge of the bed, I want him to do exercises even though it is minimal, that he feels that he is being trained" (FREYA) |
| | Return to former function | *Endurance:* "Work with the endurance by sitting for a longer period each time" (HATTIE) |
| | | *Strength*: "The patient could not stand up, I felt that we needed to focus on leg exercises, to strengthen the legs in open chain to prepare him for standing up later" (FRANK) |
| | | *Balance*: "Work with the balance by moving a little, then you go to the arms, and the balance comes into that… possibly work with some task, to reach for some items you have nearby… If you lift your arms you need to have a good balance" (FREYA) |
| | | *Functional ability*: "I help him with the movement that I think will be useful for him to gain functional independence… just a small activation now to encourage functional activation in the limbs" (HOLLY) |

(*continued on next page*)

**TABLE 3 (*continued*)**

| Category | Subcategory | A Sample of the Participants' Comments |
|---|---|---|
| | | *Long term goal to reach functional independence and return to meaningful independent life*: "What was the patient's former function? was she living at home, did she drive a car, did she walk around, did she exercise regularly, which gives you an idea about her physical function before… The final outcome is to get as close to that as possible… Or an elderly lady like this, she has been critically ill… To be able to go home with support, a walker if she needs it and more equipment and arrange for some help… But the final outcome is that she would be self-sufficient again" (HAZEL) |

ICU, intensive care unit; FITT parameters, frequency, intensity, type and time; ROM, range of movement exercises; WC chair, a portable toilet chair.

sitting over the edge of the bed and standing, if possible, to elicit tolerable gravitational stress. Second, exercises ranging from passive to active-assisted to active exercises, exercises against gravity, and functionally based exercises were prescribed by the participant, to progress each patient's mobilization session. Thus, typically, FITT parameters were modified by participants and increased correspondingly based on their patients' status and their moment-to-moment responses, as well as considering medical history.

***Expected Outcome.*** Reflection on mobilization outcomes was considered essential by the participants for their patients' well-being. It was viewed as contributing to the overall treatment aim for each patient, ie, to optimize cardiopulmonary function, reduce bed rest complications, increase alertness, and self confidence, and expedite return to the patient's previous or maximal level of physical functioning.

## Encompassing Factors

***Safety/Well-being.*** In cooperation with the nurses, participants ensured patients' safety and well-being while mobilizing them to upright with continuous assessment and evaluation of patient status including vital signs. Participants stressed the importance of defining each team member's role while mobilizing their patients as well as working cooperatively during transfers. They positioned the lines accordingly and sought nursing cooperation to ensure lines were not being compromised. They mostly assumed responsibility for directing the mobilization session and specifying the response-informed FITT parameters but acknowledged that it was helpful having the nurse oversee the endotracheal tube. Participants were vigilant about potential adverse responses to position changes and movement. With patients who could communicate, their well-being and preferences were monitored continuously to ensure movement was as comfortable as possible. Their subjective well-being and comfort were factors considered as importantly as objective measures in progressing mobilization.

***Continuous Assessment and Intervention.*** Ongoing assessment including observation of the patient by each participant was a consistent finding. The session began with each participant evaluating vital signs followed by a clinical evaluation and this continued throughout the session to gauge the patient's response to the requisite body position and exercise stimuli and to identify modifications to their parameters. Continuous evaluation of the patients' responses to being upright provided participants with a basis for modifying the type of mobilization and its duration and intensity, specifically, how much active participation could be expected within both safety and therapeutic margins.

***Individualized and Response-Driven Intervention.*** Continuous assessment of patients during the mobilization session enabled participants to analyze their hemodynamic status and prioritize their safety and well-being, eg, tolerance for mobilization within the session with the goal to activate the patient as much as possible to ensure progression of the mobilization parameters within the margins of safety and therapeutic effectiveness for each individual.

***Barriers and Solutions.*** Identification of barriers and solutions were intertwined. Mobilizing a patient who was overweight over the edge of the bed, for example, was not considered a barrier if sufficient staff members were available to assist. Some insecurity was experienced by some participants when moving patients who were mechanically ventilated through an endotracheal tube. Cooperation with the nurses however allayed that concern. Also, many ICU beds could not be sufficiently lowered for the patient's feet to reach the floor when they were sitting over the edge of the bed. One solution was use of an aerobic stepper platform. Indications for using transfer aids such as walkers, electronic hoist systems, and tilt tables were also mentioned.

## DISCUSSION

This is the first study that has investigated clinical reasoning and decision-making processes of physical therapists when initiating and progressing mobilization in patients who are critically ill. Our participants' emphasis

**TABLE 4**

Summary of Findings: A Sample of the Physical Therapists' Comments Underpinning the Development of the Encompassing Factors

| Encompassing Factors | A Sample of the Participants' Comments |
|---|---|
| Safety and well-being | "Situation that the physical therapist and nurse have to be extra careful, for example unstable vital signs" (FLORA) |
| | "You focus constantly on the lines, not to pull them or tear apart. You are very conscious about that" (FREYA) |
| | "You have experienced that a patient has a blood pressure drop during mobilization to an upright position or nausea… and you react. If it is a BP drop, you position the patient immediately in a supine position. You are never alone so that it is easy to help the patient back to bed. And if the patient needs to throw up, you hand him a tray or whatever needs to be done. Yes you react" (FINN) |
| | "If you are mobilizing a patient, you have alive person in your hands, you are always thinking about how is he experiencing this mobilization, that he is not in pain, that he can hold his head up… you are thinking about the patient's well-being with the handling you are using… this thought how can the patient be comfortable with the method that I am going to use" (FLORA) |
| Barriers and solutions | "If the patient is overweight you need more ICU staff to help and you have to think about your ergonomics" (HOLLY) |
| | "The equipment, the pillars with the infusion pumps and the monitor, you can position that behind the bed so that it is not in the way" (HATTIE) |
| | "The BiPAP was no trouble, you just have to adjust the tube" (FLORA) |
| | "The ICU beds are too high, the patient cannot touch the floor with their feet, it affects the balance and complicates standing up, but often we use the aerobic stepper platform to make it easier" (HATTIE) |
| | "It would have been good to try a high walker if it had been available. It would have made him more secure" (FELICITY) |
| Continuous assessment of the patient and intervention intertwined | "Watch the patient clinically, his complexion, is he working hard, is his tonus increasing, is he working with me and at the same time I am watching his saturation, his pulse and blood pressure" (FREYA) |
| | "You are trying to assess the patient and treat him at the same time" (HATTIE) |
| | "The physical therapist is assessing how much support she has to give the patient during the mobilization intervention" (HOLLY) |
| | "Regular evaluation of the patient's well being, get feedback from the patient… See how he reacts to every movement" (FINN) |
| Individualized and response-driven intervention | "If he can do more I try standing up, just to see how far you can go with the patient without exhausting him, does he have energy to do the next exercise I am thinking about. You build upon" (HEIDI) |
| | "She was not getting pale or anything, she denied dizziness, but it was obvious when she stood up, even though I was supporting her well, that she was a bit agitated… it was a bit of an effort for her to stand for a few seconds… I decided then, I would help her to lie down as soon as she sat down." (FLORA) |
| | "If the patient is sitting up for the first time, then you watch him closely during the process… you read the patient… you set yourself a goal, maybe start with 2 min. But because the patient sat up the day before and sat for 3 min, then I set a goal based on how he was when I met him, that he should be at least a minute longer" (FINN) |

BiPAP, Bilevel Positive Airway Pressure; BP, blood pressure; ICU, intensive care unit.

on progressive mobilization being response-driven versus protocol-driven was apparent. This is somewhat distinct from literature reporting concrete guidelines that provide specific protocols with well-defined progressions.[3,22-24] Our findings extend these guidelines by providing more depth to the processes involved in mobilizing patients in the ICU.

Our findings elucidate physical therapists' unique approach to mobilizing patients who are critically ill that requires specialized knowledge in exercise physiology and movement dysfunction. This concurs with findings that physical therapists in acute settings have expertise about movement and function distinguishing them from nurses, for example, who also mobilize patients.[25] Participants' ongoing assessment and evaluation of ICU patients during mobilization was paramount to predicting patients' capacity to effectively and safely tolerate treatment intervention and elicit the optimal response, thus mobilization was individualized and response-driven. Moment-to-moment evaluation and modification of the mobilization prescription which was based on the patient's responses as the session proceeded has been described previously[25] and

constitutes the foundation for effective and safe patient mobilization. What remains to be elucidated are the principles for guiding clinical reasoning and decision making when mobilizing patients in the ICU, that in turn inform the prescription on an iterative basis.

Our findings are consistent with those of an Australian study that examined the indicators used by experienced acute care physical therapists to assess patients' readiness and capacity for mobilization. They identified history/background indicators, physiological parameters, and observational and physical indicators.[15] Our findings extend these findings however by including the assessment of patients' cognitive function and the importance of involving patients in decision making. This is consistent with the findings of a Swedish study on the importance of sharing the clinical reasoning and decision-making processes with patients to augment cooperation.[12] This is also consistent with observations that patients, who are critically ill, wish to be involved in care decision making, if capable.[26]

The finding that the context in which the clinical reasoning process takes place, ie, the ICU, may influence a physical therapist's clinical reasoning and decision making regarding mobilizing a patient who is critically ill is consistent with similar studies[12,13] as well as studies that report technology and physical environment as factors that influence physical therapists' mobilization strategies.[13,15]

Physical therapists in our study viewed their responsibility seriously with respect to initiating patient mobilization, which, in our opinion, correspondingly influenced the team culture of the ICUs. This augmented teamwork culture also has been reflected in mobilization quality assurance planning when front-line staff are engaged.[27]

Our findings identified categories that related to the participants uniquely and influenced their clinical reasoning and decision-making processes when mobilizing patients in the ICU. These findings support those of Smith et al who also identified factors influencing decision making by acute care cardiorespiratory physical therapists such as their experience, unique knowledge base, professional identity, and preferred practice model.[13] The present findings identified insecurity by some participants in handling life-support equipment such as endotracheal tubes, which has been reported in other team contexts.[14] Similarly, patients' safety and well-being was a recurrent theme in our study in that participants wanted to share responsibility with nurses, particularly in monitoring vital signs and securing tubes, lines, and drains. Their communication skills and education role were also emphasized. This agrees with other studies regarding the importance of informing patients about the benefit of a given intervention[12] and the importance of adaptive communication skills to communicate effectively with diverse patients and health professionals.[25,28]

The physical therapists' clinical reasoning regarding the mobilization intervention was somewhat analogous to the principle of FITT, the established components of exercise training.[21] This agrees with the role of physical therapists in acute care making microlevel decisions, which includes decisions about exercise intensity and duration within 1 session based on patient examination as well as decisions about the frequency of mobilization between sessions.[25] Although the FITT components of mobilization have been detailed, the clinical reasoning and decision-making processes to initiate and progress mobilization in the ICU warrant elucidation. Recently, Sommers et al reported evidence-based expert-driven recommendations for ICU physical therapists.[24] Although distinction was made in terms of treatment progression based on arousal level, ie, passive versus active interventions, prescriptions were quantitatively defined. These conclusions were based on various studies of patients in the ICU with multiple conditions. Our findings deconstruct some of the finer points of decision-making that may result in a refinement of the assessments and treatments protocols outlined in these guidelines.

Several barriers to mobilizing ICU patients were identified by the participants who influenced their clinical reasoning and decision-making processes along with possible solutions. Mostly, these involved equipment and nonadjustable bed heights. Other studies have also reported major barriers to mobilization in the ICU, for example unit culture[29] and staffing[30]; however, this was not consistent with findings in our context.

Although our findings based on a qualitative methodology cannot be generalized to the population of ICU physical therapists and their patients, we have some confidence in their transferability, eg, that the credibility of the findings through prolonged engagement, persistent observation, triangulation, and negative case analysis[20] enhance their trustworthiness. Central to our study was an investigator's following up the observation phase with the interview phase, to probe each participant's reasoning and decision making that informed the mobilization session.

With respect to unanswered questions, our findings support the need to establish and refine principles of clinical reasoning and decision making when mobilizing patients who are critically ill, in developing physical therapist competency for maximum patient and ICU outcomes. Protocol-driven mobilization may not only have less of a role in a setting where patients are often hemodynamically precarious but could contribute to patients being under- and over-treated. Quantitatively defined treatments prescriptions even from well-controlled studies are challenging to generalize given no 2 ICU patients are alike. What remains to be elucidated are the principles for guiding clinical reasoning and decision making when mobilizing patients in the ICU, that in turn inform the prescription on an ongoing basis. Such a focus is more consistent with a research paradigm based on practice-based evidence versus evidence-based practice.

## CONCLUSIONS

Our findings support that when mobilizing patients who are critically ill, physical therapists' clinical reasoning and decision-making processes are deliberate, goal-

oriented, and tailored to each patient's unique needs based on moment-to-moment evaluation of the patient distinguishing them from other health professionals who also mobilize patients who are critically ill. Categories related to the patient and his/her problems, the ICU context, the physical therapist's attributes, and categories illuminating the task of mobilizing a patient to sitting over the edge of the bed were highlighted. Typically, the mobilization session was progressed based on ongoing assessment and evaluation of the patient, intertwined with an individualized response-driven focus with the patient's safety and well-being being paramount. The categories and factors that emerged from our findings favor patient response–driven progressive mobilization over protocol-driven mobilization and may provide a basis for structuring ICU training in preparing novice physical therapists to effectively work in the ICU.

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## APPENDIX 1.

### FORMAT FOR THE SEMISTRUCTURED INTERVIEW OF THE PHYSICAL THERAPIST PARTICIPANTS

Open-ended questions—follow ideas that come forward—use my premonition.

In this interview, I would like to find out a bit more about your clinical reasoning and decision-making processes that guided you mobilizing the patient whom I observed earlier today.

First, the on-call card consulted you to mobilize the patient. What is your understanding of the word mobilization (… *Maybe probe…. Passive/active/functionally* …)?

Can you tell me about why you decided to do what you did in terms of mobilizing this patient? Specifically, why did you decide to do…?

Can you tell me about specific factors you considered doing …?

I noticed that you progressed mobilizing the patient at point … (eg, got them sitting over the edge of the bed (… *and then standing*). What factors did you think about when you did this?
I then noticed that you continued/stopped progressing the patient at a point … What factors were you thinking about that guided this (*increasing the intensity or withdrawing*)?
I noticed that the mobilization session lasted… minutes overall. What factors determined the time the session should last… time or end ….? Can you reflect on your thoughts at that time?
If the participant says that a reason for stopping the session was time constraint, ie, other patients and things to do, follow with: I understand. If you had the time to continue what would you have done and what would you expect the outcome to be with extra time?
I noticed during the observation that you used …. method to help the patient to sit over the edge of bed, you did …. and the nurse did … Is this the method you usually use or do you sometimes choose another method?

## Now We Will Discuss Mobilization in General

Can you tell me what you think when you assess a patient's readiness to be mobilized?
Can you tell me how you assess the patient before and during mobilization (*as needed probe and follow thoughts regarding clinical assessment, function, vital signs, outcome measures*)?
Can you tell me how you assess the patient's well-being/mobilization tolerance (*as needed probe… How much would you allow the heart rate and blood pressure, or other vital signs to change*)?
Can you tell me about your general thoughts when your patient is sitting over the edge of bed … what do you focus on, how do you decide the intensity and duration of the mobilization session (*maybe probe frequency*)?
Who is responsible for the patients safety during mobilization, is it you the physical therapist or another member of the ICU team? As needed, ask; how would you ensure the patient's safety during mobilization?
How can the safety of everybody (the patient and the ICU team) be ensured during mobilization (*patients who are morbidly overweight, patients with multi trauma, patients with head trauma, patients that are disoriented.*)? *Discuss the environment, the beds, equipment, cooperation*.
Can you tell me what outcome you are trying to achieve with mobilization?
How do you prioritize mobilization when you are treating a patient who is critically ill? Is mobilization your first choice of intervention in the critically ill, and what type of mobilization?

## Barriers and Solutions

What is your opinion on how confident and well-prepared physical therapists' are about mobilizing patients in the ICU when they are on-call? How would you rate your confidence in mobilizing patients? Do you feel that you have sufficient competence in this area? (*if the physical therapist is experienced I ask her or him about the preparation for our young physical therapists regarding mobilization in the ICU during their on-call duties*)
Is there anything you can tell me from your experience and based on your needs that would enable you to mobilize patients more effectively?
Is there anything that you would like to add in relation to any of the questions?

## Participant's Characteristics (Closed Questions)

Years since graduation, hospital experience, field of experience, ICU experience, on-call experience.
The participants will be asked not to divulge the topics discussed in the study to other participants who have not yet been interviewed so that their responses and importantly their practices will not be influenced.

# Paper II

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ORIGINAL ARTICLE



# Effects of intensive upright mobilisation on outcomes of mechanically ventilated patients in the intensive care unit: a randomised controlled trial with 12-months follow-up

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**ABSTRACT**

**Objective:** To examine effects of intensive upright mobilisation on short- and long-term outcomes in critically ill mechanically ventilated patients.

**Methods:** A randomised controlled trial compared patient outcomes after intensive twice-daily ($n = 29$) or daily mobilisation ($n = 21$). Patients in the intensive care unit (ICU), mechanically ventilated for over 48 hours, were randomly assigned to one of the two groups. Outcomes were duration of mechanical ventilation, ICU and hospital lengths of stay; health-related quality of life and physical function.

**Results:** The twice-daily mobilisation group began upright mobilisation on day seven of ICU stay, and were mobilised upright on 31% of ICU days compared with the daily mobilisation group, who began upright mobilisation on day eight ($p \geq .05$), and mobilised upright on 22% of ICU days ($p = .03$). No difference between groups was observed for any variable of interest across time-points over one year.

**Conclusions:** The intensive twice-daily mobilisation group neither started upright mobilisation early nor yielded superior short- or long-term outcomes compared to the daily mobilisation group. Both groups showed poor physical health-related quality of life and exercise capacity one year after ICU discharge. Our findings support the need for targeted and tailored upright mobilisation in the ICU and after discharge.

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## Introduction

Patients surviving critical illness frequently experience profound physical and mental health impairments and poor quality of life for years following their intensive care unit (ICU) stays [1,2]. Muscle wasting has been observed in critically ill patients within the first week of ICU stay [3,4] and appears to be associated with duration of bed rest [5–7], together with the severity of acute critical illness [4,8]. Recognised underlying causes include muscle mass breakdown and depressed muscle protein synthesis [4,8].

In recent years, the focus of ICU research has been shifting from a singular focus on immediate medical survival to consideration of long-term physical and functional outcomes, as well as the quality of life [2,9–12]. To this end, physiotherapists have long practiced upright positioning of patients in the ICU and mobilising them as soon as possible [13]. However, based on decades of literature related to physiological understanding and evidence about the necessity for gravitational and exercise stress to augment oxygen transport, particularly in patients on bedrest who may or may not be on mechanical ventilation [14,15], the literature has remained equivocal regarding the optimal protocols for upright mobilisation of patients in the ICU [16,17].

Mobilisation in the ICU has been defined as moving actively or turning in bed, active limb exercises, sitting on the edge of the bed, passive or an active transfer to a chair, standing and walking [18]. However, mobilisation that is administered with the patient upright, constitutes both a gravitational and an exercise stimulus [14], which is known to augment oxygen transport and offset the negative effects of bed rest [15]. The safety and feasibility of mobilisation of patients in the ICU has been established [16,19–21]. Bed rest is, however, a generally accepted and a common approach in practice [22]. Thus, patients are rarely positioned upright, and mobilised (e.g. sitting over the edge of the bed, standing, stepping in place or taking steps [23–25]). Delaying mobilisation until after the acute phase of critical illness has been shown to negatively affect short- and long-term patient outcomes [26]. However, to integrate safe and effective upright mobilisation into ICU practice is not a 'one size fits

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all' procedure, but rather a multi-factorial process that requires a high level of clinical reasoning and decision making [27,28].

Therefore, this study's aim was to investigate the effects of intensive twice-daily upright mobilisation, starting early, i.e. on day three after initiation of mechanical ventilation, on short- and long-term outcomes, compared with once daily upright mobilisation that started later, i.e. on day five after initiation of mechanical ventilation. We hypothesised that intensive twice daily upright mobilisation instituted early, compared with once daily upright mobilisation instituted later, reduces the duration of mechanical ventilation, ICU and hospital lengths of stay; and improves health-related quality of life and physical function in patients who are mechanically ventilated for over 48 hours.

## Materials and methods

### *Study design*

A prospective, longitudinal, parallel-group, assessor-blinded, RCT was conducted, in two mixed-patient population ICUs in a 620-bed tertiary university hospital. Both ICUs have physiotherapist coverage five days a week during regular hours with on-call service evenings, weekends and holidays. The ICUs have 1:1 nurse:patient ratio and 24-hour intensivist coverage. Patients, 18–80 years of age, requiring mechanical ventilation for over 48 hours, were eligible if they were able to ambulate independently before the onset of acute illness and able to cooperate and comply with assessment and intervention for one year after ICU discharge. Patients were excluded from the study by the attending medical team (not directly involved in the study) if they had poor survival prognoses, or if they had been admitted to the hospital more than two weeks prior to admission to the ICU. Also, patients were excluded if progressive upright mobilisation was contraindicated, e.g. patients with prolonged hemodynamic instability, patients with severe head injuries or substantial unstable fractures (Figure 1). Patients were randomly assigned to one of two groups as follows. After the research team identified a patient who met the inclusion criteria, the ICU clerk drew a paper slip from a bag, randomly allocating patients to either the intensive twice-daily mobilisation group or daily mobilisation group.

### *Intervention*

Two experienced ICU physiotherapists (weekdays) and 26 on-call physiotherapists (weekends and holidays) implemented the intervention for each group. They were oriented beforehand to the different approaches applied to the two study groups. The chief intensivists in both ICUs defined a consensus recommendation for patient safety during upright mobilisation (Table 1). For patients who were mechanically ventilated, daily arousal and spontaneous breathing protocol were typically initiated at 9 am. Both groups had access to respiratory physiotherapy including airway clearance, which was added as indicated, potentially increasing the number of upright mobilisation sessions. Following ICU discharge, both groups received standard physiotherapy according to clinical practice guidelines.

The investigators defined upright mobilisation as an intervention with progressive stages, i.e. sitting over the edge of bed, standing or walking with or without assistance, which constitutes mobilisation levels 3–10 on the ICU Mobility Scale [29]. Upright mobilisation included active-assisted and active exercises, and functional, strength, balance and transfer training. Passive mobilisation was defined as passive range of motion exercises, active-assisted and active exercises in supine and passive transfer to a chair, consistent with mobilisation levels 0–2 on the ICU Mobility Scale [29]. The definition of upright and passive mobilisation applied to both groups. Based on international clinical practice guidelines, mobilising patients upright is progressed in accordance with their responses [13]. Thus, participating physiotherapists progressed patients based on their clinical judgment.

#### *Daily mobilisation group*

Intervention commenced after 96 hours of mechanical ventilation, and was based on international clinical practice guidelines for ICU patients [13] and performed once daily until ICU discharge. For patients who were mechanically ventilated, mobilisation was scheduled for approximately 9 am. The patients were often not awake, thus passive range of motion exercises were performed once daily, progressing to active-assisted and active exercises commensurate with increased patient arousal, unless upright positioning was contraindicated (Table 1). When considered appropriate by the physiotherapist, passive transfer to a reclining chair or sitting over the edge of the bed was initiated, followed by functional transfer training (Table 2).

#### *Intensive twice-daily mobilisation group*

The intervention was comparable to that for the daily mobilisation group. Differences included the intervention being initiated after 48 hours of mechanical ventilation and consisting of two sessions of progressive upright mobilisation (mobilisation levels 3–10 on the ICU Mobility Scale [29]) daily, until ICU discharge unless upright mobilisation was contraindicated (Table 1). The first mobilisation session of the day was scheduled late morning, to coincide with the daily arousal protocol. This maximised patients' capacities to cooperate and participate in their interventions. The focus of each intervention was on individualised and response-driven progressive upright mobilisation including sitting over the edge of the bed or a higher level of mobilisation. Components of the intervention were functional, strength, balance and transfer training, with the specific aim of progressing patients to standing and walking (Table 2).

### *Outcomes*

The primary outcomes were duration of mechanical ventilation, and ICU and hospital lengths of stay.

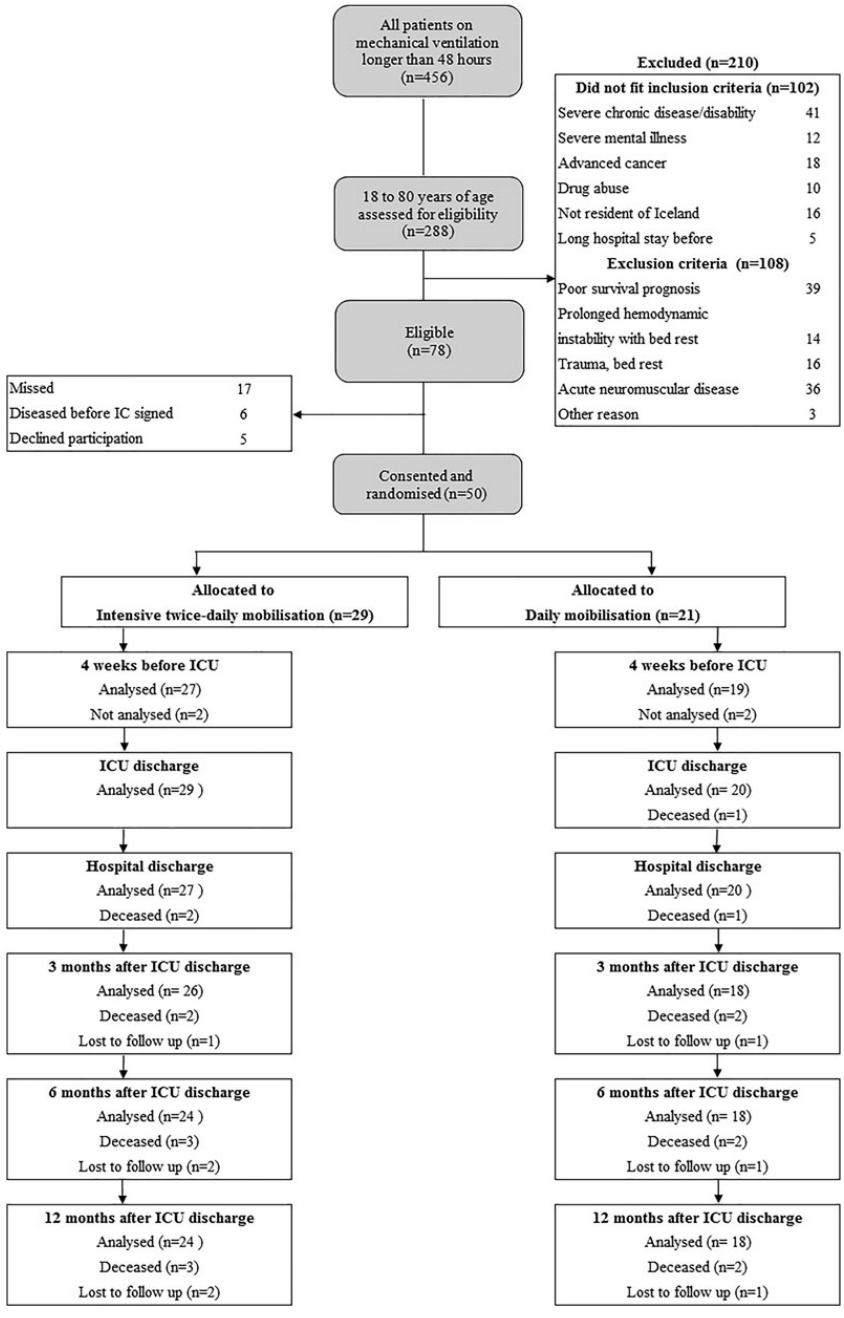


**Figure 1.** Participants' flow through the trial.

The secondary outcomes were the health-related quality of life and physical function, assessed at three to six-time points, i.e. at baseline (four weeks before ICU admission), at ICU discharge, at hospital discharge, and at 3, 6 and 12 months after ICU discharge. Health-related quality of life was assessed with the Short-Form 36 Health Survey version 2 (SF-36v2) [30]. Its outcomes are reported within eight health domains: physical function, role physical, bodily pain, general health, vitality, social function, role emotional and mental health. From the domains, a physical component score (PCS) and a mental component score (MCS) are computed; these are reported as population norm-based scores, with a mean

score of 50 and standard deviation of 10. Physical function was assessed in three ways: (i) The six-minute walk (6MW) distance based on the established 6MW test was used to assess exercise capacity [31], (ii) The Medical Research Council Sum-Score (MRC-SS) that assessed muscle strength in six muscle groups bilaterally, with score ranging from 0 (paralysis) to 60 (normal strength) [32], with a score less than 48 consistent with ICU acquired weakness [33] and (iii) the modified Barthel Index (MBI) assessed individual's functional independence in 10 activities of daily living, with scores ranging from 0 (totally dependent) to 100 (completely independent) [34].

Descriptive variables were patient baseline characteristics and their clinical data, and data on the components of each intervention. Pre-existing morbidities were assessed with the Charlson Comorbidity Index (CCI) [35], and the Functional Comorbidity Index (FCI) [36]. The severity of illness at ICU admission was assessed with the APACHE II (Acute Physiology and Chronic Health Evaluation II). The Richmond Agitation Sedation Scale (RASS) was used to assess the patient's sedation level [37].

**Table 1.** Consensus recommendations for patient safety in physiotherapy and contraindications for mobilisation to an upright position.

| | |
|---|---|
| Cardiovascular instability | |
| | Tachycardia (>130 beats/min) |
| | Bradycardia (<40 beats/min) |
| | Heart rhythm disturbances |
| | Low blood pressure (SBP <90 mmHg) |
| | Patient receiving >2 vasoactive drugs |
| | Intra-aortic balloon pump |
| | Extra Corporal Membrane Oxygenation (ECMO) |
| Open abdomen | |
| Severe respiratory failure | |
| | $FiO_2$ >0.6 |
| | PEEP >10 cm $H_2O$ |
| | Respiratory rate >35/min |
| | High-frequency oscillatory ventilation |
| High risk for haemorrhage or active bleeding | |
| Active thrombotic disease | |
| Other diseases that require heavy sedation or muscle relaxants | |

27 July 2011. Alma D Möller, Kristinn Sigvaldason

## Data collection

The primary investigator collected the patients' baseline characteristics and clinical data. After patients were transferred to the wards, she approached those patients who had had the next of kin give consent to participate in the study, in order to confirm their consents. Then, the SF-36v2 and MBI questionnaires were administered. Patients were asked to base their responses to the questions retrospectively, with respect to their health status four weeks prior to ICU admission. Assistance from next of kin was permitted.

Physiotherapists working at the hospital, who were trained in a standardised manner and blinded to the patients' group allocation, performed all physical function measurements at ICU discharge, hospital discharge and at 3, 6 and 12 months after ICU discharge. They saw the patients in the ICUs and the hospital wards on the day of discharge and recorded the MRC-SS, and completed the MBI in cooperation with each patient's nurse or nurse assistant. At 3, 6 and 12 months after ICU discharge, the patients returned to the hospital for follow-up assessment. The primary investigator first administered the SF-36v2 and MBI questionnaires, which the patients completed with assistance from relatives as

**Table 2.** The components of the interventions for the intensive twice-daily mobilisation group and the daily mobilisation group.

| | Intensive twice-daily mobilisation group | Daily mobilisation group |
|---|---|---|
| Onset | Commenced after 48 hours of mechanical ventilation | Commenced after 96 hours of mechanical ventilation |
| Frequency and duration | Two sessions daily, ≥20 minutes each | One session daily for ≥20 minutes |
| Timing | First session timed later in the morning, after sedation stop, to coincide with the patient being awake. Second session in the afternoon | Session timed at 09–10 am (usual practice) |
| Type, repetitions and intensity | Type focussed on a progressive upright mobilisation[a] with sitting over the edge of the bed or higher level of mobilisation starting as early as the patient's condition permitted. Repetitions and intensity were based on patient's responses and enhanced with increased patient's arousal and participation in the activity | Type, repetitions and intensity as considered appropriate by the physiotherapist |
| Content | Patient who was sedated or unresponsive, or if a mobilisation to an upright position was contraindicated: Passive range of motion exercises and body positioning. Consider upright position, sitting over the edge of the bed if patient was medically stable, even though not completely aroused. Patient who was medically stable and could participate: upright mobilisation with sitting over the edge of the bed, including assisted-active to active exercises. Transfer training from supine to turning in bed to sitting over the edge of the bed. Exercises in upright position included assisted-active to active exercises, functional, strength, balance and transfer training progressing to an active transfer to a chair towards standing and walking. Passive transfer to a reclining chair in cooperation with nurses | Passive range of motion exercises and body positioning. Progressing to active assisted and active exercises with increased arousal. When considered appropriate, usually after removal of the endotracheal tube, passive transfer to a reclining chair or sitting over the edge of the bed, followed by functional transfer training, standing up, transfer to a chair, standing up and walking |
| After removal of endotracheal tube | Respiratory physiotherapy, including airway clearance and mobilisation added to research protocol as needed | Respiratory physiotherapy, including airway clearance and mobilisation added to research protocol as needed |
| After discharge from ICU | Standard physiotherapy | Standard physiotherapy |

[a]The investigators defined upright mobilisation as an intervention with progressive stages, i.e. sitting over the edge of bed, standing or walking with or without assistance, which constitutes mobilisation level 3–10 on the ICU Mobility Scale by Hodgson et al. [29].

needed. Then, the trained blinded physiotherapists performed the physical function measurements of the MRC-SS and the 6MW test. If a patient was unable to return to the hospital for follow-up assessment, the MBI form and SF-36v2 were mailed or completed by telephone. Three patients who lived some distance from the hospital were able to perform the 6MW test in a standardised manner under the supervision of experienced physiotherapists in their communities.

The ICU physiotherapists recorded daily the following data: patients' current medical conditions and sedation levels (in cooperation with the bedside nurses), the results of their assessments, the intervention parameters and the patients' responses to the intervention and any reasons for missed sessions. Furthermore, all upright mobilisation sessions recorded by the nurses were documented in detail and compared with those recorded by the physiotherapists. This enabled comparison of all upright mobilisation interventions received by the patients in both groups during their ICU stays hence served as a validation check.

### Statistical analysis

Given no objective data for the three primary outcome variables of interest were available to guide power calculation to establish an optimal sample size, our sample size was based on the work of Burtin et al. [38]. Their calculations showed that a sample size of 36 participants was required for each group to detect a validated minimally clinically important difference of 50 m walking distance in the 6MW test with a statistical power of 80% and an $\alpha$ level of 0.05. We aimed to include 120 participants over three years, 60 in each group. Given the ICU setting, aiming for 60 patients in each group allowed for considerable dropout.

Primary outcomes were analysed with the Wilcoxon rank-sum test. Parametric secondary outcomes for repeated measures were analysed between groups, over time with a linear mixed effect model and non-parametric secondary outcomes with the Wilcoxon rank-sum test. Descriptive outcomes were compared with the use of the Chi-Squared test, the independent *t*-test and Wilcoxon's rank-sum test. Data were analysed with SAS software, version 9.4 (SAS Institute, Cary, NC, USA) and Microsoft Office Excel 2007 programme. Alpha was set at $<0.05$.

### Ethics

The study protocol was approved by the institutional Ethics Committee (16/2011), the Chief Medical Director (23.02.2011) and The Icelandic Data Protection Authority (2011020259ThS/-). Informed consent was obtained from the patients or their next of kin. If consent was provided by next of kin, patients confirmed their consents when and if they were well enough to do so. Registration at ClinicalTrials.gov: NCT02301273.

**Table 3.** Baseline characteristics and admission disease severity.

| | Intensive twice-daily mobilisation group $n=29$ | Daily mobilisation group $n=21$ |
|---|---|---|
| Sex, male | 19 (65.5%) | 14 (66.7%) |
| Age (years), median (IQR) | 62 (50–70) | 64 (58–74) |
| Prior residence, home | 28 (96.6%) | 21 (100%) |
| Married/cohabitation | 19 (65.5%) | 14 (66.7%) |
| BMI (kg/m$^2$), mean (95% CI) | 33.0 (28.5–37.4) | 32.1 (29.1–35.1) |
| % Obese (BMI (kg/m$^2$) $\geq$30) | 14 (48.3%) | 12 (57.1%) |
| MBI, 4 w. before admission, median (IQR) | 100 (100–100) | 100 (100–100) |
| Education, elementary school | 14 (48.3%) | 13 (61.9%) |
| Regular exercise ($\geq$150 min/week) | 6 (20.7%) | 5 (26.3%) |
| Current smoker | 10 (34.5%) | 4 (19.1%) |
| Former smoker | 9 (31.3%) | 14 (66.7%) |
| Never smoked | 10 (34.5%) | 3 (14.3%) |
| Employment status before admission to ICU | | |
| Employed | 10 (34.5%) | 10 (47.6%) |
| Retired | 9 (31.0%) | 9 (42.9%) |
| Unemployed | 3 (10.3%) | 1 (4.8%) |
| Disability | 7 (24.1%) | 1 (4.8%) |
| ICU admission diagnosis | | |
| Severe sepsis/septic shock | 11 (37.9%) | 12 (57.1%) |
| Pneumonia | 5 (17.2%) | 3 (14.3%) |
| Acute respiratory failure | 3 (10.3%) | 1 (4.8%) |
| Heart disease (medical) | 2 (6.9%) | 1 (4.8%) |
| Multi-trauma | 2 (6.9%) | 4 (19.1%) |
| Major elective surgery | 3 (10.3%) | 0 |
| Other | 3 (10.3%) | 0 |
| Admission disease severity and comorbidities | | |
| APACHE II – mean (95% CI) | 23.5 (19.7–27.2) | 22.0 (18.2–25.8) |
| Charlson Comorbidity Index – median (IQR) | 2 (1–5) | 2 (1–5) |
| 0 comorbidities | 6 (20.7%) | 4 (19.1%) |
| 1–2 comorbidities | 9 (31.0%) | 8 (38.1%) |
| $\geq$3 comorbidities | 14 (48.3%) | 9 (42.9%) |
| Functional Comorbidity Index – median (IQR) | 2 (2–4) | 2 (1–4) |
| 0 comorbidities | 3 (10.3%) | 2 (9.5%) |
| 1–2 comorbidities | 15 (51.7%) | 12 (57.1%) |
| $\geq$3 comorbidities | 11 (37.9%) | 7 (33.3%) |

APACHE II: Acute Physiology and Chronic Health Evaluation II score; BMI: body mass index; CI: confidence interval; ICU: intensive care unit; IQR: inter-quartile range; MBI: modified Barthel Index.
Data are presented as mean (95% CI), median (IQR) or *n* (%).

## Results

Participants were recruited from 2011 to 2014 with 12-month follow-up completed in 2015. Recruitment was set to be terminated after three years. A total of 3718 patients were admitted to the ICUs during that period; 1617 were mechanically ventilated, and 456 for over 48 hours. The research team screened 288 patients, 18–80 years of age (Figure 1). Fifty patients consented to participate and were randomised to one of the two groups. Baseline characteristics, severity of illness and clinical data from the ICU stay are presented in Tables 3 and 4.

A difference was not detected between the groups in primary outcomes. Duration of mechanical ventilation was a median (IQR) of 8.8 days (6.4–19.3) in the intensive twice-daily mobilisation group and 7.8 days (5.4–17.7) in the daily mobilisation group. The median (IQR) ICU length of stay was 12.4 days (8.4–19.6) in the twice-daily mobilisation group and 11.0 days (7.3–22.8) in the daily mobilisation group, and the hospital length of stay was 36.9 days (21.5–55.7) in the

twice-daily mobilisation group and 24.6 days (15.5–56.6) in the daily mobilisation group (Table 5).

There was no difference in health-related quality of life based on the scores from the SF-36v2, between the twice-daily mobilisation group and the daily mobilisation group at baseline, 3, 6 and 12 months after ICU discharge. In addition, physical function measurements: exercise capacity (6MW distance), muscle strength (MRC-SS) nor functional independence (MBI), were not different between the two groups across time points (Table 6).

The twice-daily mobilisation group received upright mobilisation on a median (IQR) of four intervention days [2–6] during the ICU stay, compared with two days [1–5] in the daily mobilisation group ($p<.05$). Participants in the twice-daily mobilisation group received their first upright mobilisation session including sitting over the edge of the bed, on a median (IQR) of day seven [5–13] from initiation of mechanical ventilation, and the daily mobilisation group on day eight [6–15], which was not different between groups.

Table 4. ICU outcomes and outcomes after ICU discharge.

| | Intensive twice-daily mobilisation group $n=29$ | Daily mobilisation group $n=21$ | $p$ Value |
|---|---|---|---|
| ICU outcomes | | | |
| Developed ARDS during ICU stay | 9 (31.0%) | 6 (28.6%) | .85 |
| Renal replacement therapy during ICU stay | 6 (20.7%) | 6 (28.6%) | .52 |
| ICU-AW indication at ICU discharge[a] | 13/20 (65.0%) | 8/13 (61.5%) | .84 |
| Discharge location from hospital | | | .23 |
| Home | 10 (34.5%) | 7 (33.3%) | |
| Nursing home | 3 (10.3%) | 0 | |
| Other hospital | 7 (24.1%) | 2 (9.5%) | |
| Rehabilitation centre | 6 (20.7%) | 8 (38.1%) | |
| Other | 1 (3.5%) | 3 (14.3%) | |
| Deceased | 2 (6.9%) | 1 (4.8%) | |
| Mortality | | | |
| 30 days mortality | 1 (3.4%) | 1 (4.8%) | .82 |
| 90 days mortality | 2 (6.9%) | 2 (9.5%) | .74 |
| 12 months mortality | 3 (10.3%) | 2 (9.5%) | .92 |
| Residence at 12 months after ICU discharge | | | .20 |
| Home | 22 (84.6%) | 19 (100%) | |
| Nursing home | 3 (11.5%) | 0 | |
| Rehabilitation centre | 1 (3.8%) | 0 | |
| Employment 12 months after ICU discharge | | | .65 |
| Employed and has returned to work | 5 (19.2%) | 5 (26.3%) | |
| Employed and has not returned to work | 4 (15.4%) | 3 (15.8%) | |
| Retired | 9 (34.6%) | 7 (36.8%) | |
| Unemployed | 1 (3.8%) | 2 (10.5%) | |
| Disability | 7 (26.9%) | 2 (10.5%) | |

ARDS: acute respiratory distress syndrome; ICU: intensive care unit; ICU-AW: intensive care unit acquired weakness; MRC-SS: Medical Research Council Sum-Score.
Data are presented as $n$ (%). Definition of ICU-AW indication: MRC-SS less than 48 at ICU discharge.
[a]Twenty participants in the intensive twice-daily mobilisation group and 13 in the daily mobilisation group could be measured at ICU discharge.

Fifteen patients in the twice-daily mobilisation group (52%) and 13 patients (65%) in the daily mobilisation group did not mobilise to an upright position for seven days or longer after initiation of mechanical ventilation. The main reason for this delay in upright mobilisation was deep sedation in 12 out of the 15 patients in the twice-daily mobilisation group (80%) and in 12 patients out of the 13 in the daily mobilisation group (92%). The twice-daily mobilisation group received upright mobilisation (mobilisation levels 3–10 on the ICU Mobility Scale [29]) on significantly higher percentage of ICU days, compared with the daily mobilisation group, 31% of ICU days compared with 22% in the daily mobilisation group. Further, the twice-daily mobilisation group received upright mobilisation with any health care provider in the ICU on an average of 35% of ICU days compared with 24% in the daily mobilisation group which was statistically significant (Table 7).

## Discussion

The discussion has four parts: general findings; strengths and limitations; clinical and research implications, and implication for future studies. Although the findings of this RCT may be limited by being underpowered, i.e. limited in participants due to termination of the study after the three-year timeframe and, in part, the setting, the findings do have important implications clinically and for researchers regarding methodological issues when conducting physiotherapy ICU research. These implications are detailed below.

### *General findings*

In this RCT, the effect of intensive twice-daily upright mobilisation instituted early, compared with once daily upright mobilisation instituted later, in mechanically ventilated ICU patients, with a 12-month follow-up was studied. The hypothesis that intensive twice-daily upright mobilisation instituted early of mechanically ventilated ICU patients augments outcomes over once daily upright mobilisation was not supported. Specifically, no differences were observed between the two study groups, i.e. twice-daily mobilisation and daily mobilisation, in primary outcomes of the duration of mechanical ventilation, lengths of ICU and hospital stay (Table 5). In addition, the secondary outcomes of health-related quality of life and physical function were not different between the groups over time. Both groups showed poor physical health-related quality of life and low exercise capacity one year after ICU discharge (Table 6).

The primary outcomes of this study were similar to those of six previous ICU RCTs studying physiotherapy

Table 5. Primary outcomes.

| | Intensive twice-daily mobilisation group $n=29$ | Daily mobilisation group $n=21$ | Median difference | $Z/p$ value |
|---|---|---|---|---|
| Duration of mechanical ventilation | 8.8 (6.4–19.3) | 7.8 (5.4–17.7) | –0.8 (–4.3 to 3.0) | –0.14/.89 |
| ICU length of stay | 12.4 (8.4–19.6) | 11.0 (7.3–22.8) | –0.5 (–5.3 to 4.6) | –0.18/.86 |
| Hospital length of stay | 36.9 (21.5–55.7) | 24.6 (15.5–56.6) | –5.1 (–19.8 to 6.0) | –1.10/.29 |

CI: confidence interval; ICU: intensive care unit; IQR: inter-quartile range.
Outcomes are presented as days. Data are presented as median (IQR) and median difference (95% CI).

**Table 6.** Secondary outcomes: health-related quality of life assessed with the Short Form-36 Health Survey version 2, physical function measured with the six-minute walk distance, the Medical Research Council – muscle strength Sum Score and the modified Barthel Index for functional activities.

| | | Baseline 4 weeks before ICU | | ICU discharge | | Hospital discharge | | 3 months after ICU discharge | | 6 months after ICU discharge | | 12 months after ICU discharge | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Least squares means (95% CI) | *n* | Least squares means (95% CI) | *n* | Least squares means (95% CI) | *n* | Least squares means (95% CI) | *n* | Least squares means (95% CI) | *n* | Least squares means (95% CI) | *n* |
| SF-36v2 PCS | Intensive twice-daily mobilisation group | 44.1 (40.1–48.0) | 26 | | | | | 36.3 (32.3–40.3) | 25 | 38.5 (34.4–42.6) | 24 | 38.3 (34.2–42.4) | 23 |
| | Daily mobilisation group | 46.1 (41.4–50.9) | 18 | | | | | 37.4 (32.6–42.3) | 18 | 37.3 (32.3–42.2) | 18 | 40.2 (35.5–45.0) | 18 |
| | Mean difference | −2.1 (−11.7 to 7.6) | | | | | | −1.1 (−10.9 to 8.7) | | 1.2 (−8.8 to 11.3) | | −1.9 (−11.7 to 7.9) | |
| | *t* Value/*p* value | −0.66/1.0 | | | | | | −0.34/1.0 | | 0.37/1.0 | | −0.60/1.0 | |
| SF-36v2 MCS | Intensive twice-daily mobilisation group | 46.8 (42.5–51.1) | 26 | | | | | 44.4 (40.1–48.8) | 25 | 47.5 (43.0–51.9) | 24 | 47.3 (42.9–51.8) | 23 |
| | Daily mobilisation group | 52.9 (47.7–58.1) | 18 | | | | | 47.9 (42.7–53.2) | 18 | 48.9 (43.6–54.3) | 18 | 50.3 (45.1–55.4) | 18 |
| | Mean difference | −6.1 (−16.5 to 4.4) | | | | | | −3.5 (−14.1 to 7.2) | | −1.5 (−12.3 to 9.4) | | −3.0 (−13.6 to 7.6) | |
| | *t* Value/*p* value | −1.79/.63 | | | | | | −1.01/.97 | | −0.42/1.0 | | −0.86/.99 | |
| 6MWT | Intensive twice-daily mobilisation group | | | | | | | 419.3 (346.8–491.8) | 22 | 451.1 (378.3–523.9) | 21 | 477.6 (404.1–551.1) | 18 |
| | Daily mobilisation group | | | | | | | 415.4 (331.9–498.9) | 16 | 467.9 (384.4–551.4) | 16 | 480.0 (395.9–564.2) | 14 |
| | Mean difference | | | | | | | 3.9 (−158.9 to 166.8) | | −16.9 (−179.9 to 146.2) | | −2.5 (−166.9 to 162.0) | |
| | *t* Value/*p* value | | | | | | | 0.07/1.0 | | −0.3/1.0 | | −0.04/1.0 | |
| MRC-SS | Intensive twice-daily mobilisation group | | | 40.2 (37.1–43.4) | 20 | 48.8 (45.7–52.0) | 20 | 52.9 (50.0–55.8) | 26 | 55.0 (52.1–58.0) | 24 | 56.9 (53.8–59.9) | 23 |
| | Daily mobilisation group | | | 42.4 (38.5–46.2) | 13 | 52.3 (48.8–55.8) | 18 | 54.6 (50.8–58.4) | 14 | 54.4 (50.8–58.1) | 15 | 55.9 (52.2–59.6) | 15 |
| | Mean difference | | | −2.2 (−10.2 to 5.9) | | −3.5 (−11.1 to 4.1) | | −1.7 (−9.5 to 6.0) | | 0.6 (−7.1 to 8.3) | | 0.9 (−6.8 to 8.7) | |
| | *t* Value/*p* value | | | −0.86/.99 | | −1.47/.90 | | −0.71/1.0 | | 0.25/1.0 | | 0.39/1.0 | |
| | | Median (IQR) | *n* | Median (IQR) | *n* | Median (IQR) | *n* | Median (IQR) | *n* | Median (IQR) | *n* | Median (IQR) | *n* |
| MBI | Intensive twice-daily mobilisation group | 100 (100–100) | 27 | 3 (0–15) | 29 | 88.5 (44–98) | 26 | 99 (81–100) | 26 | 100 (93–100) | 24 | 100 (91.5–100) | 24 |
| | Daily mobilisation group | 100 (100–100) | 19 | 4 (0–14) | 19 | 86 (60.5–98) | 20 | 100 (95–100) | 17 | 100 (90–100) | 18 | 100 (98–100) | 17 |
| | Median difference | 0.0 (0.0 to 0.0) | | −4.0 (0.0 to 4.0) | | −9.0 (0.0 to 18.0) | | 0.0 (0.0 to 4.0) | | 0.0 (0.0 to 0.0) | | 0.0 (0.0 to 4.0) | |
| | Z/*p* value | 0.71/.48 | | −0.34/.74 | | 0.29/.77 | | 0.82/.41 | | −0.19/.85 | | 0.85/.40 | |

CI: confidence interval; ICU: intensive care unit; IQR: interquartile range; MBI: modified Barthel Index; MRC-SS: Medical Research Council – Sum Score; SF-36v2: Short Form-36 Health Survey version 2; PCS: physical component score; MCS: mental component score; 6MWT: Six-Minute Walk Test.
Data are presented as least squares means (95% CI), median (IQR), mean difference (95% CI), and median difference (95% CI).

**Table 7.** Implementation and components of the intervention for the intensive twice-daily mobilisation and the daily mobilisation groups.

| | Intensive twice-daily mobilisation group $n = 29$ | Daily mobilisation group $n = 21$ | $Z/p$ |
|---|---|---|---|
| Days in the ICU (median (IQR)) | | | |
| ICU length of stay (days) | 12.4 (8.4–19.6) | 11.0 (7.3–22.8) | −0.18/.86 |
| ICU days before initiation of MV | 0.1 (0–1.1) | 0.0 (0–0.5) | −0.98/.33 |
| ICU days from initiation of MV until ICU discharge (protocol days) | 11 (8.1–19) | 11 (7.2–22.1) | −0.18/.86 |
| Implementation and content of intervention (median (IQR)) | | | |
| ICU days including physiotherapy (intervention days) | 9 (5–17) | 7 (3–16) | −1.29/.20 |
| Intervention days, with adequate sedation level (RASS level −1 to +1) | 4 (3–9) | 3 (2–5) | −1.35/.18 |
| Intervention days with upright mobilisation | 4 (2–6) | 2 (1–5) | −1.98/<.05 |
| Intervention days with passive mobilisation | 5 (3–11) | 4 (2–14) | −0.76/.45 |
| Intervention sessions | 16 (8–32) | 8 (4–16) | −2.27/.02 |
| Intervention sessions with upright mobilisation | 5 (3–9) | 3 (1–6) | −2.35/.02 |
| Milestones achieved on day of protocol (median (IQR)) | | | |
| First intervention on day | 3 (3–3) | 5 (4–6) | 5.00/<.0001 |
| First upright mobilisation session on day | 7.5 (5–13) | 8.5 (6–15) | 0.62/.53 |
| First ambulation session on day | 8 (5–11) | 12 (8–23) | 1.77/.08 |
| Amount of upright mobilisation during ICU stay (mean (SD)) | | | |
| Proportion of ICU days that included intervention with upright mobilisation | 31% (13.4%) | 22% (17.2%) | 2.23/.03 |
| Proportion of ICU days that included upright mobilisation with any health provider | 35% (16.8%) | 24% (18.4%) | 2.33/.02 |
| Main reasons for delay in upright mobilisation for one week or longer ($n$ (%)) | | | |
| No upright mobilisation for one week or longer after initiation of MV | 15/29 (51.7%) | 13/20[a] (65%) | |
| Deep sedation | 12/15 (80%) | 12/13 (92.3%) | |
| Vasopressors | 9/15 (60%) | 7/13(53.8%) | |
| Continuous renal replacement therapy | 3/15 (20%) | 4/13 (30.8%) | |

ICU: intensive care unit; IQR: interquartile range; MV: mechanical ventilation; RASS: Richmond Agitation Sedation Scale; SD: standard deviation.
Protocol days are defined as days from initiation of MV until ICU discharge; intervention days are defined as the number of days that the patients received physiotherapy intervention; intervention days with upright mobilisation are defined as days in physiotherapy that included mobilisation in an upright position, sitting on edge of bed, or standing up or walking with or without assistance (ICU Mobility Scale, levels 3–10), including assisted active, active exercises, functional, balance and transfer training in those positions. Intervention days with passive mobilisation are defined as days in physiotherapy that included passive range of motion exercises, assisted-active or active exercises in supine and passive transfer to a reclining chair (ICU Mobility Scale, levels 1–2). Adequate sedation level was defined when the patient was evaluated with RASS sedation level from −1 to +1. Deep sedation was defined when the patient was on continuous intravenous sedation and his RASS sedation level was from −4 to −5 during physiotherapy for seven days or longer after initiation of MV. Vasopressors: patients were on continuous intravenous infusion of 1–3 vasopressors for seven days or longer from initiation of mechanical ventilation. Continuous renal replacement therapy: patients were on hemofiltration for seven days or longer from initiation of MV.
Data are presented as median (IQR), mean (SD) or number (%).
[a]One patient was excluded from the final analysis due to missing values.

interventions, including mobilisation [10–12,38–40], but different from the findings of a trial that examined whole body rehabilitation with sedation interruption, and reported more ventilator-free days in the intervention group, compared with the standard group, in which no physiotherapy was routinely provided for the first two weeks of ICU stay [41]. The duration of mechanical ventilation in the current study was longer than that reported by Schweickert et al. [41]. This difference may be explained by higher median age and higher severity of illness scores (APACHE II) in the current study.

Secondary outcomes of health-related quality of life are consistent with that reported by three other RCTs with 6 or 12 months follow-up, reporting no difference between groups [10,12,39]. The mean PCS of SF-36v2 in the twice-daily mobilisation group and in the daily mobilisation group was lower by one standard deviation than general population norms at 3, 6 and 12 months after ICU discharge. That indicated that the patients assessed their physical health-related quality of life as poor at three months after ICU discharge, and it remained so at one year after ICU discharge. However, the mean MCS of SF-36v2 was close to population norms in both groups at baseline, and for 3, 6 and 12 months after ICU discharge, indicating that the patients evaluated their mental health-related quality of life similar to the general population before and after the ICU discharge. Exercise capacity (6MW distance) in the current study, was similar to the findings of two RCT trials with 3 [10,12], 6 [10,12] and 12 months [12] follow-up, that reported no difference between study groups in walking distance across time points [10,12]. However, the mean distance walked in the current study remained below that of age-matched controls [42], at 12 months after ICU discharge. Muscle strength measured with the MRC-SS in the current study was similar to results of other RCTs, reporting no difference between groups at ICU [9,21] and hospital discharge [21,41].

The intensive twice-daily mobilisation group received more intervention days that included upright mobilisation during the ICU stay than the daily mobilisation group (four days compared with two days). This agrees with the outcomes of a multi-centred pilot feasibility RCT reporting higher activity level achieved by critically ill patients assigned to early goal-directed mobilisation during the ICU stay [40]. The twice-daily mobilisation group in the current study initiated upright mobilisation, sitting over the edge of the bed or higher level of mobilisation, first on day seven from initiation of mechanical ventilation, which was later than anticipated. Out of the 15 patients in the twice-daily mobilisation group that did not mobilise to an upright position during the first seven days of the trial, 12 were deeply sedated. This may have had a negative impact on the frequency of

sessions including upright mobilisation in the twice-daily mobilisation group, who only received upright mobilisation on 31% of ICU days; although, it was significantly higher proportion than the 22% in the daily mobilisation group. In addition, the twice-daily mobilisation group received a significantly higher proportion of upright mobilisation days with any health care provider, 35% of ICU days compared with 24% in the daily mobilisation group. Thus, both groups received similar or higher levels of upright mobilisation than those reported in studies from the United States (out of bed mobility on 16% of total patient days in 42 ICUs) [25], from Europe (24% of patients sitting over the edge of the bed or higher level of mobilisation in 116 ICUs over 24 hour period) [24], and from Australia (active mobilisation on 22% of patient days in one ICU) [43].

Several factors could have contributed to the poor physical health-related quality of life and low exercise capacity at 12 months after ICU discharge. First, the twice-daily mobilisation group started their upright mobilisation later than expected. Second, the patients' health status at baseline was poor, most had one or more co-morbidities. A recent five-year follow-up study reported that co-morbidity before ICU admission and older age were associated with poorer physical health in ARDS survivors [5]. Third, the severity of the current illness, reflected in relatively high APACHE II score in the current study, compared with other RCTs (with the exception of those reported by Kayambu et al. [9] and Burtin et al. [38]), may have had a negative impact on the outcome. Cohort follow-up studies have reported similar findings for health-related quality of life [1,44] and exercise capacity [1], as the current study, consistent with functional limitations in survivors, persisting for up to five years after critical illness [1].

### Strengths and limitations

The strengths of our trial include the repeated measurements for up to 12 months after ICU discharge adds value to ICU research and helps shed light on the trajectory of recovery after critical illness. In addition, the physiotherapists who performed the intervention in the ICU were highly experienced. Those who performed the measurements were blinded to patient group assignment and had been well trained in assessment procedures beforehand.

The limitations include: the trial was single centred and included only patients who were ambulating before their ICU admissions. The participants evaluated their baseline health-related quality of life and functional independence retrospectively, after discharge from the ICU, which could have introduced recall bias. The physiotherapists who performed the intervention in the ICUs could not be blinded to the patient group assignment. The protocol of daily arousal and spontaneous breathing in the ICUs had not been fully implemented, with optimal sedation level in less than half of the intervention days in the twice-daily mobilisation group, which may have delayed upright mobilisation and reduced the frequency of sessions. Standard physiotherapy practice in the ICU includes upright mobilisation, thus withholding this intervention from participants in a control group would have been unethical. Finally, our trial needed to be terminated prematurely due to its three-year timeframe.

### Clinical and research implications

Despite the apparent underpowering of this study, this result itself was an important finding both clinically and research methodologically as described below.

Participating physiotherapists reported guiding interventions based on on-going assessment of each patient's responses, which is consistent with clinical practice guidelines [13]. However, the degree to which they report being confident in doing so may have been questionable at times [27]. It is conceivable that response-driven upright mobilisation was below the therapeutic threshold necessary to demonstrate objective short- and long-term benefits.

Much attention is being paid to not overly sedating mechanically ventilated patients. When such sedation is required, guidelines are emerging to reduce or lighten sedation daily. Thus, for physiotherapists to prescribe therapeutic upright mobilisation with maximal patient cooperation, they need to work closely with intensivists to maximise these windows of opportunity, i.e. periods of lightened sedation in their patients.

Our findings also elucidated limitations of RCTs in examining physiotherapy ICU interventions such as upright mobilisation, a singularly important intervention in the ICU based on extensive physiological and observational literature. Given the structure of an RCT in defining strict inclusion and exclusion criteria, we were unable to achieve a sample size consistent with adequate statistical power over three years. RCTs lend themselves to independent variables that are structured rather than variable. This is not how physiotherapy is typically practiced. Thus, studies are needed to better elucidate the clinical reasoning processes of physiotherapists in managing patients in the ICU, particularly with respect to upright positioning and mobilising them with the goal of walking. Such studies will identify how to set therapeutic parameters for a given patient, within and throughout each mobilisation session, within their margins of safety. Response-driven interventions are advocated in the ICU clinical practice guidelines; however, the principles for guiding such response-driven progression of mobilisation warrant further elucidation.

### Implications for future studies

The RCT methodology is limited with respect to evaluating physiotherapy interventions in ICU patients who are not only unique from each other but also whose status can change from moment-to-moment. Studies with mixed methods designs may have a role in establishing principles of response-driven interventions for use clinically, that help identify patients' readiness for being positioned upright and mobilised, and to maximise treatment responses within margins of safety. For example, qualitative studies and Delphi exercises may help elucidate physiotherapists' clinical

reasoning practices in the ICU context, which can provide a foundation for refining practice principles based on extensive physiologic literature. Quantitative studies require more appropriate research designs, e.g. serial single subject designs and time series that can better integrate multi-morbidity, patients' changing hemodynamic status, variable intervention parameters, as well as changes in ICU practices and policies, e.g. arousal and sedation lightening protocols such as in this RCT.

Another implication is the need for physiotherapists to work cooperatively with intensivists to so that they can capitalise on periods of greater arousal in patients being moved as previously described. Sedation protocols are central to initiating upright mobilisation of ICU patients on mechanical ventilation early and perform it regularly. Further, the parameters of mobilisation protocols in the literature are diverse and incompletely described, which makes interpretation of outcomes challenging [17]. Therefore, studying the implementation of the type and dose of therapy to determine the ideal intensity, duration, and frequency for each patient's individual need is warranted [45].

Last, cross-sectional retrospective studies could help identify the characteristics of those patient populations most likely to benefit from early upright mobilisation in the ICU, as well as those parameters and their timing that were most beneficial in achieving long-term functional outcomes. Despite such potentially large cohort studies and usefulness of their findings, responsibility rests with the physiotherapist regarding establishing the optimal prescriptive parameters of intervention for a given ICU patient.

## Conclusions

The intensive twice-daily mobilisation group neither started upright mobilisation early, nor yielded superior short- or long-term outcomes compared to the daily mobilisation group. Much was learned from this trial that necessarily needed to be terminated at three years, vis-à-vis clinical and research implications. In particular, we needed to explain why no trends were observed in our cohort of acutely and critically ill mechanically ventilated ICU patients, why the twice-daily upright mobilisation group appeared not to exhibit superior short- or long-term outcomes compared with those who underwent daily mobilisation. One potential significant confounding factor affecting the twice-daily mobilisation group was their deep sedation for several days after initiation of mechanical ventilation. Also, although the apparent lack of effect of response-driven intensive mobilisation could be explained by our RCT being underpowered statistically, detailed study of the construct of guiding intervention by patients' moment-to-moment responses could help reconcile this. The poor physical quality of life and low exercise capacity both groups displayed one year after ICU discharge supports the need for targeted and tailored upright mobilisation of patients in the ICU and the prescription of exercise well after ICU discharge.

## Disclosure statement

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# Paper III

# Female gender predicts poor long-term physical recovery after intensive care unit stay

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## Abstract

**Background:** Understanding the factors that influence the physical recovery processes of survivors after an intensive care unit (ICU) stay is paramount for long-term outcomes to be optimised. Therefore, it is feasible to identify predictors for poor long-term physical recovery in ICU survivors.

**Methods:** Based on secondary analysis of a trial of ICU patients undergoing mobilisation and one-year follow-up, linear regression analysis examined the association of exposure variables, i.e., baseline characteristics, severity of illness variables, ICU-related variables, and length of ICU and hospital stay, on physical recovery variables measured one year after ICU discharge, i.e., muscle strength, exercise capacity, and self-reported physical function.

**Results:** When the data was adjusted for age, female gender was associated with lower muscle strength ($p=0.003$), lower exercise capacity ($p<0.0001$) and worse self-reported physical function ($p=0.01$). Older age, when adjusted for gender, was associated with lower exercise capacity ($p<0.001$). After adjusting for gender and age, an association was observed between a lower score on one or two physical recovery variables and the following exposure variables: high body mass index, low functional independence, functional comorbidity and low self-reported physical function at baseline, muscle weakness at ICU discharge, and longer hospital stay.

**Conclusions:** Female gender is significantly associated with poor physical recovery one year after ICU discharge. Elucidation of the trajectory of physical recovery after critical illness could augment early intervention for at-risk patients, thereby maximising their long-term functional recovery.

**Keywords:** critical care, intensive care unit, gender, physical functional performance, physical recovery.

## Introduction

Many survivors of critical illness experience incomplete physical [1-6], and psychological [3,5,7] recovery for years after discharge from the intensive care unit (ICU). In recent years, the focus of ICU research has expanded towards understanding factors that influence patients' recovery processes and how long-term outcomes can be optimised [8,9]. ICU patients are a heterogeneous group and their trajectory of physical recovery is diverse [1,10]. Gender [1,10,11], older age [1,2,10,12,13], comorbidity [2,14], duration of continuous sedation [10], duration of bed rest [6,15] and ICU length of stay (LOS) [10,12,15], have all been reported to impact physical recovery in ICU survivors. Men have been reported to experience better physical recovery after critical illness than women [1,11]. Younger women with a shorter duration of sedation and length of ICU stay had better physical recovery than three other trajectory groups after acute respiratory failure, whereas older patients with a longer duration of sedation and ICU stay demonstrated the worst physical recovery of the four groups [10].

Women have been reported to have a higher incidence of ICU-acquired weakness (ICU-AW) after an ICU stay than men [16,17], a complication that is associated with long-term functional dependency after ICU discharge [16,18]. A recent meta-analysis identified several risk factors for developing ICU-AW [17]. These include female gender, greater severity of illness, multiple organ failure, systemic inflammatory response syndrome, sepsis, pharmacologic treatment (e.g., neuromuscular blocking agents, norepinephrine, and aminoglycosides), duration of mechanical ventilation, parental nutrition during the first week in the ICU, hyperglycaemia, electrolyte disturbances, hyperosmolarity and high lactate levels.

The growing number of patients surviving critical illness suggests that the approach to their care should be revisited to understand and improve their long-term function and quality of life [19]. Furthermore, identifying modifiable and non-modifiable risk factors in physical recovery is essential for prescribing physiotherapy in the ICU and after discharge from the

ICU [20]. Identifying risk factors for poor physical recovery can assist physical therapists in prescribing tailored interventions to improve patients' physical recovery during and after the ICU stay.

The objective of this study was to identify predictors of poor long-term physical recovery after critical illness. The hypothesis was that patients´ baseline characteristics (including age and gender), variables related to the severity of illness, ICU-related variables, and LOS increase the risk of poor physical recovery for at least one year after ICU discharge.

## Materials and methods

*Study design and setting*

A secondary analysis was conducted using data from a randomised controlled trial (RCT) that evaluated the effect of intensive twice-daily compared with once-daily physiotherapy, including upright positioning and mobilisation [21]. The original study included two mixed-patient population ICUs in a 620-bed tertiary care university hospital. Fifty adult patients who had been mechanically ventilated for longer than 48 hours participated. They ambulated independently before the ICU admission, and could cooperate in serial assessments over one year after ICU discharge. Excluded were patients with a poor survival prognosis, who had been in hospital for more than two weeks prior to the ICU admission, and who had contraindications for progressive upright mobilisation in the ICU.

*Outcomes*

Three outcome measures characterising the patients' physical recovery one year after ICU discharge were used as dependent variables. They reflected the three principal levels of the World Health Organization´s International Classification of Functioning, Disability and Health framework (ICF) [22]. The first level is limitation of body functions and structures and was represented by muscle strength in this study. Muscle strength was measured with the

Medical Research Council sum score (MRC-SS), which is a six-point scale that is used to grade muscle strength bilaterally in six muscle groups, ranging from 0 (no visible contraction) to 5 (normal strength) in each muscle group measured, with a potential maximum total score of 60 [23]. In the ICU setting, a score lower than 48 is consistent with a clinical diagnosis of ICU-AW [24,25]. The second ICF level is limitation of activities representing exercise capacity. Exercise capacity was assessed based on the distance walked in the six-minute walk (6MW) test (metres), performed in a standardised manner [26]. The third level of the ICF is limitation of participation represented by physical function. Self-reported physical function was evaluated with the Short-Form 36 Health Survey version 2, using the Physical Function domain (SF-36v2 PF domain) raw score, ranging from 0 (lowest score) to 100 (highest score) with higher scores indicating greater self-reported physical function [27]. The exposure variables were patients' baseline characteristics, variables related to illness severity, ICU-related variables, and ICU and hospital LOS. Each patient's functional independence was assessed with the Modified Barthel Index (MBI) [28]. Functional independence was assessed in ten activities of daily living, with a score ranging from 0 (totally dependent) to 100 (completely independent). The Charlson Comorbidity Index (CCI) [29], and the Functional Comorbidity Index (FCI) [30] were used to assess comorbidity at ICU admission. Severity of illness at ICU admission was assessed with the APACHE II (Acute Physiology and Chronic Health Evaluation II) scale.

*Statistical analysis*

Descriptive analysis was performed on the exposure variables i.e., baseline characteristics, severity of illness variables, ICU-related variables, and length of stay, as well as the three physical recovery variables i.e., MRC-SS, 6MW distance, and SF-36v2 PF domain displaying the trajectory of physical recovery at three, six and 12 months after ICU discharge. Continuous variables were described with means and standard deviations if they were

normally distributed and by median and interquartile range (IQR) if they had skewed distributions. Categorical variables were described by counts (n) and percentages (%). The descriptive analysis was tested for difference between gender using an independent t-test, Wilcoxon rank-sum test, or Chi-squared test.

Regression analysis was performed in three steps on each of the three dependent physical recovery variables at 12 months after ICU discharge, i.e., MRC-SS, 6MW distance, and SF-36v2 PF domain, versus the exposure variables, i.e., baseline characteristics, severity of illness variables, ICU-related variables, and ICU and hospital length of stay. First, to examine the bivariate association between each of the three physical recovery variables and the exposure variables, a Pearson correlation coefficient was calculated for normally distributed continuous variables and ordinal variables, and a Spearman correlation coefficient was calculated for continuous variables with skewed distributions. Second, a separate linear regression model was used to evaluate the associations of each of the exposure variables, one at a time with each of the physical recovery variables, while adjusting for gender and age. Third, the same model was then used to evaluate associations of the baseline characteristics of gender and age on each physical recovery variable at 12 months after ICU discharge. The association of gender and age with each physical recovery variable was tested first by reciprocally adjusting only for these two variables. Then, the association was again tested by additionally adjusting for each exposure variable, separately. Semi-partial squared correlation (type II) and semi-partial eta-square were calculated, respectively. Data were analysed with SAS software, version 9.4 (SAS Institute, Cary, NC, USA), and the Microsoft Office Excel 2007 program was used for data manipulation. Alpha was set at $<0.05$.

*Ethics approval and consent to participate:*

The parent RCT was approved by Landspitali - The National University Hospital of Iceland Ethics Committee (16/2011) and The Icelandic Data Protection Authority (2011020259ÞS/-).

The patients or next of kin signed informed consent. Registration at ClinicalTrials.gov for the RCT study: NCT02301273.

## Results

The original sample of 50 patients consisted of 33 males with a median (IQR) age of 62 (54-73) years and 17 females with a median (IQR) age of 63 (60-71) years. All were ambulating and independent in activities of daily life before the onset of critical illness (Table 1). The most common admission diagnoses were severe sepsis, pneumonia, acute respiratory failure and multi-trauma. With respect to employment status, more men were employed than women. The latter had a greater degree of unemployment and were receiving more disability benefits ($p<0.01$).

The physical recovery over the follow-up period of three, six and 12 months after ICU discharge, based on the three physical recovery variables, is shown in Table 2. Muscle strength (MRC-SS) was lower among women compared to men at three months ($p<0.001$), six months ($p<0.001$), and 12 months ($p<0.001$) after ICU discharge. Exercise capacity (6MW distance) was also lower among women than men at six months ($p<0.001$) and 12 months ($p<0.001$) after ICU discharge. Self-reported physical function (SF-36v2 PF domain) was not different between genders at baseline (Table 1), but lower among women at three months ($p<0.01$), six months ($p<0.001$) and 12 months ($p=0.01$) after ICU discharge (Table 2).

Bivariate associations of each exposure variable expressing the patients´ baseline characteristics, severity of illness, ICU-related variables and ICU and hospital LOS, with each physical recovery variable at 12 months after ICU discharge were analysed and are reported in supplementary tables 1 and 2.

Table 1. Baseline characteristics, severity of illness variables, ICU-related variables and length of stay

| | Women n=17 | | Men n=33 | | p value |
|---|---|---|---|---|---|
| Baseline characteristics | | | | | |
| Age | 63 | (60-71) | 62 | (54-73) | .52 |
| Residence, home | 17 | 100% | 32 | 97% | .47 |
| Married or cohabiting | 12 | 71% | 21 | 64% | .62 |
| Elementary school education (ISCED 1,2) | 11 | 65% | 16 | 48% | .28 |
| Employment status | | | | | <0.01 |
| Employed | 3 | 18% | 17 | 52% | |
| Retired | 5 | 29% | 13 | 39% | |
| Unemployment | 3 | 18% | 1 | 3% | |
| Disability | 6 | 35% | 2 | 6% | |
| Regular exercise (> 150 min/week) | 1 | 7% | 10 | 30% | .06 |
| BMI ($kg/m^2$) | 36.0 | (28.4-43.7) | 30.8 | (28.9-32.7) | .07 |
| Modified Barthel Index (MBI) | 100 | (100-100) | 100 | (100-100) | .06 |
| SF-36v2 PF domain (raw score) | 60.0 | (41.3-78.7) | 72.5 | (63.6-81.4) | .16 |
| Charlson Comorbidity Index (CCI) | 3 | (2-5) | 2 | (0-4) | .09 |
| Functional Comorbidity Index (FCI) | 2 | (2-4) | 2 | (1-4) | .08 |
| Severity of illness | | | | | |
| ICU admission diagnosis | | | | | .39 |
| Severe sepsis / septic shock | 9 | 53% | 14 | 42% | |
| Pneumonia | 4 | 24% | 4 | 12% | |
| Acute respiratory failure | 2 | 12% | 2 | 6% | |
| Multi-trauma | 0 | 0% | 6 | 18% | |
| Major elective surgery | 0 | 0% | 3 | 9% | |
| Cardiac | 1 | 6% | 2 | 6% | |
| Other | 1 | 6% | 2 | 6% | |
| APACHE II score | 23.8 | (18.6-29.0) | 22.4 | (19.2-25.5) | .61 |
| Sepsis during ICU stay | 11 | 65% | 15 | 45% | .20 |
| ARDS during ICU stay | 6 | 35% | 9 | 27% | .56 |
| Renal replacement therapy in ICU | 5 | 29% | 7 | 21% | .52 |
| ICU-related variables | | | | | |
| No upright mobilisation $\geq$ first 7 days | 10 | 59% | 18 | 56% | .86 |
| Upright mobilisation started on day | 8 | (5-22) | 8 | (5-13) | .43 |
| Duration of MV (days) | 15 | (6-22) | 7.5 | (5-11) | .07 |
| MRC-SS at ICU discharge | 36.9 | (28.3-45.5) | 43.1 | (37.7-48.6) | .20 |
| MRC-SS at ICU discharge, % of full score | 61.5 | (47.2-75.8) | 71.9 | (62.8-81.0) | .20 |
| ICU-AW indication (MRC-SS < 48) | 8 | 80% | 13 | 57% | .20 |
| Modified Barthel Index at ICU discharge | 2 | (0-5) | 7 | (0-16) | .21 |
| Length of stay (LOS) | | | | | |
| ICU LOS (days) | 19.2 | (8-24) | 10.7 | (7-19) | .12 |
| Hospital LOS (days) | 40.6 | (24–57) | 28 | (16-50) | .16 |

Data is presented as mean (95%CI), median (IQR) or number (%). Abbreviations: APACHE II score, Acute Physiology and Chronic Health Evaluation II score; ARDS, acute respiratory distress syndrome; BMI, body mass index; CI, confidence interval; ICU, intensive care unit; ICU-AW, intensive care unit acquired weakness; ISCED, International Standard Classification of Education; IQR, inter-quartile range; MBI, Modified Barthel Index; MRC-SS, Medical Research Council sum score; SF-36v2 PF domain, Short-Form 36 Health Survey version 2 Physical Function domain. ICU-AW indication is defined: MRC-SS < 48 points; Upright mobilisation is defined: Sitting on edge of bed, or standing up or walking with or without assistance consistent with level 3-10 on the ICU Mobility Scale [31], including assisted active, active exercises, functional, balance and transfer training in those positions.

Table 2. Trajectory of physical recovery after ICU discharge

| | Women n=17 | | Men n=33 | | p value |
|---|---|---|---|---|---|
| 3 months after ICU discharge | | | | | |
| MRC-SS | 48.7 | (45.4-51.9) | 56.0 | (54.2-57.8) | <0.001 |
| MRC-SS, % of full score | 81.1 | (75.7-86.6) | 93.3 | (90.4-96.3) | <0.001 |
| 6MW distance | 380.6 | (306.0-455.2) | 480.3 | (414.8-545.7) | 0.09 |
| 6MW distance, % predicted value | 61.8 | (51.1-72.6) | 68.9 | (60.1-77.8) | 0.37 |
| SF-36v2 PF domain (raw score) | 30.8 | (14.9-46.6) | 57.9 | (46.5-69.3) | <0.01 |
| SF-36v2 PF domain (norm-based score) | 31.0 | (25.0-37.1) | 41.4 | (37.1-45.8) | <0.01 |
| 6 months after ICU discharge | | | | | |
| MRC-SS | 50.1 | (48.5-51.7) | 57.3 | (56.1-58.6) | <0.001 |
| MRC-SS, % of full score | 83.5 | (80.8-86.2) | 95.6 | (93.5-97.7) | <0.001 |
| 6MW distance | 346.0 | (230.3-461.7) | 539.8 | (480.6-599.0) | <0.001 |
| 6MW distance, % predicted value | 55.9 | (38.3-73.6) | 77.9 | (70.1-85.7) | <0.01 |
| SF-36v2 PF domain (raw score) | 28.2 | (15.8-40.6) | 65.2 | (52.9-77.5) | <0.001 |
| SF-36v2 PF domain (norm-based score) | 30.1 | (25.3-34.8) | 44.2 | (39.5-48.9) | <0.001 |
| 12 months after ICU discharge | | | | | |
| MRC-SS | 54.2 | (51.6-56.7) | 57.8 | (56.7-59.0) | <0.001 |
| MRC-SS, % of full score | 90.3 | (86.0-94.6) | 96.4 | (94.5-98.3) | <0.001 |
| 6MW distance | 281.9 | (132.5-431.3) | 557.3 | (500.5-614.1) | <0.001 |
| 6MW distance, % predicted value | 45.9 | (22.6-69.1) | 81.2 | (73.8-88.5) | <0.001 |
| SF-36v2 PF domain (raw score) | 43.2 | (30.3-56.1) | 66.0 | (55.3-76.7) | 0.01 |
| SF-36v2 PF domain (norm-based score) | 35.8 | (30.9-40.7) | 44.5 | (40.4-48.6) | 0.01 |

Data is presented as mean (95%CI). Abbreviations: CI, confidence interval; ICU, intensive care unit; MRC-SS, Medical Research Council sum score; SF-36v2 PF domain Short-Form 36 Health Survey version 2 Physical Function domain; 6MW distance, six-minute walk distance. MRC-SS measures manual muscle strength in six muscle groups bilaterally (shoulder abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, ankle dorsiflexors)with a MRC-SS ranging from 0 to 60. Reference value for % predicted value in 6MW test for gender and age [32]. SF-36v2 PF domain raw score, range from 0-100, higher score indicating better physical function, SF-36v2 PF domain (norm-based score) has a mean of 50 with a SD = 10.

Using multivariate linear regression models, after adjusting for gender and age, we observed associations between six exposure variables and outcome in one or two physical recovery variables at 12 months after ICU discharge (Tables 3a, 3b and 3c). When adjusted for age and gender, the associations for the four baseline exposure variables were: 1) Higher BMI was associated with shorter walking distance (6MW test) (p=0.03). 2) Higher comorbidity measured with the FCI was associated with shorter walking distance (6MW test) (p=0.01). 3) Lower self-reported physical function measured with the SF-36v2 PF domain was associated with shorter walking distance (6MW test) (p=0.01) and with lower self-reported physical function (SF-36v2 PF domain) (p<0.02). 4) Lower functional independence (MBI) was associated with lower self-reported physical function (SF-36v2 PF domain) (p=0.04). One ICU-related variable, adjusted for age and gender, was associated

with two physical recovery variables at 12 months. Lower muscle strength measured at ICU discharge was associated with muscle weakness (MRC-SS) ($p=0.01$) and with lower self-reported physical function (SF-36v2 PF domain) ($p=0.03$). One LOS variable, adjusted for age and gender, was associated with two physical recovery variables at 12 months. Hospital LOS was associated with muscle weakness (MRC-SS) ($p<0.02$) and with shorter walking distance (6MW test) ($p<0.03$).

The results of the multivariate regression models adjusting for age only, showed that the female gender had an association with all three physical recovery variables at 12 months after ICU discharge: with muscle weakness (MRC-SS) (Eta-Square 0.21, CI (-0.75 to -0.17), $p=0.003$); with shorter walking distance (6MW test) (Eta-Square 0.40, CI (-0.87 to -0.40), $p<0.0001$); and with lower self-reported physical function (SF-36v2 PF domain), (Eta-Square 0.14, CI (-0.68 to -0.09), $p=0.01$). The models, after adjusting for both age and each exposure variable, showed that the female gender had an association with muscle weakness (MRC-SS) at 12 months after ICU discharge for all exposure variables, except for one ICU-related exposure variable, i.e., muscle strength (MRC-SS) at ICU discharge (Table 3a). The models showed that the female gender had an association with shorter walking distance (6MW test) at 12 months after ICU discharge when adjusted for both age and each exposure variables (Table 3b). Furthermore, the models showed that the female gender had an association with lower self-reported physical function (SF-36v2 PF domain) at 12 months after ICU discharge, when adjusted for both age and each exposure variable except for four exposure variables, namely employment status, self-reported physical function (SF-36v2 PF domain) at baseline, muscle strength at ICU discharge (MRC-SS) and ICU-AW at ICU discharge (Table 3c).
The findings from the multivariate regression models, when adjusted for gender only, showed that age was associated with shorter walking distance (6MW test) 12 months after ICU discharge (Eta-Square 0.20, CI (-0.68 to -0.21), $p<0.001$). The same models, after adjusting

for both gender and each exposure variable, showed that age was associated with shorter walking distance at 12 months after ICU discharge for all exposure variables except two, i.e., employment status and ICU-AW at ICU discharge (Table 3b).

Table 3a. Exposure variables and the physical recovery variable muscle strength at 12 months after ICU discharge

| Model: Linear Regression Model<br>Dependent Variable: MRC-SS at 12 months after ICU discharge | | | | |
|---|---|---|---|---|
| Parameter Estimates | | | | |
| Variable | Standardised Estimate | Squared Semipartial r / Eta-Square | 95% CI | p Value |
| Gender | -0.46 | 0.21 | -0.75 to -0.17 | 0.003 |
| Age | -0.27 | 0.07 | -0.56 to 0.02 | 0.065 |
| Married or cohabiting | 0.05 | 0.00 | -0.25 to 0.35 | 0.745 |
| Gender | -0.46 | 0.21 | -0.76 to -0.17 | 0.003 |
| Age | -0.28 | 0.08 | -0.58 to 0.02 | 0.065 |
| Elementary school education (ISCED 1.2) | 0.04 | 0.00 | -0.26 to 0.34 | 0.789 |
| Gender | -0.47 | 0.22 | -0.77 to -0.17 | 0.003 |
| Age | -0.27 | 0.07 | -0.56 to 0.02 | 0.068 |
| Employment status | | 0.01 | | 0.955 |
| Gender | | 0.17 | | 0.008 |
| Age | | 0.01 | | 0.557 |
| Regular exercise (>150 min/week) | 0.11 | 0.01 | -0.20 to 0.41 | 0.473 |
| Gender | -0.43 | 0.18 | -0.73 to -0.13 | 0.006 |
| Age | -0.29 | 0.08 | -0.58 to 0.01 | 0.055 |
| BMI ($kg/m^2$) at baseline | -0.13 | 0.02 | -0.44 to 0.19 | 0.420 |
| Gender | -0.41 | 0.17 | -0.72 to -0.10 | 0.012 |
| Age | -0.29 | 0.08 | -0.58 to 0.00 | 0.053 |
| Modified Barthel Index (MBI) at baseline | -0.02 | 0.00 | -0.31 to 0.28 | 0.913 |
| Gender | -0.46 | 0.21 | -0.75 to -0.17 | 0.003 |
| Age | -0.27 | 0.07 | -0.57 to 0.02 | 0.071 |
| SF-36v2 PF domain at baseline | -0.09 | 0.01 | -0.44 to 0.26 | 0.593 |
| Gender | -0.45 | 0.20 | -0.77 to -0.12 | 0.008 |
| Age | -0.32 | 0.10 | -0.65 to 0.01 | 0.054 |
| Charlson Comorbidity Index (CCI) | 0.22 | 0.05 | -0.10 to 0.53 | 0.169 |
| Gender | -0.48 | 0.23 | -0.77 to -0.19 | 0.002 |
| Age | -0.36 | 0.13 | -0.67 to -0.05 | 0.025 |
| Functional Comorbidity Index (FCI) | -0.15 | 0.02 | -0.47 to 0.16 | 0.325 |
| Gender | -0.43 | 0.18 | -0.72 to -0.14 | 0.005 |
| Age | -0.22 | 0.05 | -0.53 to 0.09 | 0.152 |
| ICU admission diagnosis | | 0.11 | | 0.521 |
| Gender | | 0.15 | | 0.011 |
| Age | | 0.10 | | 0.034 |
| APACHE II | 0.10 | 0.01 | -0.21 to 0.41 | 0.524 |

| | | | | |
|---|---|---|---|---|
| Gender | -0.46 | 0.21 | -0.75 to -0.17 | 0.003 |
| Age | -0.30 | 0.09 | -0.61 to 0.01 | 0.054 |
| Sepsis during ICU stay | -0.07 | 0.00 | -0.38 to 0.24 | 0.665 |
| Gender | -0.44 | 0.19 | -0.74 to -0.14 | 0.005 |
| Age | -0.26 | 0.07 | -0.56 to 0.04 | 0.089 |
| ARDS during ICU stay | -0.04 | 0.00 | -0.35 to 0.27 | 0.799 |
| Gender | -0.46 | 0.21 | -0.75 to -0.17 | 0.003 |
| Age | -0.28 | 0.08 | -0.60 to 0.03 | 0.073 |
| Renal replacement therapy during ICU stay | 0.21 | 0.04 | -0.07 to 0.50 | 0.137 |
| Gender | -0.48 | 0.23 | -0.77 to -0.20 | 0.002 |
| Age | -0.29 | 0.08 | -0.57 to 0.00 | 0.048 |
| No upright mobilisation $\geq$ first 7 days | -0.18 | 0.03 | -0.48 to 0.12 | 0.236 |
| Gender | -0.42 | 0.18 | -0.72 to -0.13 | 0.006 |
| Age | -0.24 | 0.06 | -0.54 to 0.06 | 0.108 |
| Upright mobilisation started on day | -0.01 | 0.00 | -0.32 to 0.30 | 0.946 |
| Gender | -0.43 | 0.18 | -0.74 to -0.12 | 0.008 |
| Age | -0.30 | 0.09 | -0.60 to 0.01 | 0.056 |
| Duration of MV | 0.03 | 0.00 | -0.28 to 0.35 | 0.824 |
| Gender | -0.47 | 0.22 | -0.77 to -0.16 | 0.004 |
| Age | -0.28 | 0.08 | -0.58 to 0.02 | 0.069 |
| MRC-SS at ICU discharge | 0.45 | 0.20 | 0.11 to 0.80 | 0.012 |
| Gender | -0.29 | 0.08 | -0.61 to 0.04 | 0.082 |
| Age | -0.15 | 0.02 | -0.48 to 0.19 | 0.375 |
| ICU-AW indication (MRC-SS < 48) | -0.33 | 0.11 | -0.72 to 0.06 | 0.098 |
| Gender | -0.35 | 0.12 | -0.69 to -0.01 | 0.045 |
| Age | -0.13 | 0.02 | -0.52 to 0.26 | 0.488 |
| MBI at ICU discharge | 0.17 | 0.03 | -0.24 to 0.58 | 0.412 |
| Gender | -0.42 | 0.18 | -0.72 to -0.11 | 0.009 |
| Age | -0.16 | 0.03 | -0.56 to 0.23 | 0.412 |
| ICU LOS | 0.04 | 0.00 | -0.28 to 0.35 | 0.813 |
| Gender | -0.47 | 0.22 | -0.78 to -0.16 | 0.004 |
| Age | -0.28 | 0.08 | -0.58 to 0.02 | 0.068 |
| Hospital LOS | -0.35 | 0.12 | -0.64 to -0.07 | 0.017 |
| Gender | -0.34 | 0.12 | -0.63 to -0.06 | 0.020 |
| Age | -0.24 | 0.06 | -0.51 to 0.03 | 0.078 |

Missed data for MRC-SS at 12 months. Female: 3 diseased; 2 telephone/mail contact. Male: 2 diseased; 2 trauma; 3 lost to follow up.

Table 3b. Exposure variables and the physical recovery variable exercise capacity at 12 months after ICU discharge

| Model: Linear Regression Model<br>Dependent Variable: 6MW distance at 12 months after ICU discharge | | | | |
|---|---|---|---|---|
| Parameter Estimates | | | | |
| Variable | Standardised Estimate | Squared Semipartial r / Eta-Square | 95% CI | p Value |
| Age | -0.45 | 0.20 | -0.68 to -0.21 | <.001 |
| Gender | -0.63 | 0.40 | -0.87 to -0.40 | <.0001 |
| Married or cohabiting | 0.04 | 0.00 | -0.22 to 0.30 | 0.756 |
| Gender | -0.64 | 0.41 | -0.88 to -0.39 | <.0001 |
| Age | -0.46 | 0.21 | -0.72 to -0.20 | 0.001 |
| Elementary school education (ISCED 1.2) | -0.11 | 0.01 | -0.35 to 0.13 | 0.365 |
| Gender | -0.61 | 0.37 | -0.85 to -0.37 | <.001 |
| Age | -0.44 | 0.19 | -0.67 to -0.20 | 0.001 |
| Employment status | | 0.03 | | 0.581 |
| Gender | | 0.21 | | <.001 |
| Age | | 0.03 | | 0.137 |
| Regular exercise (> 150 min/week) | 0.23 | 0.05 | 0.00 to 0.46 | 0.055 |
| Gender | -0.58 | 0.34 | -0.81 to -0.36 | <.0001 |
| Age | -0.48 | 0.23 | -0.71 to -0.26 | 0.000 |
| BMI ($kg/m^2$) at baseline | -0.27 | 0.07 | -0.52 to -0.03 | 0.030 |
| Gender | -0.52 | 0.27 | -0.76 to -0.28 | <.0001 |
| Age | -0.51 | 0.26 | -0.73 to -0.28 | <.000 |
| Modified Barthel Index (MBI) at baseline | 0.14 | 0.02 | -0.11 to 0.40 | 0.254 |
| Gender | -0.59 | 0.35 | -0.83 to -0.34 | <.0001 |
| Age | -0.42 | 0.18 | -0.11 to 0.40 | 0.001 |
| SF-36v2 PF domain at baseline | 0.35 | 0.12 | 0.08 to 0.63 | 0.014 |
| Gender | -0.50 | 0.25 | -0.74 to -0.27 | <.0001 |
| Age | -0.29 | 0.08 | -0.55 to -0.02 | 0.035 |
| Charlson Comorbidity Index (CCI) | -0.04 | 0.00 | -0.32 to 0.24 | 0.795 |
| Gender | -0.62 | 0.38 | -0.87 to -0.38 | <.000 |
| Age | -0.43 | 0.18 | -0.71 to -0.16 | 0.003 |
| Functional Comorbidity Index (FCI) | -0.30 | 0.09 | -0.53 to -0.07 | 0.014 |
| Gender | -0.54 | 0.29 | -0.77 to -0.32 | <.0001 |
| Age | -0.38 | 0.14 | -0.60 to -0.16 | <.002 |
| ICU admission diagnosis | | 0.16 | | 0.458 |
| Gender | | 0.28 | | <.0001 |
| Age | | 0.08 | | 0.002 |
| APACHE II | -0.11 | 0.01 | -0.36 to 0.15 | 0.400 |
| Gender | -0.62 | 0.38 | -0.86 to -0.38 | <.0001 |
| Age | -0.41 | 0.17 | -0.66 to -0.16 | 0.003 |
| Sepsis during ICU stay | -0.13 | 0.02 | -0.39 to 0.12 | 0.293 |
| Gender | -0.59 | 0.35 | -0.84 to -0.35 | <.0001 |
| Age | -0.42 | 0.18 | -0.66 to -0.17 | <.002 |
| ARDS during ICU stay | 0.06 | 0.00 | -0.21 to 0.33 | 0.646 |
| Gender | -0.62 | 0.38 | -0.86 to -0.38 | <.0001 |

| | | | | |
|---|---|---|---|---|
| Age | -0.42 | 0.18 | -0.69 to -0.16 | <.003 |
| Renal replacement therapy during ICU stay | 0.21 | 0.04 | -0.02 to 0.43 | 0.072 |
| Gender | -0.65 | 0.42 | -0.88 to -0.42 | <.0001 |
| Age | -0.45 | 0.20 | -0.68 to -0.23 | <.0001 |
| No upright mobilisation ≥ first 7 days | 0.06 | 0.00 | -0.19 to 0.31 | 0.620 |
| Gender | -0.64 | 0.41 | -0.89 to -0.39 | <.0001 |
| Age | -0.44 | 0.19 | -0.69 to -0.20 | 0.001 |
| Upright mobilisation started on day | -0.02 | 0.00 | -0.28 to 0.25 | 0.885 |
| Gender | -0.61 | 0.37 | -0.88 to -0.35 | <.0001 |
| Age | -0.44 | 0.19 | -0.69 to -0.18 | 0.001 |
| Duration of MV | -0.11 | 0.01 | -0.37 to 0.15 | 0.392 |
| Gender | -0.59 | 0.35 | -0.85 to -0.34 | <.0001 |
| Age | -0.43 | 0.18 | -0.67 to -0.18 | 0.001 |
| MRC-SS at ICU discharge | 0.25 | 0.06 | -0.16 to 0.65 | 0.219 |
| Gender | -0.42 | 0.18 | -0.80 to -0.03 | 0.035 |
| Age | -0.38 | 0.14 | -0.73 to -0.04 | 0.033 |
| ICU-AW indication (MRC-SS <48) | -0.20 | 0.04 | -0.61 to 0.21 | 0.329 |
| Gender | -0.47 | 0.22 | -0.83 to -0.11 | 0.013 |
| Age | -0.36 | 0.13 | -0.75 to 0.02 | 0.063 |
| MBI at ICU discharge | -0.05 | 0.00 | -0.39 to 0.29 | 0.774 |
| Gender | -0.65 | 0.42 | -0.91 to -0.38 | <.0001 |
| Age | -0.48 | 0.23 | -0.80 to -0.16 | <.005 |
| ICU LOS | -0.08 | 0.01 | -0.33 to 0.18 | 0.551 |
| Gender | -0.61 | 0.37 | -0.86 to -0.35 | <.0001 |
| Age | -0.44 | 0.19 | -0.68 to -0.19 | <.001 |
| Hospital LOS | -0.27 | 0.07 | -0.52 to -0.03 | 0.028 |
| Gender | -0.51 | 0.26 | -0.76 to -0.27 | <.0001 |
| Age | -0.45 | 0.20 | -0.67 to -0.23 | <.0001 |

Missed data for 6MW test at 12 months. Female: 3 diseased; 1 trauma; 3 declined outcome measure; 2 telephone/mail contact. Male: 2 diseased; 3 lost to follow up; 4 declined outcome measure.

Table 3c. Exposure variables and the physical recovery variable self reported physical function (SF-36v2 PF domain) at 12 months after ICU discharge

| Model: Linear Regression Model<br>Dependent Variable: SF-36v2 Physical function domain at 12 months after ICU discharge | | | | |
|---|---|---|---|---|
| Parameter Estimates | | | | |
| Variable | Standardised Estimate | Squared Semipartial r / Eta-Square | 95% CI | p Value |
| Gender | -0.38 | 0.14 | -0.68 to -0.09 | 0.013 |
| Age | -0.18 | 0.03 | -0.47 to 0.12 | 0.236 |
| Married or cohabiting | -0.20 | 0.04 | -0.50 to 0.10 | 0.188 |
| Gender | -0.39 | 0.15 | -0.68 to -0.09 | 0.012 |
| Age | -0.13 | 0.02 | -0.43 to 0.18 | 0.404 |
| Elementary school education (ISCED 1.2) | -0.22 | 0.05 | -0.51 to 0.08 | 0.145 |
| Gender | -0.36 | 0.13 | -0.65 to -0.06 | 0.018 |
| Age | -0.17 | 0.03 | -0.46 to 0.13 | 0.256 |
| Employment status | | 0.04 | | 0.622 |
| Gender | | 0.07 | | 0.076 |
| Age | | 0.00 | | 0.641 |
| Regular exercise (> 150 min/week) | 0.17 | 0.03 | -0.14 to 0.49 | 0.262 |
| Gender | -0.33 | 0.11 | -0.64 to -0.02 | 0.037 |
| Age | -0.20 | 0.04 | -0.50 to 0.10 | 0.186 |
| BMI ($kg/m^2$) at baseline | -0.15 | 0.02 | -0.47 to 0.17 | 0.352 |
| Gender | -0.33 | 0.11 | -0.65 to -0.01 | 0.041 |
| Age | -0.20 | 0.04 | -0.50 to 0.10 | 0.186 |
| Modified Barthel Index (MBI) at baseline | 0.30 | 0.09 | 0.01 to 0.59 | 0.041 |
| Gender | -0.37 | 0.14 | -0.65 to -0.08 | 0.013 |
| Age | -0.12 | 0.01 | -0.41 to 0.17 | 0.402 |
| SF-36v2 PF domain at baseline | 0.39 | 0.15 | 0.07 to 0.70 | 0.018 |
| Gender | -0.29 | 0.08 | -0.58 to 0.00 | 0.054 |
| Age | -0.03 | 0.00 | -0.34 to 0.28 | 0.834 |
| Charlson Comorbidity Index (CCI) | -0.15 | 0.02 | -0.48 to 0.18 | 0.362 |
| Gender | -0.38 | 0.14 | -0.68 to -0.08 | 0.014 |
| Age | -0.11 | 0.01 | -0.44 to 0.22 | 0.501 |
| Functional Comorbidity Index (FCI) | -0.24 | 0.06 | -0.54 to 0.07 | 0.127 |
| Gender | -0.35 | 0.12 | -0.64 to -0.05 | 0.022 |
| Age | -0.11 | 0.01 | -0.41 to 0.19 | 0.461 |
| ICU admission diagnosis | | 0.13 | | 0.459 |
| Gender | | 0.09 | | 0.048 |
| Age | | 0.04 | | 0.183 |
| APACHE II | -0.12 | 0.01 | -0.44 to 0.19 | 0.435 |
| Gender | -0.38 | 0.14 | -0.68 to -0.08 | 0.014 |
| Age | -0.14 | 0.02 | -0.45 to 0.18 | 0.389 |
| Sepsis during ICU stay | -0.04 | 0.00 | -0.36 to 0.28 | 0.809 |
| Gender | -0.37 | 0.14 | -0.69 to -0.05 | 0.023 |
| Age | -0.17 | 0.03 | -0.48 to 0.14 | 0.268 |
| ARDS during ICU stay | 0.17 | 0.03 | -0.15 to 0.48 | 0.293 |
| Gender | -0.39 | 0.15 | -0.68 to -0.09 | 0.012 |

| | | | | |
|---|---|---|---|---|
| Age | -0.12 | 0.01 | -0.44 to 0.19 | 0.443 |
| Renal replacement therapy during ICU stay | 0.07 | 0.00 | -0.24 to 0.37 | 0.660 |
| Gender | -0.39 | 0.15 | -0.70 to -0.09 | 0.012 |
| Age | -0.18 | 0.03 | -0.48 to 0.12 | 0.231 |
| No upright mobilisation for ≥ first 7 days | 0.04 | 0.00 | -0.28 to 0.35 | 0.820 |
| Gender | -0.37 | 0.14 | -0.68 to -0.06 | 0.020 |
| Age | -0.22 | 0.05 | -0.53 to 0.09 | 0.160 |
| Upright mobilisation started on day | 0.00 | 0.00 | -0.32 to 0.32 | 0.978 |
| Gender | -0.40 | 0.16 | -0.72 to -0.09 | 0.015 |
| Age | -0.17 | 0.03 | -0.49 to 0.14 | 0.265 |
| Duration of MV | -0.17 | 0.03 | -0.48 to 0.15 | 0.284 |
| Gender | -0.34 | 0.12 | -0.65 to -0.04 | 0.030 |
| Age | -0.14 | 0.02 | -0.44 to 0.16 | 0.350 |
| MRC-SS at ICU discharge | 0.42 | 0.18 | 0.04 to 0.80 | 0.033 |
| Gender | -0.23 | 0.05 | -0.59 to 0.15 | 0.215 |
| Age | -0.00 | 0.00 | -0.37 to 0.36 | 0.99 |
| ICU-AW indication (MRC-SS <48) | -0.38 | 0.14 | -0.79 to 0.04 | 0.075 |
| Gender | -0.29 | 0.08 | -0.66 to 0.07 | 0.112 |
| Age | 0.06 | 0.00 | -0.35 to 0.47 | 0.755 |
| MBI at ICU discharge | 0.14 | 0.02 | -0.27 to 0.56 | 0.487 |
| Gender | -0.37 | 0.14 | -0.68 to -0.05 | 0.024 |
| Age | -0.08 | 0.01 | -0.48 to 0.32 | 0.690 |
| ICU LOS | -0.09 | 0.01 | -0.41 to 0.22 | 0.548 |
| Gender | -0.36 | 0.13 | -0.67 to -0.05 | 0.024 |
| Age | -0.16 | 0.03 | -0.46 to 0.15 | 0.300 |
| Hospital LOS | -0.22 | 0.05 | -0.52 to 0.09 | 0.167 |
| Gender | -0.32 | 0.10 | -0.62 to -0.01 | 0.045 |
| Age | -0.17 | 0.03 | -0.46 to 0.13 | 0.261 |

Missed data for SF-36v2 at 12 months. Female: 3 diseased. Male: 2 diseased; 3 lost to follow up; 1 declined outcome measure.

## Discussion

The main result of this study was that women who were ambulating and functionally independent before an onset of critical illness had significantly poorer physical recovery at one year after ICU discharge compared with men. Our hypothesis was supported, six baseline characteristics (female gender, higher age, higher BMI, lower functional independence, higher functional comorbidity, lower self-reported physical quality of life), one ICU-related variable (muscle weakness at ICU discharge) and longer hospital LOS were associated with incomplete physical recovery one year after discharge from the ICU.

When we analysed the trajectory of physical recovery of our ICU patient cohort at three, six and 12 months after ICU discharge, we observed poorer long-term physical recovery, both in the raw and predicted scores for women compared to men (Table 2). However, no statistical difference was observed between genders in baseline characteristics, severity of illness, ICU-related variables and LOS, except that more women were unemployed or receiving disability benefit than men (Table 1). No difference was detected in muscle strength between genders at ICU discharge (Table 1). However, at three, six and 12 months after ICU discharge, women showed lower muscle strength measured with the MRC-SS then men. Interestingly, the women in the present study had similar MRC-SS at ICU discharge and lower MRC-SS at three and six months after ICU discharge than patients diagnosed with ICU-AW in a recent study [16]. In the present study, 80% of women were diagnosed clinically with ICU-AW at ICU discharge, which could explain their low muscle strength. Our finding that exercise capacity was limited at three, six and 12 months after ICU discharge was similar to the results of Fan and colleagues, who reported impairment in six-minute walking distance in survivors after acute lung injury [6], and also similar to the findings of Herridge and colleagues in survivors of ARDS one year after ICU discharge [33]. The present study, however, identified more severe limitations in exercise capacity in women compared with

men, which agrees with the findings of a recent systematic review and meta-analysis reporting that the female gender was associated with shorter 6MW distance after critical illness [34]. In addition, the women in our study had lower self-reported physical function (SF-36v2 PF domain) at three and six months after ICU discharge than patients who were diagnosed with ICU-AW during their ICU stay [16]. A recent post-hoc analysis of a multi-centre trial of sepsis patients reported no gender difference in health-related quality of life one year after ICU discharge [35].

In the present study, the female gender had a high association with poorer outcome in one self-reported and two performance-based physical recovery variables when adjusted for age, which has not previously been reported. When the model was adjusted for age and each exposure variable, one at a time, female gender had an association with poorer outcome in all three physical recovery variables after adjusting for age and 61 of the 66 exposure variables. An association has been reported between male gender and greater physical recovery after ICU stay [1,11], and an association has been reported between younger women with fewer days of sedation and greater physical recovery after acute respiratory failure compared with three other trajectory groups [10]. The women in the present cohort may have been prone to poor physical outcome; they were older, had longer duration of mechanical ventilation and ICU length of stay compared with the women in the study of Gandotra and colleagues [10], and additionally, 80% were diagnosed clinically with ICU-AW at ICU discharge. The only gender difference in baseline characteristics in the present study was employment status, with more women unemployed and on disability benefits than in the general population in Iceland [36,37]. Those women receiving disability benefits were ambulating and independent in activities of daily life and did not have severe physical disability before admission to the ICU. However, employment status, after adjustment for age and gender, was not independently associated with any of the three physical recovery variables.

In the present cohort, age when adjusted for gender, was negatively associated with walking distance (6MW test) at 12 months after ICU discharge, but no association was observed with muscle strength (MRC-SS) or self-reported physical function (SF-36v2 PF domain). Older age has been reported to negatively influence physical recovery in ICU survivors [1,2,12]. Furthermore, older age and comorbidity or a high level of premorbid disability were associated with poor physical outcome after critical illness [2,13]. Gandotra and colleagues [10] reported that age was not the only determinant of physical recovery after critical illness, but age, gender, sedation time, length of ICU stay, all influenced physical recovery after acute respiratory failure.

Both women and men with high BMI, with low self-reported physical function (SF-36v2 PF domain) at baseline, with low functional independence (MBI) at baseline, and with higher functional comorbidity (FCI) are at risk for poor long-term physical recovery. A recent study reported that functional comorbidity (FCI) was strongly associated with lower health-related quality of life in survivors in the year following critical illness [14]. A study of ARDS survivors reported an association between comorbidities (CCI), and physical decline measured with the same three physical recovery variables as in the present study during a five year follow-up [2]. Muscle weakness at ICU discharge (MRC-SS), had a negative association with two physical recovery variables at 12 months after ICU discharge. This agrees with the findings of Hermans and colleagues [38], which suggested that muscle weakness, clinically diagnosed in the ICU with MRC-SS, influences the patient´s health beyond hospital discharge. Furthermore, ICU-AW diagnosed in the ICU has been associated with low physical function (SF-36v2 PF domain) at six months after ICU discharge [39]. In the present study, longer hospital stay had an association with muscle weakness (MRC-SS) and shorter walking distance (6MW test) at 12 months after ICU discharge. Interestingly, no severity of illness variables: i.e., admission diagnoses, APACHE II score, sepsis, ARDS, or renal replacement

therapy, had an association with poor physical recovery at 12 months after ICU discharge. This agrees with the findings of a recent study that reported no association between APACHE II scores or ventilator days and health-related quality of life at six months after ICU discharge [14].

The strengths of our study include the one self-reported (SF-36v2 PF domain) and two performance-based (MRC-SS and 6MW test) physical recovery outcomes, consistent with the ICF framework, describing patients' physical recovery at 12 months after ICU discharge. Measuring distinct constructs of physical function, both performance-based and self-reported constructs are important for follow-up assessment of physical recovery in ICU survivors [40]. Gender as well as age are corrected for in equations that predict 6MW distance in healthy populations [26], and in constructing norm-based scores for the SF-36v2 PF domain [27]. However, in the multivariate linear regression models, it was decided to use the raw scores and adjust for age and gender with other baseline characteristics.

The limitations of this study were that it was observational, which precludes inferences about the causality of the associations that we report. Low statistical power, due to a small number of participants, was also a limitation of the analysis. Furthermore, no adjustment was made for cumulative type I error rate as a result of the large number of statistical models presented. There were fewer women than men, and they had more disability, a higher degree of unemployment, and more missing data in the 6MW test measurement at 12 months after ICU discharge than men. The MRC-SS was used for the clinical diagnosis of ICU-AW at ICU discharge with MRC-SS <48 points [24,25]. Connolly and colleagues [41] have demonstrated limited applicability of clinical muscle strength testing in critically ill patients [41,42].

The results of this study have implications for physical therapists and the ICU team with respect to identifying patients on their ICU admission that are at risk for poor physical outcome. ICU clinicians need to be aware that women who are admitted to the ICU with

mechanical ventilation for longer than 48 hours, might need targeted interventions to expedite maximal physical recovery. Additionally, a better understanding of factors that mediate the difference in physical recovery between genders is needed [1]. Survivors of critical illness have identified their main health challenges after ICU discharge as weakness, fatigue and decreased walking capacity [43]. These reports emphasise the need for core physical outcomes consistent with patients' priorities and preferences. The results of this study can be used to help build a core set of physical recovery outcomes to be implemented in the ICU, where physiotherapists and other ICU health care providers can identify patients who are at risk of poor physical recovery and can provide targeted exercise interventions during and after the ICU stay. This is consistent with our earlier findings of the need for tailored and targeted individualised rehabilitation for ICU patients [44].

## Conclusions

In our cohort of ICU patients, the female gender was associated with poor physical recovery one year after ICU discharge. Other predictors of poor physical recovery after adjustment for age and gender were: high BMI, low functional independence (MBI), functional comorbidity (FCI) and low physical function (SF-36v2 PF domain) at baseline, muscle weakness (MRC-SS) at ICU discharge, and longer hospital LOS. It is suggested that these variables can be used to form a clinical tool to be systematically implemented in ICU practice for physiotherapists to identify those patients who are at risk of poor physical recovery, and who may need enhanced, targeted, and individualised mobilisation and exercise interventions during the ICU stay and long after it.

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Supplementary table 1. Bivariate association between exposure variables and physical recovery variables

| Pearson Correlation Coefficients<br>Prob > \|r\| under H0: Rho=0<br>Number of Observations | | | | |
|---|---|---|---|---|
| | | MRC-SS at 12 months after ICU discharge | 6MW test at 12 months after ICU discharge | SF-36v2 PF domain at 12 months after ICU discharge |
| Gender | Correlation | -0.47 | -0.64 | -0.40 |
| | p value | <.01 | <.0001 | 0.01 |
| Married or cohabiting | Correlation | -0.06 | -0.21 | -0.24 |
| | p value | 0.74 | 0.24 | 0.14 |
| Elementary school education (ISCED 1,2) | Correlation | -0.09 | -0.28 | -0.27 |
| | p value | 0.58 | 0.13 | 0.09 |
| Employment status | Correlation | -0.18 | -0.50 | -0.32 |
| | p value | 0.27 | <.01 | 0.04 |
| Regular exercise (>150 min/week | Correlation | 0.17 | 0.28 | 0.25 |
| | p value | 0.31 | 0.13 | 0.12 |
| BMI ($kg/m^2$) at baseline | Correlation | -0.24 | -0.38 | -0.23 |
| | p value | 0.15 | 0.03 | 0.14 |
| SF-36v2 PF domain at baseline | Correlation | 0.19 | 0.65 | 0.47 |
| | p value | 0.27 | <.0001 | <.01 |
| ICU admission diagnosis | Correlation | 0.29 | 0.41 | 0.29 |
| | p value | 0.08 | 0.02 | 0.06 |
| APACHE II | Correlation | -0.03 | -0.32 | -0.19 |
| | p value | 0.84 | 0.08 | 0.23 |
| Sepsis during ICU stay | Correlation | -0.24 | -0.41 | -0.19 |
| | p value | 0.15 | 0.02 | 0.23 |
| ARDS during ICU stay | Correlation | 0.09 | 0.37 | 0.21 |
| | p value | 0.60 | 0.04 | 0.19 |
| Renal replacement therapy during ICU stay | Correlation | 0.14 | 0.14 | -0.01 |
| | p value | 0.42 | 0.46 | 0.94 |
| No upright mobilisation $\geq$ first 7 days | Correlation | -0.30 | -0.12 | -0.06 |
| | p value | 0.07 | 0.51 | 0.72 |
| MRC-SS at ICU discharge | Correlation | 0.58 | 0.58 | 0.50 |
| | p value | <.01 | <.01 | 0.01 |
| ICU-AW indication (MRC-SS < 48) | Correlation | -0.45 | -0.54 | -0.41 |
| | p value | 0.01 | 0.01 | 0.03 |

Supplementary table 2. Bivariate association between exposure variables and physical recovery variables

| Spearman Correlation Coefficients<br>Prob > \|r\| under H0: Rho=0<br>Number of Observations | | | | |
|---|---|---|---|---|
| | | MRC-SS at 12 months after ICU discharge | 6MW test at 12 months after ICU discharge | SF-36v2 PF domain at 12 months after ICU discharge |
| Age | Correlation | -0.29 | -0.53 | -0.22 |
| | p value | 0.08 | <.01 | 0.17 |
| Modified Barthel Index (MBI) at baseline | Correlation | 0.12 | 0.30 | 0.24 |
| | p value | 0.49 | 0.09 | 0.13 |
| Charlson Comorbidity Index (CCI) | Correlation | -0.05 | -0.52 | -0.21 |
| | p value | 0.75 | <.01 | 0.18 |
| Functional Comorbidity Index (FCI) | Correlation | -0.30 | -0.58 | -0.34 |
| | p value | 0.07 | <.001 | 0.03 |
| Upright mobilisation started on day | Correlation | -0.32 | -0.25 | -0.16 |
| | p value | 0.06 | 0.18 | 0.35 |
| Duration of MV | Correlation | -0.39 | -0.43 | -0.34 |
| | p value | 0.02 | 0.01 | 0.03 |
| MBI at ICU discharge | Correlation | 0.60 | 0.63 | 0.47 |
| | p value | <.0001 | 0.0001 | <.01 |
| ICU LOS | Correlation | -0.38 | -0.36 | -0.28 |
| | p value | 0.02 | 0.04 | 0.07 |
| Hospital LOS | Correlation | -0.51 | -0.39 | -0.36 |
| | p value | <.01 | 0.03 | 0.02 |

# Appendices

## Appendix 1. Study I

1) The observation sceme that the principal investigator used during the observation of the physiotherpists during mobilization session in the ICU

| | | | |
|---|---|---|---|
| Notice nonverbal behavior | | Participant nr: | |
| People present: | | Verbal agreement from patient: | |
| Date: | Location | Starts and finishes (time): | |
| Has this physical therapist mobilized this patient before?: | | | |
| **Patient (observation from primary investigator):** | | | |
| Wellbeing | | | |
| Alert, RASS scale: | | Can patient communicate? | |
| Disabilities, morbid obesity, main problem: | | | |
| | | | |
| **Equipment:** | | | |
| Ventilator? | Lines, drains: | | |
| | | | |
| Bed: | Stepstool: | Hoist system used? | |
| **Physical therapist´s preparation before mobilization:** | | | |
| Interaction with ICU team: | | | |
| | | | |
| Interaction with patient: | | | |
| | | | |
| Assessment of readiness to be mobilized: | | | |
| | | | |
| **Contraindication to be mobilized, reason:** | | | |
| | | | |
| **The mobilization: Type, method, to sit on edge of bed** | | | |
| | | | |
| Does the patient participate, and how much? | | | |
| | | | |
| Interaction with patient during the mobilization: | | | |
| | | | |
| Interaction with ICU team during mobilization, staff participation: | | | |
| | | | |
| Patient´s reaction to mobilization: | | | |
| | | | |
| Physical therapist´s reaction to the patient´s reaction: | | | |
| | | | |
| Mobilization stopped, reason: | | | |
| | | | |
| | | Time of mobilization: | |
| Interaction with patient after mobilization: | | | |
| | | | |
| Interaction with ICU team after mobilization: | | | |
| | | | |
| Primary investigators notes after mobilization: | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| Abbreviations: RASS scale, Richmond Agitation Sedation Scale; ICU, intensive care unit. | | | |

2) The format for the semi-structured interview of the physical therapist

Open-ended questions – follow ideas that come forward – use my premonition

In this interview, I would like to find out a bit more about your clinical reasoning and decision-making processes that guided you mobilizing the patient whom I observed earlier today.

First, the on-call card consulted you to mobilize the patient. What is your understanding of the word mobilization *(… Maybe probe…. Passive / active / functionally … )*

Can you tell me about why you decided to do what you did in terms of mobilizing this patient? Specifically, why did you decide to do…….?

Can you tell me about specific factors you considered doing ……?

I noticed that you progressed mobilizing the patient at point … (e.g., got them sitting over the edge-of-the-bed *(… and then standing*). What factors did you think about when you did this?

I then noticed that you continued/stopped progressing the patient at a point ... What factors were you thinking about that guided this *(increasing the intensity or withdrawing)*

I noticed that the mobilization session lasted.....minutes overall. What factors determined the time the session should last…..time or end ….? Can you reflect on your thoughts at that time.

*If the participant says that a reason for stopping the session was time constraint, i.e., other patients and things to do, follow with:*

I understand. If you had the time to continue what would you have done and what would you expect the outcome to be with extra time?

I noticed during the observation that you used …. method to help the patient to sit over the edge of bed, you did …. and the nurse did …… Is this the method you usually use or do you sometimes choose another method?

**Now we will discuss mobilization in general**

Can you tell me what you think when you assess a patient's readiness to be mobilized

Can you tell me how you assess the patient before and during mobilization (*as needed probe and follow thoughts regarding clinical assessment, function, vital signs, outcome measures)*

Can you tell me how you assess the patient's wellbeing/mobilization tolerance *(as needed probe… How much would you allow the heart rate and blood pressure, or other vital signs to change)*

Can you tell me about your general thoughts when your patient is sitting over the edge of bed …… what do you focus on, how do you decide the intensity and duration of the mobilization session *(maybe probe frequency)*

Who is responsible for the patients safety during mobilization, is it you the physical therapist or another member of the ICU team

*As needed, ask, how would you ensure the patient's safety during mobilization*

How can the safety of everybody (the patient and the ICU team) be ensured during mobilization *(discuss morbidly overweight patients, multi-trauma, head trauma, patients that are disoriented) Discuss the environment, the beds, equipment, cooperation*

Can you tell me what outcome you are trying to achieve with mobilization

How do you prioritize mobilization when you are treating a patient who is critically ill? Is mobilization your first choice of intervention in the critically ill, and what type of mobilization?

Barriers and solutions

What is your opinion on how confident and well-prepared physical therapists' are about mobilizing ICU patients when they are on-call. How would you rate your confidence in mobilizing patients? Do you feel that you have sufficient competence in this area? (*if the physical therapist is experienced I ask her or him about the preparation for our young physical therapists regarding mobilization in the ICU during their on-call duties)*

Is there anything you can tell me from your experience and based on your needs that would enable you to mobilize patients more effectively?

Is there anything that you would like to add in relation to any of the questions?

**Participant's characteristics (closed questions)**

Years since graduation, hospital experience, field of experience, ICU experience, on-call experience.

The participants will be asked not to divulge the topics discussed in the study to other participants who have not yet been interviewed so that their responses and importantly their practices will not be influenced

## Appendix 2 Study II

The two research sheets that were filled out daily be the physiotherapists who implemented the intervention for the patients in the twice-daily mobilisation group and in the once-daily mobilisation group

**AWAKE AND EXERCISING IN AN UPRIGHT POSITION**

**Enhanced physiotherapist-directed mobilization group**

Physiotherapy starts on day 3 after initiation of mechanical ventilation, 2x daily, all days.

| | |
|---|---|
| Use resistance, weights, elastic bands ect. Write down if used | Research number<br>Date |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Breathing support : MV ..... $\%O_2$ / Bi-PAP..... $\%O_2$ / ..... $LO_2$ on mask /..... $LO_2$ nose | | | | | | | | |
| Awake and spontaneous breating program? | **RASS score** physiothearpy: am (hour) | | | | pm (hour) | | | |
| The patients main problems today | | | | | | | | |
| No physiotherapy am (reason) | | | | | | | | |
| No physiotherap pm (reason) | | | | | | | | |
| Mobilization to an upright position contraindicated am (reason) | | | | | | | | |
| Mobilization to an upright position contraindicated pm (reason) | | | | | | | | |
| **Vital signs** | **HR** | | **BP** | | **$O_2$ saturation** | | **RR** | |
| | **am** | **pm** | **am** | **pm** | **am** | **pm** | **am** | **pm** |
| Before mobilization to an upright position | | | | | | | | |
| During mobilization | | | | | | | | |
| After mobilization | | | | | | | | |

| | | |
|---|---|---|
| **PHYSIOTHERAPY: Duration of session** | minutes am | minutes pm |
| **Duration of upright mobilization** | minutes am | minutes pm |
| Passive range of motion and muscle streatches | am | pm |
| Active exercises in supine with assistance | am | pm |
| Active exercises in supine without assistance | am | pm |
| Active exercises sitting on edge of bed | am | pm |
| Active exercises sitting in a chair | am | pm |
| Sit on edge of bed | am | pm |
| Sit in a chair | am | pm |
| Stand up and sit | am | pm |
| Transfer training | am | pm |
| Exercises in a standing position | am | pm |
| Walk on the spot | am | pm |
| Walk from bed (support, walking frame) | am | pm |
| Self exercises | am | pm |
| Education | am | pm |
| Cardio position (time/degrees) | am | pm |
| Transport with hoist system to a chair (upright chair, reclining chair) | | |
| | | |
| Lung physiotherpy after extubation, number of treatments, is the patient mobilized to an upright position, for how long | | |
| | | |
| | | |
| | | |
| Comments: | | |
| | | |
| | | |

## AWAKE AND EXERCISING IN AN UPRIGHT POSITION

**Standard of care physiotherapy**

Physiotherapy starts on day 5 after initiation of mechanical ventilation, 1x daily.

| | |
|---|---|
| | Research number<br>Date |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Breathing support : Mechanical ventilation ..... $\%O_2$ / Bi-PAP..... $\%O_2$ / ..... $LO_2$ on mask /..... $LO_2$ nose | | | | | | | | |
| Awake and spontaneous breating program? | | **RASS score** in physiotherapy (hour): | | | | | | |
| The patients main problems today | | | | | | | | |
| No physiotherapy today (reason) | | | | | | | | |
| Mobilization to an upright position contraindicated today (reason) | | | | | | | | |
| **Vital signs** | **HR** | | **BP** | | **$O_2$ saturation** | | **RR** | |
| Before and after physiotherapy | | | | | | | | |
| **PHYSIOTHERAPY:** | | | | | | | | |
| **Duration of session (min):** | **Duration of mobilization to an upright position (min):** | | | | | | | |
| Short description of physiotherapy | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
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