MONASH University

Physical rehabilitation in the intensive care unit

Yi Tian Wang

Bachelor of Physiotherapy

A thesis submitted for the degree of Doctor of Philosophy at

Monash University in 2021

School of Primary and Allied Health Care

Faculty of Medicine, Nursing and Health Sciences

Copyright notice

Abstract

Intensive care unit (ICU) services cost the Australian economy at least 2.1 billion dollars annually, excluding the cost of care to manage long-term morbidity. Patients with intensive care unit-acquired weakness (ICU-AW) have poor short- and long-term physical outcomes and consume a disproportionate number of these resources. Thus, improving strategies for the prevention and treatment of ICU-AW is of high public health importance.

Prediction and prevention of muscle weakness in critically ill patients are difficult, due to insufficient understanding of molecular pathophysiology along with practical limitations and methodological variability when implementing physical activity programs in this population. Few studies have investigated the extent to which bench-top and clinical physiological findings are linked. Critically ill patients requiring continuous renal replacement therapy are routinely immobilised, therefore, at higher risk of developing ICU-AW. They are a cohort that highlights the practical limitations of implementing physical activity in this setting. The safety and feasibility of early mobilisation in this cohort are uncertain. The efficacy of physical rehabilitation in the ICU is also unclear, with multiple systematic reviews reporting inconsistent results. Reviews to date have not considered the type of rehabilitation intervention and the dosage of therapy received by the control group as sources of heterogeneity.

This program of research involved two prospective studies and one systematic review. First, a prospective cohort study was conducted to investigate the relationship between activin A, a negative regulator of muscle mass, and patient outcomes. Thirty-six critically ill patients from two ICUs were recruited. Serum activin A levels were measured daily in ICU. In

addition, standardised muscle strength and physical function outcome measures with established clinometric properties were used throughout the ICU and acute hospital stay. Elevated peak activin A concentration was associated with worse outcomes at first time sitting out of bed, ICU, and hospital discharge. Thus, Activin A appears to be a promising pharmacological target for physical disability in critical illness.

Second, a novel prospective, quasi-experimental study investigated the safety and feasibility of a physical activity program conducted with patients on renal replacement therapy in the ICU. A total of 33 patients undergoing continuous renal replacement therapy via femoral, subclavian or internal jugular vascular access catheters were enrolled. Patients underwent one of three levels of mobilisation intervention as appropriate: (1) passive bed exercises, (2) sitting on the bed edge, or (3) standing and marching. Catheter dislodgement, haematoma, and bleeding during and following interventions were evaluated. No episodes of filter occlusion or failure occurred during any of the interventions. No adverse events were detected. Thus, mobilisation during renal replacement therapy via a vascular catheter in critically ill patients was safe and feasible.

Finally, a systematic review and meta-analysis of 60 trials investigated the effectiveness of physical rehabilitation that began in the intensive care unit. Outcomes included muscle strength, physical function, duration of mechanical ventilation, length of stay in ICU and hospital, mortality, and health-related quality of life. In addition, the effect of control group therapy dosage and the impact of task-specific rehabilitation was explored with subgroup analysis. Our review found that physical rehabilitation in the ICU improved physical function at hospital discharge, reduced intensive care unit and hospital length of stay. However, it had no impact on the other outcomes. Important confounders to the effectiveness of

physical rehabilitation included the task-specificity of exercises and the amount of physical rehabilitation available to the control group participants.

In conclusion, Activin A is a promising pharmacological target to reduce physical disability in critical illness. Mobilisation of patients during continuous renal replacement therapy via a is safe and feasible. Physical rehabilitation that begins in the ICU improves physical function at hospital discharge, reduces ICU and hospital length of stay.

Publications during enrolment

Wang YT, Haines TP, Ritchie P, Walker C, Ansell TA, Ryan DT, Lim PS, Vij S, Acs R, Fealy N, Skinner EH (2014). Early mobilisation on continuous renal replacement therapy is safe and may improve filter life. Critical Care, 18(4), 1-10.

Wang YT, Harrison CA, Skinner EH, Haines KJ, Holdsworth C, Lang JK, Hibbert E, Scott D, Eynon N, Tiruvoipati R, French CJ, Stepto NK, Bates S, Walton KL, Crozier TM, Haines TP (under review). Activin A level is associated with muscle strength and physical function in critically ill patients.

Wang YT, Lang JK, Haines KJ, Skinner EH, Haines TP (under review). Physical rehabilitation in the intensive care unit, a systematic review and meta-analysis.

Oral presentations by the candidate

Serum activin A concentration in intensive care predicts mortality and physical function, Australian and New Zealand Intensive Care Society (ANZCIS) Conference, 2017

Serum activin A concentration in intensive care predicts mortality and physical function, Peninsula Health Research Week, 2017

Physical rehabilitation in the Intensive Care Unit – a systematic review and meta-analysis. Peninsula Health Research Week, 2019

Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes one original paper published in peer-reviewed journals and two submitted publications. The core theme of the thesis is physical rehabilitation in the intensive care unit. The ideas, development, and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the School of Primary and Allied Health Care under the supervision of Professor Terry Haines.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapters 3, 4, and 5, my contribution to the work involved the following:

Thesis Chapter	**Publication Title**	**Status** *(published, in press, accepted or returned for revision, submitted)*	**Nature and % of student contribution**	**Co-author name(s) Nature and % of Co-author's contribution***	**Co-author(s), Monash student Y/N***
3	Activin A level is associated with muscle strength and physical function in critically ill patients	submitted	Conception and design of the work, acquisition, analysis, and interpretation of data for the work; completed the first draft of the manuscript and revising it critically for important intellectual content. 55%	Craig A Harrison, conception and design of the work, analysis, and interpretation of data for the work; drafting the work and revising it critically for important intellectual content.10% Elizabeth H Skinner; conception and design of the work, analysis, and interpretation of data for the work;	Jenna K Lang is a current Monash student, and nil other co-authors are current students.

				drafting the work and revising it critically for important intellectual content. 5% Kimberley J Haines, design of the work, acquisition, analysis, and interpretation of data for the work; drafting the work and revising it critically for important intellectual content. 5% Clare Holdsworth; design of the work, acquisition of data for the work; drafting the work and revising it critically for important intellectual content. 4% Jenna K Lang, acquisition of data for the work; drafting the work and revising	

				it critically for important intellectual content. 2.5% Elizabeth Hibbert, acquisition of data for the work; drafting the work and revising it critically for important intellectual content. 2.5% David Scott, design of the work, interpretation of data for the work; drafting the work and revising it critically for important intellectual content. 2.5% Nir Eynon, design of the work, drafting the work and revising it critically for important intellectual content. 1% Ravindranath Tiruvoipati, design of the work; drafting the work and revising it	

				critically for important intellectual content. 1% Craig J French, design of the work; drafting the work and revising it critically for important intellectual content. 1% Nigel K Stepto, design of the work; drafting the work and revising it critically for important intellectual content. 1% Samantha Bates, design of the work, acquisition of data for the work; drafting the work and revising it critically for important intellectual content. 1% Kelly L Walton, acquisition of data for the work; drafting the work and revising	

				it critically for important intellectual content. 1% Tim M Crozier, design of the work, interpretation of data for the work; drafting the work and revising it critically for important intellectual content. 1% Terry P Haines, conception and design of the work, analysis, and interpretation of data for the work; drafting the work and revising it critically for important intellectual content. 6.5%	
4	Early mobilisation on continuous renal replacement therapy is safe	Published	Involved in the conception and design of the study, led patient recruitment, data collection, data analysis, interpretation of	Terry P Haines, involved in the data analyses, interpretation and reviewed the manuscript for intellectually important content. 10%	No co-authors are current Monash students

	and may improve filter life		the study, completed the first draft of the manuscript, and reviewed the manuscript for intellectually important content. 60%	Paul Ritchie, involved in the design of the study, data analysis, and reviewed the manuscript for intellectually important content. 2% Craig Walker, involved in the design of the study, data analysis and reviewed the manuscript for intellectually important content. 2% Teri A Ansell, involved in the design of the study, data collection and reviewed the manuscript for intellectually important content. 1% Danielle T Ryan, involved in the conception of the study and reviewed the manuscript for intellectually important content. 1%	

				Phaik-Sim Lim, involved in the design of the study, data collection and reviewed the manuscript for intellectually important content. 5% Sanjiv Vij, involved in the design of the study and reviewed the manuscript for intellectually important content. 1% Rebecca Acs, involved in the design of the study, data collection and reviewed the manuscript for intellectually important content. 1% Nigel Fealy, involved in the conception of the study, interpretation, reviewed the manuscript for intellectually important content. 2% Elizabeth H Skinner led the conception and design of the study; was involved	

				in patient recruitment, data collection, data analysis, interpretation; and reviewed the manuscript for intellectually important content. 15%	
5	Physical rehabilitation in the intensive care unit, a systematic review and meta-analysis.	In press	Guarantor of this review, conceived this review and designed the first draft of its protocol, screened records for inclusion into the review, managed review data, performed statistical inferences, and drafted the final manuscript. 65%	Jenna K Lang screened records for inclusion into the review, managed review data, and participated in the drafting of the final manuscript. 15% Kimberley J Haines participated in the drafting of the final manuscript. 5% Elizabeth H Skinner conceived this review and designed the first draft of its protocol, participated in the drafting of the final manuscript. 5% Terry P Haines, conceived this review and designed the first draft of its protocol. TH performed statistical	Jenna K Lang is a current Monash student, and nil other co-authors are current students.

				inferences and participated in the drafting of the final manuscript. 10%	

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student name: Yi Tian Wang

Student signature: **Date:** 12th April 2021

I hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor name: Terry Haines

Main Supervisor signature: **Date:** 12th April 2021

Acknowledgements

I am indebted to my family, especially my wife, Mia. Without you, none of this would have been possible. Thank you for your love and understanding. Thank you for the countless times that you have taken up my share of the duty as a husband and a father so that I can spend more time being a student. I thank my children, who, through no choice of their own, received less love and attention than I would have liked to give.

I acknowledge my supervisors, Terry, Lizzie, and Kimberley. Thank you for your unwavering support and belief in me. Thank you for teaching me so much over the last ten years. This Ph.D. journey has always been fulfilling but challenging at times. But even through a global pandemic that threatened us all, you made time to support me with my work. Lizzie, you were the reason that I pursued a career as an ICU physiotherapist. Your enthusiasm for research to improve patient-centred outcomes had me hooked from the start. Terry, thank you for being my mentor and pillar of support. We will never forget that time you prayed for us in your office. Kimberley, thank you for believing in me; as an undergraduate student on his first cardiorespiratory placement and again as a Ph.D. student behind recruitment schedule, I would not be here today if you did not believe in me.

I want to thank my colleagues at the physiotherapy departments of Peninsula Health and Monash Health for your support with dedicated research time, conference leave and for letting me use the office for hours and hours of data collection. I want to thank my current manager, Sally Harrowfield, particularly. Without your support with study leave and flexible work arrangements, I would not have completed this research program. I thank my colleagues of the cardiorespiratory stream at Peninsula Health, past and present, for

collecting data, centrifuging blood samples, and covering ICU so I could take study leave. Finally, I thank Tess Baker for your support with our clinical workload and for being the best proofreader.

My heartfelt thanks to the patients and their families from Monash Medical Centre, Dandenong Hospital, Sunshine Hospital, and Frankston Hospital. You were willing to participate in research that had little or no benefit to yourself but may benefit others to come. I would like to thank my co-investigators, without whom the projects would not have been possible. I especially want to acknowledge Professor Boyd Strauss for his input and guidance on body composition measurements in critically ill patients.

This research was supported by an Australian Government Research Training Program (RTP) Scholarship. I would also like to acknowledge the grants from Western Health and Australian Institute for Musculoskeletal Science that has also supported this research.

Dedication

I dedicate this thesis to my family, Mia, Lucas, and Ella. Your love, sacrifice, and understanding made this work possible.

Table of Contents

List of tables

List of figures

List of appendices

List of abbreviations

6MWT	Six-minute walk test
ACCCN	Australian College of Critical Care Nurses
ActRIIB	Activin receptor type IIB
ALS	Autophagic-lysosomal system
APACHE	Acute Physiological and Chronic Health Evaluation
APTT	Activated partial thromboplastin time
ARDS	Acute respiratory distress syndrome
CCT	Controlled clinical trial
CI	Confidence interval
CICM	College of Intensive Care Medicine
CIM	Critical illness myopathy
CINM	Critical illness neuromyopathy
CIP	Critical illness polyneuropathy
CON	Control group intervention
COVID-19	Coronavirus disease 2019
CRRT	Continuous renal replacement therapy
CVVHD	Continuous veno-venous haemodialysis
CVVHDF	Continuous veno-venous haemodiafiltration
EMS	Electrical muscle stimulation
EQ-5D	Euro-QoL 5D
EXP	Experimental group intervention
H1N1	Influenza A virus subtype H1N1
Hb	Haemoglobin

HRQoL	Health-related quality of life
ICU-AW	Intensive care unit acquired weakness
ICU	Intensive care unit
INR	International normalised ratio
IQR	Inter-quartile range
LOS	Length of stay
MD	Mean difference
MOF	Multi-organ failure
MRC	Medical Research Council
MRC-SS	Medical Research Council Sum Score
MV	Mechanical ventilation
NASA-TLX	NASA Task Load Index
NEMS	Nine Equivalents of Nursing Manpower use score
NMES	Neuromuscular electrical stimulation
PFIT	Physical function ICU test
PFIT-s	Physical function ICU test scored
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised controlled trial
RD	Risk difference
RoB2	Version 2 of the Cochrane risk-of-bias tool for randomized trials
ROBINS-I	The Risk Of Bias In Non-randomized Studies – of Interventions
ROM	Range of motion

SD	Standard deviation
SF-36	Short Form-36
SIRS	Systemic inflammatory response syndrome
SMD	Standardised mean difference
SOEOB	Sit on the edge of the bed
SOFA	Sequential Organ Failure Assessment
SOOB	Sit out of bed
SPSS™	Statistical Package for the Social Sciences
SUIB	Sit up in bed
TGF-β	Transforming growth factor-beta
TUG	Timed 'Up and Go' test
UPS	Ubiquitin-proteasome system
US	The United States (see also USA)
USA	The United States of America (see also US)

Chapter 1. Introduction

1.1. Statement of the problem

Intensive Care Unit (ICU) services cost the Australian economy at least 2.1 billion dollars annually (Hicks et al., 2019), excluding the cost of long-term morbidity. Patients with a prolonged length of stay in the ICU (> 10-14 days) consume a disproportionate number of resources, with 11% of patients using 45% of ICU days and 55% of mechanical ventilation days (Arabi et al., 2002; Carson & Bach, 2002).

Up to 65% of patients with prolonged critical illness exhibit a severe weakness syndrome attributable to ICU (Ali et al., 2008; Sharshar et al., 2009). This syndrome is thought to be from a combination of muscle mass loss, myopathy (Derde et al., 2012; Puthucheary et al., 2013), and polyneuropathy (Bolton et al., 1984). In the absence of plausible cause other than critical illness, this acute clinical weakness acquired in the ICU is termed ICU-acquired weakness (ICU-AW). Weakness can occur early in the ICU admission and is associated with prolonged weaning from mechanical ventilation (MV) (De Jonghe et al., 2007; De Jonghe, Bastuji-Garin, et al., 2004; De Jonghe et al., 2002), increased ICU (De Jonghe et al., 2002; Garnacho-Montero et al., 2005) and hospital length of stay (LOS) (Garnacho-Montero et al., 2005). ICU-AW is also associated with increased mortality in ICU (Sharshar et al., 2009), in-hospital (Ali et al., 2008; Sharshar et al., 2009), and for at least 12 months following discharge (Hermans et al., 2014). In patients who survive, ICU-AW is also associated with poorer

physical function and health-related quality of life (HRQoL) up to 12 months after ICU discharge (Dowdy et al., 2005).

The pathophysiology of ICU-AW is complex and is not fully understood, making prevention and treatment challenging. Both preclinical and clinical studies provide evidence that multiple contributing pathophysiologic mechanisms are involved in the evolution of ICU-AW (Bloch et al., 2012; Hermans & Van den Berghe, 2015; Schefold et al., 2010). Acute skeletal muscle wasting is a frequent complication in critical illness (Dos Santos et al., 2016; Hayes et al., 2018; Kirby P. Mayer et al., 2020; Puthucheary et al., 2013; Sheean et al., 2014), occurring early in the intensive care unit admission and lasting up to 6 months after ICU discharge (Dos Santos et al., 2016). Lower limb muscle cross-sectional area can decrease by up to 18.5% in the first 7 to 10 days of an ICU admission (Hayes et al., 2018; Kirby P. Mayer et al., 2020; Puthucheary et al., 2013). Muscle wasting is associated with muscle weakness and worse physical function in the ICU (Hayes et al., 2018), at hospital discharge (Kirby P. Mayer et al., 2020), and in the 12 months after ICU admission (Chan et al., 2018). Muscle wasting in critical illness occurs via decreased muscle protein synthesis (Puthucheary et al., 2013) and increased protein degradation (Derde et al., 2012; Puthucheary et al., 2013), in particular the degradation of myofibrillar proteins (Hasselgren et al., 1989; Long et al., 1981). Protein degradation in critical illness is due to the upregulation of the two major protein degradation pathways (Helliwell et al., 1998; Levine et al., 2008) - the ubiquitin-proteasome system (UPS) (Constantin et al., 2011; Schmidt et al., 2014; Tiao et al., 1997) and the autophagic-lysosomal system (ALS) (Constantin et al., 2011; Mofarrahi et al., 2012).

Several studies have investigated the functional sequelae of ICU-AW (Burtin et al., 2009; Eikermann et al., 2006; Finn et al., 1996; Reid et al., 2008; Schweickert et al., 2009), but few have investigated the extent to which bench-top and clinical physiological findings are linked.

Activin A is a protein complex that belongs to the transforming growth factor-beta (TGF-β) ligands family and is a negative regulator of muscle mass. Activin A binds to Activin receptor type 2B (ActRIIB), a high-affinity activin A receptor in muscle. The activin A-Smad3 pathway is the primary negative regulator of protein synthesis (Schiaffino et al., 2013), its activation directly inhibiting protein synthesis (Gumucio et al., 2015). The activin pathway also initiates a signalling cascade leading to increased expression of genes involved in the UPS and ALS to induce muscle protein degradation (Lokireddy et al., 2011; Marino et al., 2015; Tisdale, 2010; Zhou et al., 2010). Elevated levels of activin A induce loss of muscle mass, endomysial fibrosis, decreased peak force-generating capacity, and reduced fatigue resistance (Chen et al., 2014), features commonly observed in critical illness myopathy (CIM) (Eikermann et al., 2006; Herridge et al., 2003). Serum Activin A is elevated in critically ill patients with sepsis (Lee et al., 2016; Michel et al., 2003), coronavirus disease 2019 (COVID-19) (Synolaki et al., 2021), influenza A virus subtype H1N1 (H1N1) (Linko et al., 2014), and acute respiratory failure (de Kretser et al., 2013). But the relationship between serum activin A, muscle strength, and physical function in critically ill patients is currently unclear.

The role of activin A in critically ill patients is of particular significance because inhibition of ActRIIB has been shown to increase muscle mass in healthy volunteers (Attie et al., 2013) and patients with chronic obstructive pulmonary disease (Polkey et al., 2019). Pharmacological agents such as bimagrumab (Polkey et al., 2019) and muscle regulator ACE-031 (Attie et al., 2013) antagonise the activin A pathway and have been used safely in humans. Suppose activin A is an influential factor in the muscle catabolism observed in critical illness survivors. In that case, it can become a predictor of patient outcome and a potential therapeutic target. The relationship between serum activin A levels, muscle strength, and physical function at ICU and hospital discharge needs to be described.

While ICU-AW has mixed pathophysiology, the bedrest and immobilisation associated with the monitoring and management of critically ill patients have real and deleterious consequences. Australian and international prospective cohort and point prevalence studies have shown that patient mobilisation events were infrequent (Berney et al., 2013) or delayed (Marc R. Nickels et al., 2020) in the ICU, particularly those managed with invasive mechanical ventilation (Berney et al., 2013; Capell et al., 2019; Hodgson et al., 2015; Jolley et al., 2017; Nydahl et al., 2014; Timenetsky et al., 2020).

Critically ill patients with acute renal failure are particularly susceptible to ICU-AW. Acute renal failure occurs in 5.5-6.0% of patients admitted to the ICU. Almost three-quarters of these patients require continuous renal replacement therapy (CRRT) via temporary double-lumen vascular catheters (Uchino et al., 2005). Historically, patients with femoral vascular catheters have been restricted to bed rest (Berney et al., 2012; Leditschke et al., 2012; Pohlman et al., 2010) to avoid catheter dislodgement,

infection, and thrombosis (Schwab & Beathard, 1999). Patient movement may alter fluid dynamics, pressures, and blood flow of the CRRT circuit (Talley et al., 2013). Although early mobilisation in ICU is safe in the presence of femoral arterial catheters (Damluji et al., 2013; Perme et al., 2011), delivery of CRRT via a femoral catheter precludes hip flexion in practice and research (Pohlman et al., 2010). Several studies have reported data on the safety and feasibility of mobilisation in patients with femoral catheters (including arterial, venous, and haemodialysis) (Al-Wakeel et al., 1998; Damluji et al., 2013; Perme et al., 2011; Talley et al., 2013) but none specifically report CRRT data during mobilisation. Maintenance of the filter circuit is vital as premature disconnection results in blood loss, increased nursing workload, and increased costs (Joannidis & Oudemans-van Straaten, 2007). Therefore, Filter life is an essential indicator of CRRT efficacy (Uchino et al., 2003). The specific effects of mobilisation on the vascular catheter, circuit pressures, and blood flow in patients receiving CRRT via dual-lumen femoral vascular catheters are uncertain. The safety and feasibility of mobilisation in ICU patients with femoral vascular catheter placement during CRRT must be investigated to ensure patients are not subject to unnecessary immobilisation.

Physical rehabilitation is an integral part of the management of the physical sequelae of critical illness (Davidson et al., 2013; Needham et al., 2011; Schweickert et al., 2009). Therapy begins in the ICU, with the intent to reverse muscle catabolism, mitigate neuropathy, and minimise the effects of immobility (Truong et al., 2009). Consequently, physical rehabilitation has been extensively investigated as the treatment of choice for ICU-AW. Early systematic reviews have concluded that exercise rehabilitation in ICU is safe and feasible (Stiller, 2013); effective in improving physical function (Adler & Malone, 2012; Kayambu et al., 2013), HRQoL, muscle

strength, ventilator-free days, and ICU LOS (Kayambu et al., 2013). However, in recent years randomised control trials have been unable to achieve separation between groups in physical outcome measures (Denehy, Skinner, et al., 2013; Hodgson et al., 2016; Morris et al., 2016). The lack of separation between groups for these studies may be explained by the heterogeneous standard practice and the highly diverse rehabilitation interventions investigated.

There is considerable heterogeneity in routine physical rehabilitation practices in ICUs around the world (Bakhru et al., 2016; Harrold et al., 2015; Skinner et al., 2008), and standard practice has evolved since the earliest trials where significant benefits were found (Burtin et al., 2009; Morris et al., 2008; Schweickert et al., 2009). The amount of physical rehabilitation available to the control group is an important source of heterogeneity from trials investigating physical rehabilitation in the ICU. Physical rehabilitation in the ICU consists of numerous exercise modalities, including passive range of motions exercises, resistance training, positioning, functional mobility, and neuromuscular electrical stimulation. Task-specific exercises such as lifting head, rolling, sitting up, sitting balance, standing, transferring, and walking are more effective than impairment-based training in non-ICU patients (de Vreede et al., 2005; Di Monaco et al., 2009; Lowe et al., 2009; Nadeau et al., 2013), but in the ICU they involve more complex decision-making affecting sedation optimisation, feasibility, and safety.

The effect of physical rehabilitation in the ICU has been investigated in eleven relevant systematic reviews and meta-analyses (D. E. Anekwe et al., 2020; Castro-Avila et al., 2015; Ding et al., 2019; Fuke et al., 2018; Kayambu et al., 2013; Menges et al., 2021;

Okada et al., 2019; Tipping et al., 2017; Worraphan et al., 2020; Zang et al., 2020; Zhang et al., 2018). The first review (Kayambu et al., 2013) had a broad scope and found physical rehabilitation was associated with significant improvements in muscle strength, physical function, MV-free days, HRQoL, reduced ICU and hospital LOS. Meta-analyses since have been more restricted in the included interventions.

Reviews have included trials with interventions that were high dose (Castro-Avila et al., 2015); initiated early (D. E. Anekwe et al., 2020; Ding et al., 2019; Fuke et al., 2018; Okada et al., 2019; Worraphan et al., 2020; Zang et al., 2020; Zhang et al., 2018); active exercises only (Tipping et al., 2017), or protocolised (Menges et al., 2021). In some of these reviews, heterogeneity in the confidence intervals of the reported results has been high, while the results and conclusions across these meta-analyses have been inconsistent.

No reviews have considered the amount of physical rehabilitation available to the control group participants as a part of routine care as a source of heterogeneity. Nor had any review investigated the effectiveness of task-specific training in the ICU. Task-specific exercises such as sitting on the side of the bed, standing, and walking involve more complex decision-making incorporating sedation management, feasibility, and safety. A review with broad inclusion criteria is needed to examine whether the inconsistency in findings and conclusions in this field, along with the heterogeneity in the confidence intervals of the reported results, could be explained through examination of these factors.

1.2 Justification for research

In summary, the critically ill patient is frequently subject to physical inactivity and immobilisation, putting them at more risk of ICU-AW. This is particularly the case in patients requiring continuous renal replacement therapy, who may be restricted to bed rest for days. However, there are no empirical data to support the practice of routine immobilisation of patients having continuous renal replacement therapy.

Acute muscle wasting is a frequent complication in critical illness and is associated with worse outcomes in the 12 months after ICU admission. However, the pathophysiology of acute muscle wasting is not fully understood, and currently, there are no treatments with proven efficacy. Therefore, we must further our understanding of the pathophysiology of this condition and identify new potential targets for therapy.

Physical rehabilitation is a commonly adopted approach to manage the physical sequelae of critical illness. However, the results of recent systematic reviews have been conflicting. Reviews to date have not considered the amount of physical rehabilitation available to the control group as a confounding factor and source of heterogeneity. Moreover, it is unclear what type of exercise intervention is most effective.

1.3. Research aims

There are three primary aims of the body of work presented in this thesis:

1. To investigate the relationship between serum activin A, muscle strength, and physical function in critically ill patients.

2. To evaluate the safety and feasibility of mobilisation in ICU patients with femoral vascular catheter placement during CRRT.

3. To investigate the effectiveness of physical rehabilitation that begins in the ICU, focusing on task-specific interventions and with clear reference to the dosage of control group therapy.

In the context of the research aims, the research question to be addressed in this thesis are as follows:

1. Is activin A level related to muscle strength in critically ill patients?

2. Is activin A level related to the physical function in critically ill patients?

3. Are movement and mobilisation in ICU patients with femoral vascular catheter placement during CRRT safe?

4. How do movement and mobilisation during CRRT affect the life of the CRRT filter?

5. Does physical rehabilitation that begins in the ICU improve outcomes?

6. Do task-specific rehabilitation interventions in ICU produce more benefits than non-task-specific interventions?

7. How does the dose of control therapy impact the effectiveness of experimental interventions in trials investigating physical rehabilitation in the ICU?

The following thesis overview describes the studies designed to address these research questions; the chapters present the studies.

1.4. Thesis overview

Chapters 2 provide a substantive literature review of the Australian intensive care unit environment, ICU service delivery, and the patient population that utilise this service. A detailed review of literature on the pathophysiology and treatments of ICU-AW concludes this chapter.

Chapter 3 describes the relationship between serum activin A, muscle strength, and physical function in critically ill patients.

The results of the second clinical study will be presented in **Chapter 4**. This was a prospective interventional cohort study, where the intervention of movement and mobilisation was trialled in a cohort of critically ill patients on continuous renal replacement therapy.

Chapter 5 will report the results of a systematic review and meta-analysis that investigates the effectiveness of physical rehabilitation that began in the intensive care unit.

The final chapter of the thesis, **Chapter 6**, presents a summary of the research findings. The clinical significance, strengths, and limitations of the body of research presented in this thesis are discussed. Finally, recommendations for further investigation and collaboration are presented.

Chapter 2. Problems with care emergent in ICU

2.1. Introduction

This chapter will focus on the published literature in the relevant background areas to work presented in this thesis, to provide a substantial backdrop to the relevance and importance of the studies presented in chapters 3 to 5. In addition, the narrative review presented in this chapter will cover the ICU environment, barriers to physical activity in the ICU, the physical impairments associated with critical illness, and treatment options.

2.2. The Intensive Care Unit

The College of Intensive Care Medicine (CICM) of Australia and New Zealand defines an ICU as "a specially staffed and equipped, separate and self-contained area of a hospital dedicated to the management of patients with life-threatening illnesses, injuries and complications, and monitoring of potentially life-threatening conditions (CICM, 2016).” An ICU is usually located near areas such as the emergency department, the operating theatres, radiology, interventional cardiology, and other high acuity wards where relevant.

2.3. Staffing

The staffing profile of the ICU is dependent on the needs of the individual ICU and the hospital, comprising medical, nursing, allied health, and support staff. There is a lack of international standardised staffing requirements for intensive care units. However, in Australia, there are minimum standards for medical and nursing staffing

levels for critical care. The medical staff includes ICU specialists, with at least one ICU specialist always rostered per 8 to 15 beds (CICM, 2016). Australian College of Critical Care Nurses (ACCCN) guidelines require a minimum of 1:1 for ventilated and other critically ill patients and 1:2 nursing staff for lower acuity patients (ACCCN, 2003). In addition, other staff such as physiotherapists, social workers, occupational therapists, and pastoral care staff are required depending on the unit's needs.

2.4. Clinical area

Patients are cared for in either single open cubicles or single rooms of 20 square metres in size. There must be an adequate number of service outlets depending on the purpose of the unit. For example, a level III unit will require at least four oxygen, three air, three suction and four data outlets, and at least 16 power points for each bedspace. In addition, there must be adequate access to the head of each bed and enough space to store equipment such as a ventilator, infusion pumps, continuous renal replacement therapy, and chairs for the patient and visitors (CICM, 2016).

2.5. The critically ill patient

The critically ill patient requires monitoring and treatment because one or more organ functions are threatened, with the potential for developing life-threatening conditions (Bersten, 2019). These patients have an existing failure of one or more organ functions but with a reasonable chance of meaningful functional recovery (Bersten, 2019). There are various causes for patient admission into the ICU, with more than 100 Acute Physiology and Chronic Health Evaluation (APACHE) III-J

diagnostic codes and 400 sub-diagnosis codes (Australian and New Zealand Intensive Care Society, 2020). The critically ill patient is a heterogenous population with life-threatening illnesses, injuries, or complications.

2.6. Physical inactivity and immobilisation in the ICU

Bedrest and immobilisation are often associated with the monitoring and management of a critically ill patient. Prospective cohort and point prevalence studies have shown that patient mobilisation events were low (Berney et al., 2013) or delayed (Marc R. Nickels et al., 2020) in the ICU, particularly those managed with invasive mechanical ventilation (Berney et al., 2013; Capell et al., 2019; Hodgson et al., 2015; Jolley et al., 2017; Nydahl et al., 2014; Timenetsky et al., 2020).

The main barriers to physical activity in the ICU fit into five main themes: patient physical, physiological and psychological capability; safety concerns; environmental factors; culture and team; motivation and beliefs about physical activity (Parry et al., 2017).

Patient physical, physiological, and psychological capability

Symptoms of pain, fatigue, and weakness are common barriers to physical activity in the critically ill (Berney et al., 2013; Castro et al., 2015; Harrold et al., 2015; Hodgson et al., 2016; Needham & Korupolu, 2010; Nydahl et al., 2014; Pohlman et al., 2010). In addition, the patient's physical capability may be limited by the level of alertness (Appleton et al., 2011; Berney et al., 2013; Jolley et al., 2015; Leditschke et al.,

2012; Winkelman & Peereboom, 2010), delirium (Bassett et al., 2015; Capell et al., 2019; Engel et al., 2013; Jolley et al., 2014; Leditschke et al., 2012; Needham & Korupolu, 2010; Pohlman et al., 2010), or agitation (Berney et al., 2012; Berney et al., 2013; Capell et al., 2019; Dammeyer et al., 2013; Hodgson et al., 2013; Leditschke et al., 2012; Maiden et al., 2020).

The patient's participation in physical activity may be limited by the severity of illness, including neurologic, haemodynamic, or respiratory instability (Berney et al., 2013; Brummel et al., 2014; Capell et al., 2019; Castro et al., 2015; Dafoe et al., 2015; Dammeyer et al., 2013; Engel et al., 2013; Harrold et al., 2015; Hodgson et al., 2013; Holdsworth et al., 2015; Knott et al., 2015; Leditschke et al., 2012; Morris et al., 2008; Needham & Korupolu, 2010; Nydahl et al., 2014; Pohlman et al., 2010; Winkelman & Peereboom, 2010). In addition, the presence of an endotracheal tube was a common barrier to mobilisation (Berney et al., 2015; Harrold et al., 2015; Hodgson et al., 2013; Holdsworth et al., 2015; Jolley et al., 2015; Knott et al., 2015; Nydahl et al., 2014), due to concerns for dislodgement of the airway, and the increased number of staff required for out-of-bed activities.

Psychological barriers to physical rehabilitation in the ICU include anxiety and depression. The incidence of anxiety and depression is high in patients admitted to an ICU (Bashar et al., 2018; Fumis et al., 2012; Yousefzadeh-Chabok et al., 2018). Anxiety, fear, and lack of motivation from patients were identified as barriers by ICU clinicians (David E. Anekwe et al., 2020; Hodgson et al., 2018; Williams & Flynn, 2013), which negatively impacts participation and adherence to physical activities.

Safety concerns

Safety concerns regarding lines are also common barriers to physical activity (Capell et al., 2019; Castro et al., 2015; Engel et al., 2013; Harris & Shahid, 2014; Hodgson et al., 2013; King & Crowe, 1998; Knott et al., 2015; Leditschke et al., 2012; Needham & Korupolu, 2010; Pohlman et al., 2010; Winkelman & Peereboom, 2010). This is particularly true for patients with renal impairment requiring continuous renal replacement therapy via a multiple lumen vascular access catheter (Berney et al., 2012; Berney et al., 2015; Dinglas et al., 2013; Garzon-Serrano et al., 2011; Harrold et al., 2015; Pohlman et al., 2010) (Figure 2.1). Historically, patients with femoral haemodialysis catheters have been restricted to bed rest (Berney et al., 2012; Pohlman et al., 2010) to avoid catheter dislodgement, infection, thrombosis, disruption of vascular access, and to facilitate CRRT deliverables (Morris, 2007; Talley et al., 2013). However, there is a lack of evidence to support the immobilisation of these patients. The continued practice of bed rest for these patients reflects a culture of risk aversion and unchallenged tradition.

Figure 2.1 A critically ill patient in ICU illustrating the attachments, lines, tubes, and associated equipment that may make the physical activity of a conscious patient difficult. (photo was taken and is shared with consent from the patient)

Environmental factors

Sedation is a frequent and important barrier to physical activity and rehabilitation in the ICU (Barber et al., 2015; Berney et al., 2012; Berney et al., 2013; Capell et al., 2019; Castro et al., 2015; Dafoe et al., 2015; Dammeyer et al., 2013; Engel et al., 2013; Harrold et al., 2015; Hodgson et al., 2016; Needham & Korupolu, 2010; Nydahl et al., 2014; Pohlman et al., 2010). Patients who are intubated and mechanically ventilated are often managed with continuous intravenous sedation. Addressing other barriers to mobilisation with education, leadership roles, and

improving communication without addressing sedation practices did not improve patient mobilisation outcomes (Dafoe et al., 2015). In contrast, addressing sedation practices alone reduced the incidence of delirium, increased the number of rehabilitation sessions, improved functional mobility, and decreased ICU length of stay (Needham & Korupolu, 2010).

Several authors have argued that the lack of funding and access to physiotherapy services are barriers to physical activity in the ICU (Barber et al., 2015; Castro et al., 2015; Dammeyer et al., 2013; Engel et al., 2013; Malone et al., 2015; Morris et al., 2008; Needham et al., 2010). The lack of equipment, resources, and staffing also impact the feasibility of physical activity (Bassett et al., 2015; Carrothers et al., 2013; Castro et al., 2015; Engel et al., 2013; Harrold et al., 2015; Knott et al., 2015; Malone et al., 2015; Morris et al., 2008; Needham & Korupolu, 2010). In addition, time constraints and competing priorities are barriers to mobilisation for the multidisciplinary team (Barber et al., 2015; Berney et al., 2012; Berney et al., 2013; Capell et al., 2019; Castro et al., 2015; Dafoe et al., 2015; Dammeyer et al., 2013; Harrold et al., 2015; Leditschke et al., 2012; Pohlman et al., 2010; Schweickert et al., 2009). Lack of resources such as skilled staffing, rehabilitation equipment, and time constraints are barriers to physical activity in the intensive care setting.

ICU staffing structure varies internationally, including nurse-to-patient ratios and the availability of dedicated physiotherapists (Bakhru et al., 2016). Surveys of ICU physiotherapists in Australia (Skinner et al., 2008), Europe (Norrenberg et al., 2000), Canada (Koo et al., 2016), the US (Malone et al., 2015), and international surveys (Bakhru et al., 2016; Harrold et al., 2015) have described considerable variations in

staffing profiles and practice between countries. Consequently, mobility practices also varied considerably by country and were significantly associated with the nurse-to-patient ratio, the presence of a dedicated physiotherapist, multidisciplinary rounds, and daily goal setting (Bakhru et al., 2016).

Culture and training

The culture of an intensive care unit can have a significant impact on the practice of mobilisation. For example, a culture of risk aversion (Barber et al., 2015; Bassett et al., 2012; Boehm et al., 2020; Engel et al., 2013), lack of multidisciplinary teamwork (David E. Anekwe et al., 2020; Balas et al., 2013; Barber et al., 2015; Carrothers et al., 2013; Dafoe et al., 2015; Dammeyer et al., 2013), and lack of mobility champions (Dafoe et al., 2015; Dammeyer et al., 2013; Needham & Korupolu, 2010) are barriers to early mobility activities in the ICU.

Insufficient training of staff is also a barrier to early rehabilitation of patients (Balas et al., 2013; Barber et al., 2015; Bassett et al., 2015; Carrothers et al., 2013; Castro et al., 2015; Dafoe et al., 2015; Engel et al., 2013; Malone et al., 2015; Morris et al., 2008; Needham & Korupolu, 2010). There is no international standardised training for physiotherapists working in the ICU, so the role and skillset differ internationally (Norrenberg et al., 2000; Skinner et al., 2015). In a survey of ICU physical therapists in the US, 12% of respondents reported having received no training in rehabilitation in the ICU (Malone et al., 2015). Similarly, a lack of conviction and knowledge regarding the benefit of early mobilisation was a limiting factor in a survey of Canadian ICU clinicians (David E. Anekwe et al., 2020).

The above barriers to physical activity result in the immobilisation of the critically ill patient, which is a risk factor for the development of physical problems after intensive care, such as Intensive care unit acquired weakness (ICU-AW). They also lead to considerable heterogeneity in the routine mobility practices of ICU across the world, adding complexity to the study of physical rehabilitation in the prevention or treatment of ICU-AW.

2.7. Intensive Care Unit acquired weakness.

Intensive Care Unit acquired weakness (ICU-AW) is an acute clinical weakness in a critically ill patient without plausible cause other than critical illness. It can be further classified into critical illness myopathy (CIM), critical illness polyneuropathy (CIP), or critical illness neuromyopathy (CINM) (Stevens et al., 2009). In addition, muscle atrophy is a frequent complication in critical illness and can occur with or without the presence of CIM or CIP (Schefold et al., 2020) (Figure 2.2).

Critical illness polyneuropathy (CIP) is an axonal polyneuropathy affecting limb and respiratory muscles (Bolton et al., 1984). Pathological findings demonstrate primary distal axonal degeneration of both sensory and motor fibres, with no evidence of demyelination or inflammation (Bolton et al., 1984). Muscle biopsies from these same patients show changes characteristic of denervation but may also reveal myopathy (Latronico et al., 1996; Zochodne et al., 1987).

Critical illness myopathy (CIM) is the most common subcategory of ICU-AW (Koch et al., 2011; Latronico & Bolton, 2011) and is a primary myopathy where both force

generation capacity and muscle mass are affected (Batt et al., 2013). These contribute to the limbs' symmetrical and flaccid weakness, more pronounced in the proximal muscles than in the distal muscles.

Muscle wasting is a frequent complication in critical illness (N. L. Diaz et al., 1998; Puthucheary et al., 2013), developing in 80% of patients receiving more than seven days of mechanical ventilation and 100% of patients in ICU with multiorgan failure (Koukourikos et al., 2014). Much of the wasting occurs early and rapidly, more severely in patients with multiple organ failure (Puthucheary et al., 2013). Studies of muscle atrophy in healthy people have shown that the loss rate is between 4-5% every week of immobilisation (Stein & Wade, 2005). The interaction of immobilisation in conjunction with sepsis or systemic inflammatory response syndrome enhances the loss of muscular proteins (Finn et al., 1996; Paddon-Jones et al., 2006). The atrophy of myofibers preferentially affects type 2 fast-twitch fibres more than type 1 slow-twitch fibres (N. L. Diaz et al., 1998; Sander et al., 2002). The difference in the pathophysiology of these sub-types of ICU acquired weakness will be discussed later in this chapter.

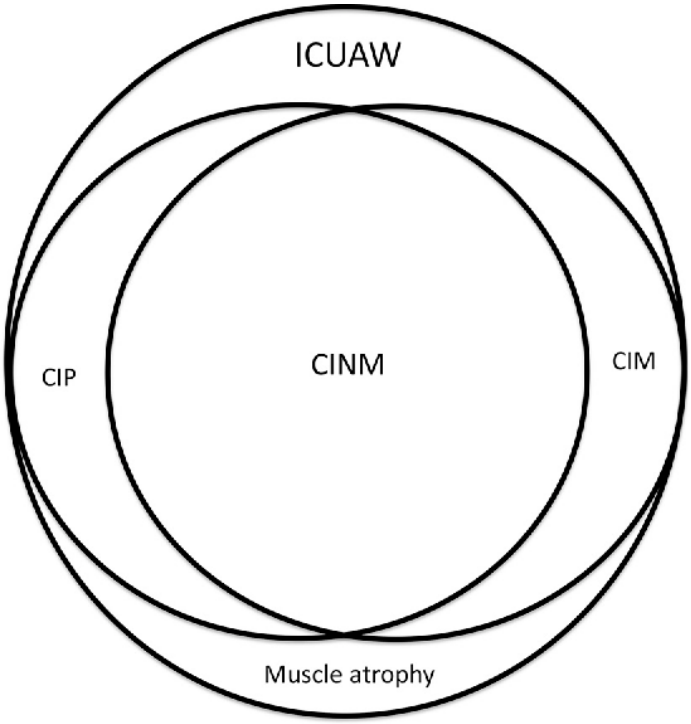


Figure 2.2 Association between ICU-AW, CINM, CIP, CIM, and muscle atrophy. Critically ill patients who develop clinical signs of weakness have ICU-AW. Most patients with ICU-AW have evidence of nerve or muscle dysfunction and are further characterized as having CIP or CIM, respectively. The term CINM is used to describe the common co-occurrence of CIP and CIM in the individual patient. Muscle atrophy also plays a role in the development of ICU-AW and may coexist with CINM. Figure reproduced with permission from (Kramer, 2017).

2.7.1. Investigation and Diagnosis

A framework for diagnosing and classifying patients with ICU-AW was first proposed by Stevens and colleagues in 2009 (Stevens et al., 2009). This has since been supplemented by narrative reviews and clinical guidelines over the last decade (Fan, Cheek, et al., 2014; Hermans & Van den Berghe, 2015; Latronico et al., 2017; Vanhorebeek et al., 2020).

By definition, the diagnosis of ICU-AW is a clinical diagnosis of exclusion involving detailed clinical history, including functional status before ICU admission, and clinical examination to identify other possible causes of generalised weakness (Stevens et al., 2009). The clinical context includes acute severe illness requiring prolonged mechanical ventilation or sepsis and multiorgan support (Stevens et al., 2009). Patients with ICU-AW may present with flaccid tetraparesis, respiratory muscle weakness, hyporeflexia, loss of muscle mass, and high fatigability (Dres et al., 2017; Eikermann et al., 2006; Herridge et al., 2003). It is recommended that clinical examination evaluate key functional domains, including consciousness and cognitive function, cranial nerves, motor and sensory systems, deep tendon reflexes, and coordination. Motor assessment should include a consideration of tone and bulk in addition to strength (Stevens et al., 2009).

Assessment of peripheral muscle strength

Manual muscle testing is graded by the Medical Research Council (MRC) score, an ordinal scale grading muscle contraction from 0 to 5 (Medical Research Council, 1976). The sum of predefined individual scores can provide a global measure of muscle function. In several early studies, ICU-AW was defined by an MRC Sum Score (MRC-SS) of less than 48 of out 60 (Ali et al., 2008; De Jonghe et al., 2007; De Jonghe, Sharshar, et al., 2004; De Jonghe et al., 2002), and since then it has become the reference standard (Fan, Cheek, et al., 2014). The MRC-SS appoints a value between 0 and 5 for each of six muscle groups bilaterally, including wrist extension, elbow flexion, shoulder abduction, hip flexion, knee extension, and ankle dorsiflexion (Table 2.1). The MRC-SS has good interobserver reliability in patients

with Guillain-Barré syndrome (Kleyweg et al., 1991) and has been implemented successfully in critically ill patients (De Jonghe et al., 2002).

Table 2.1 Medical Research Council Sum Score (Kleyweg et al., 1991; Medical Research Council, 1976)		
Muscle group evaluated		**Score 0-5**
Wrist extension	Left	
	Right	
Elbow flexion	Left	
	Right	
Shoulder abduction	Left	
	Right	
Hip flexion	Left	
	Right	
Knee extension	Left	
	Right	
Ankle dorsiflexion	Left	
	Right	
	Total score (out of 60)	
Appointed score		
0, no visible/palpable contraction 1, visible/palpable contraction without movement of the limb 2, some movement of the limb, but not against gravity 3, movement against gravity 4, movement against gravity and some resistance 5, normal		

However, the accurate application of the MRC-SS requires a patient who is awake, cooperative, and capable of contracting the extremities with maximal force (Vanpee et al., 2014). It is also an ordinal scale, in which differentiation between 4 (movement against gravity and some resistance) and 5 (normal) is subjective (Hermans et al., 2012). The subjectivity of the scale is problematic for clinicians and researchers, so other objective measures of strength have been validated.

Handgrip dynamometry can be used as a quick diagnostic screen for ICU-AW. Portable dynamometry permits the measurement of force on a continuous scale and has been reported to be reproducible in the ICU (Baldwin et al., 2013; Vanpee et al., 2011). Handgrip strength of less than 11 kg-force for males and less than seven kg-force for females resulted in the maximum combination of sensitivity and specificity for the diagnosis of ICU-AW when compared with ICU-AW diagnosis by MRC exam (Ali et al., 2008). Grip strength measured by dynamometry predicted difficulty weaning from mechanical ventilation (Cottereau et al., 2015), correlated with MRC-SS, and was independently predictive of hospital mortality, suggesting that it may be a good surrogate measure of global strength (Ali et al., 2008). Like the MRC-SS, handgrip dynamometry requires maximal voluntary muscle contraction, which may be compromised by pain, level of alertness, and ability to understand instructions. These are significant limitations to the current methods of muscle strength testing, as the incidence of delirium in critically ill patients is high (Ely et al., 2001).

Further investigations of ICU-AW may include nerve conduction studies, electromyography, a biopsy of nerve, muscle electric or magnetic neuromuscular twitch stimulation, and ultrasound to assess muscle mass and architecture (Bittner et

al., 2009; Connolly et al., 2015; Stevens et al., 2009). These investigations may further diagnose the subcategory of ICU-AW. CIP is identified in patients who have electrophysiological evidence of sensorimotor axonal polyneuropathy. A diagnosis of CIM is made in patients who have myopathic features on electromyography or myopathic muscle biopsy. Critical illness neuromyopathy has characteristics of both CIM and CIP (Stevens et al., 2009). However, using ancillary investigations to refine diagnosis remains mainly for research purposes because the tests are time-consuming, costly, and do not currently alter the clinical management of the ICU-AW.

Assessment of respiratory muscle strength

Respiratory muscle strength can be evaluated by the maximal inspiratory pressure, either by standardised volitional methods or by non-volitional calibrated stimulation of the phrenic nerve (ATS/ERS, 2002). The gold standard method for assessing respiratory muscle strength measures transdiaphragmatic pressure generated by twitch magnetic stimulation of the phrenic nerves (Watson et al., 2001). This method is independent of the patient's efforts or their level of alertness. However, the measurement of transdiaphragmatic pressure requires oesophageal and gastric balloons. Instead, the endotracheal tube pressure measured by twitch magnetic stimulation of the phrenic nerves is a reliable surrogate widely used in studies investigating diaphragm force. Diaphragm ultrasound can also be used to measure the thickening fraction of the diaphragm and diaphragmatic excursion. Respiratory muscle weakness can be defined as having twitch endotracheal tube pressure of less than 11 cmH20 (ATS/ERS, 2002; Hamnegåard et al., 1995) or having a

diaphragm excursion of less than 1.1 cm during tidal volume breathing (Kim et al., 2011).

Volitional methods such as maximal static inspiratory and expiratory pressure, measured with the mechanical ventilator or a handheld manometer, are more widely used in the clinical setting (ATS/ERS, 2002). Normal values for maximal inspiratory pressure are well described, ranges from 105 to 129 cmH20 for males and 70 to 98 cmH20 for females (ATS/ERS, 2002). However, accurate measurement requires the patient's full cooperation; therefore, a low score may reflect a lack of motivation or inability to follow commands rather than respiratory muscle weakness.

2.7.2. Incidence and epidemiology

ICU-AW is a common problem in the intensive care setting. The reported incidence varies depending on the patient cohort studied and the timing of evaluation. ICU-AW at first awakening is present in 26–65 % of patients who were mechanically ventilated for 5 – 7 days (Ali et al., 2008; Sharshar et al., 2009), and 25% of these remained weak for at least another seven days after awakening (De Jonghe et al., 2002). In patients who have stayed in ICU for more than 24 hours, the rate of ICU-AW was 11% (Nanas et al., 2008), this increased to 23.8% – 55% after staying in ICU for more than 7 – 10 days respectively (Hermans et al., 2014; Nanas et al., 2008). ICU-AW is highly prevalent in patients with acute respiratory distress syndrome (ARDS), whereby 60% have ICU-AW on awakening (Bercker et al., 2005). At the time of hospital discharge, the prevalence of ICU-AW remains at 36% (Fan, Dowdy, et al., 2014).

2.7.3. Risk factors for ICU-AW

Numerous independent risk factors for ICU-AW have been reported, although most are from observational studies. Comparisons between studies are complex due to heterogeneity in patient populations and the definitions used to diagnose ICU-AW

Patient demographics

Age was not a risk factor for ICU-AW in a meta-analysis of 5 studies (odds ratio, 95% confidence interval) (1.01, 0.99 to 1.03) (T. Yang et al., 2018). Female sex was an independent risk factor for ICU-AW in a single prospective study (odds ratio, 95% confidence interval) (4.66, 1.19 to 18.30) (De Jonghe et al., 2002). Currently, there are no human data on the effect of pre-morbid obesity on the risk of ICU-AW. However, in a mice study, premorbid obesity, not nutrition, was an independent protective factor against ICU-AW development (Goossens et al., 2017).

The pre-ICU functional status influences the absolute level of recovery and the rate of recovery (Barnato et al., 2011; Ferrante et al., 2015; Iwashyna et al., 2012). However, the relationship between premorbid frailty and risk of developing ICU-AW has not been reported until recently, with one prospective observational study (Raurell-Torredà et al., 2021) finding that a higher prehospital Barthel Index was protective against the development of ICU-AW (odds ratio, 95% confidence interval) (0.97, 0.95 to 0.99).

It is highly plausible that pre-ICU frailty or physiological reserve could impact patient outcomes, as the extent of functional decline or recovery may depend on pre-ICU

status. This is particularly the case if the ICU-AW is diagnosed with an MRC-SS cut-off score of 48, because patients who were already weak before their critical illness would perform worse.

The severity of illness

The severity of illness (APACHE II score) was significantly associated with ICU-AW in a meta-analysis of five studies (odds ratio, 95% confidence interval) (1.05, 1.01 to 1.10) (T. Yang et al., 2018), and independently associated with increased risk in two other prospective observational studies (Campellone et al., 1998; de Letter et al., 2001). Numerous changes occur in critical illness that may contribute to ICU-AW, which is discussed in detail later in this chapter. The risk associated with the severity of illness may reflect a range of changes in critical illness. However, higher severity of illness is also likely to expose patients to many of the other risk factors listed below.

Sepsis, systemic inflammatory response syndrome, and shock

Sepsis is a syndrome characterised by a dysregulated inflammatory response leading to organ damage in response to microbial infection (Michie, 1996). A systematic review found sepsis was associated with ICU-AW in six of the twelve included studies (odds ratio, 95% confidence interval) ranged from 2.4 (0.8 – 6.8) to 49 (4.7 – 519) (Stevens et al., 2007). Prospective observational studies since have supported this finding, where sepsis (odds ratio, 95% confidence interval) (2.20, 1.30 to 3.71) (Hermans et al., 2013), and days with sepsis (hazard ratio, 95% confidence

interval) (1.48, 1.22 to 1.81) (Brunello et al., 2010) were also identified as risk factors for ICU-AW.

Systemic inflammatory response syndrome (SIRS) is a non-specific body response to a series of conditions causing inflammation, including infection, burns, acute pancreatitis, trauma, and others (Levy et al., 2003). The presence of SIRS (odds ratio, 95% confidence interval) (3.75, CI 1.59 to 8.86) (Nguyen The & Nguyen Huu, 2015) and the duration of SIRS (odds ratio, 95% confidence interval) (1.36, 1.16 to 1.48) (Bednarík et al., 2005) were independent risk factors for ICU-AW in prospective observational studies.

Shock is defined as a state of cellular and tissue hypoxia due to an imbalance of oxygen supply and demand (Standl et al., 2018). Shock was an independent risk factor for ICU-AW (odds ratio, 95% confidence interval) (2.58, 1.02 to 6.51) in a prospective observational study (Nguyen The & Nguyen Huu, 2015).

Sepsis is associated with an overall catabolic state leading to the breakdown of carbohydrates, lipid, and protein stores (Michie, 1996). The systemic dysregulated inflammatory response in sepsis and SIRS can result in microvascular disturbances and the release of proinflammatory mediators (Lush & Kvietys, 2000), contributing to the development of ICU-AW. Severe sepsis can lead to shock, in which macrovascular disturbances can directly injure cells and interfere with mitochondria metabolism (Russell et al., 2018). The management of patients with sepsis, SIRS, and shock is inevitably associated with other risk factors such as mechanical ventilation and immobility. However, in animal models where sepsis can be

separated from confounding factors such as mechanical ventilation and immobility, sepsis alone has not reproduced the selective myosin loss seen in critical illness myopathy (Friedrich et al., 2015).

Multiple organ dysfunction

The extent of multiple organ dysfunction is measured by the Sequential Organ Failure Assessment (SOFA) score, usually on admission to ICU and every 24-hours. The SOFA score was not associated with ICU-AW in a meta-analysis of two studies (odds ratio, 95% confidence interval) (0.99, 0.92 to 1.08) (T. Yang et al., 2018). However, admission SOFA score of more than 7 (relative risk, 95% confidence interval) (2.03, 1.02 to 4.12), and a total first-week SOFA of more than 45 (RR, 95% confidence interval) (2.38, 1.02 to 5.53) were independent risk factors for ICU-AW in a prospective observational study (Bednarík et al., 2005). In addition, the number of days with dysfunction of 2 or more organs (odds ratio, 95% confidence interval) (1.28, 1.11 to 1.49) was an independent risk factor in a prospective multicentre observational study (De Jonghe et al., 2002).

The lack of robust data to implicate SOFA score as an independent risk factor for ICU-AW development is not surprising. Multiple organ dysfunction is closely associated with sepsis and the severity of critical illness. The Sequential Organ Failure Assessment score was previously known as the Sepsis-related Organ Failure Assessment (J. L. Vincent et al., 1996). The pathophysiology of multiple organ dysfunction, with or without sepsis, shares many common features that may

contribute to ICU-AW, such as systemic inflammatory response, endothelial disruption, oxidative stress, and mitochondria dysfunction.

Renal replacement therapy

Renal replacement therapy was not an independent risk factor for the development of ICU-AW in a systematic review and meta-analysis of 3 studies (odds ratio, 95% confidence interval) (0.02, 0.02 to 7.05) (T. Yang et al., 2018).

However, acute renal failure and renal replacement therapy are closely associated with sepsis, shock, and multiple organ dysfunction (Neveu et al., 1996; Ronco et al., 2001), which are independently associated with the development of ICU-AW. In critically ill patients with acute renal failure, raised potassium ion levels in the extracellular space can cause resting membrane depolarisation and reduced excitability of nerve and muscle cells. Continuous renal replacement therapy is also a common barrier to mobilisation in the ICU (Berney et al., 2012; Pohlman et al., 2010), resulting in long periods of bed rest. Therefore, the routine immobilisation of patients with acute renal failure requiring continuous renal replacement therapy needs to be addressed.

Noradrenaline

Noradrenaline use was not a risk factor for ICU-AW in a meta-analysis of two studies (odds ratio, 95% confidence interval) (1.04, 0.99 to 1.09) (T. Yang et al., 2018). However, the use of vasoactive medication was an independent risk factor for ICU-

AW in a post hoc analysis of a randomized control trial on early mobilisation (Wolfe et al., 2018).

Vasoactive therapy such as noradrenaline is often used in the intensive care unit to increase systemic vascular resistance in patients with hemodynamic instability. Hemodynamic instability is a frequently reported barrier to mobilisation in the ICU (see section 2.6), precluding participation in functional exercises such as standing and walking. However, recent studies have shown mobilisation is safe and feasible in patients receiving vasoactive therapy (Jacob et al., 2021; Rebel et al., 2019).

Use of antibiotics

Results of two systematic reviews and meta-analyses with three (T. Yang et al., 2018) and ten (Yang et al., 2020) included studies found that the use of aminoglycoside antibiotics was significantly associated with ICU-AW (odds ratio, 95% confidence interval) (2.27, 1.07 to 4.81) and (2.06, 1.33 to 3.21), respectively.

Aminoglycoside therapy has been associated with neuromuscular blockade (Grill & Maganti, 2011) by inhibiting acetylcholine release from the axonal terminal (Wright & Collier, 1977). This class of antibiotics is commonly used to treat severe bacterial infections in critically ill patients. Therefore the association between aminoglycoside use and other risk factors such as sepsis should also be considered.

Vancomycin use was also a risk factor for the development of ICU-AW in a posthoc analysis of an observational cohort study (Wieske et al., 2015). Other antibiotics

such as clindamycin, erythromycin, quinolones, polymyxin, tetracycline may also affect the neuromuscular junction (Howard et al., 2008) but have so far not been independently associated with ICU-AW (Wieske et al., 2015).

Neuromuscular blocking agents

Results of two systematic review and meta-analyses with nineteen (Price et al., 2016) and five (T. Yang et al., 2018) included studies demonstrated the use of neuromuscular blocking agents was significantly associated with ICU-AW (odds ratio, 95% confidence interval) (1.25, 1.06 to 1.48) and (2.03, 1.22 to 3.40), respectively.

Neuromuscular blocking agents can cause prolonged neuromuscular blockade if there are issues in the drug's metabolism or result in denervation atrophy if used for extended periods (see below section 2.7.4).

Corticosteroids

While the association between glucocorticoid and myopathy has been well known (Pereira & Freire de Carvalho, 2011), its association with the development of ICU-AW remains uncertain. In a meta-analysis of four studies, corticosteroids use not a risk factor for ICU-AW (odds ratio, 95% confidence interval) (1.92, 0.95 to 3.88) (T. Yang et al., 2018). A larger systematic review and meta-analysis later found that it was a risk factor for ICU-AW in a meta-analysis of eighteen studies (odds ratio, 95% confidence interval) (1.84. 1.26 to 2.67) (Tao Yang et al., 2018). In the

subgroup of patients with sepsis in this meta-analysis, corticosteroids use was not associated with the development of ICU-AW (odds ratio, 95% confidence interval) (1.96, 0.61 to 6.30). In contrast, in another meta-analysis of seven studies in patients with sepsis only, corticosteroids use was a significant risk factor for ICU-AW (relative risk, 95% confidence interval) (1.21, 1.01 to 1.52) (Rochwerg et al., 2018).

The relationship between corticosteroids and ICU-AW may not be straightforward, as corticosteroids may decrease exposure to other risk factors or indirectly contribute to ICU-AW by inducing hyperglycaemia. In a sub-analysis of a randomised trial comparing intensive insulin versus conventional therapy in critically ill medical patients, corticosteroids had a protective effect against the development of ICU-AW in the intensive insulin group (odds ratio, 95% confidence interval) (0.97, 0.94 to 0.99) (Hermans et al., 2007). However, the association between corticosteroids and ICU-AW in a heterogeneous critically ill cohort remains unclear. Further research in homogenous patient populations is required.

Hyperglycaemia

Patients with ICU-AW had significantly higher blood glucose levels in 5 out of 6 studies included in a systematic review (Stevens et al., 2007). In two prospective observations studies, hyperglycaemia was an independent risk factor for the electrophysiological (Witt et al., 1991) and clinical diagnosis of ICU-AW (odds ratio, 95% confidence interval) (2.86, 1.30 to 6.30) (Nanas et al., 2008). Uncontrolled hyperglycaemia in patients with critical illness disrupts cell endothelium, impairs

mitochondria function, and may promote muscle protein degradation (Flakoll et al., 1993; Fram et al., 2010; Langouche et al., 2005).

Parenteral nutrition

Parental nutrition was an independent risk factor for ICU-AW in a prospective cohort study of patients with sepsis (odds ratio, 95% confidence interval) (5.11, 1.14 to 22.88) (Garnacho-Montero et al., 2001). In addition, late parental nutrition was a protective factor for ICU-AW in the sub-analysis of a randomised controlled trial comparing early to late parental nutrition (odds ratio, 95% confidence interval) (0.68, 0.47 to 0.99) (Hermans et al., 2013).

Early parenteral nutrition suppressed autophagy, while other signs of muscle atrophy were not affected by nutrition strategies (Hermans et al., 2013). Therefore, it is hypothesised that suppressed autophagy in critical illness, crucial in the quality control of skeletal muscle, may impair myofiber integrity and function (Hermans et al., 2013).

ICU Length of stay

ICU length of stay was an independent risk factor for ICU-AW (odds ratio, 95% confidence interval) (1.05, 1.03 to 1.08) in a secondary analysis of a randomised trial dataset (Van den Berghe et al., 2005). The number of days in the ICU before the first electrophysiologic examination was associated with the development of electrophysiologic signs of ICU-AW in a prospective observational study (Witt et al.,

1991). Time to first awakening and measurement of MRC was independently associated with ICU-AW (odds ratio, 95% confidence interval) (1.05, 1.01 to 1.10) in the secondary analysis of a randomised trial dataset (Hermans et al., 2013), after adjusting for other risk factors. Awakening in this study was assessed systematically using five standard commands (De Jonghe et al., 2002).

Despite studies attempting to adjust for confounding factors, a higher length of stay in ICU may still reflect the severity of illness and exposure to other risk factors associated with ICU care, such as immobility and the duration of mechanical ventilation.

Duration of mechanical ventilation

In a systematic review and meta-analysis with fourteen studies, more prolonged exposure to mechanical ventilation was associated with a significant increase in the incidence of ICU-AW (ICU-AW was diagnosed in 33% of patients mechanically ventilated for five days or less, vs. 43% in those who have been ventilated for seven days or more) (Fan, Cheek, et al., 2014).

However, the relationship between the duration of mechanical ventilation and the risk of ICU-AW could be reciprocal, as ICU-AW can lead to difficulties in weaning. At the same time, prolonged periods of critical illness such as sepsis and multi-organ failure are also independent risk factors for ICU-AW. In addition, mechanical ventilation, and the sedation that usually accompanies it, may result in “mechanical silencing”

(loss of weight-bearing and internal strain caused by activation of contractile proteins), which is discussed further in section 2.7.4.

Immobility and sedation

In a secondary analysis of a randomised controlled trial of early occupational and physical therapy, early mobilisation reduced the incidence of ICU-AW (odds ratio, 95% confidence interval) (0.18, 0.06 to 0.55) (Patel et al., 2014). In a prospective cohort of 98 patients who have been ventilated for at least seven days, the duration of mechanical ventilation before awakening was independently associated with the occurrence of ICU-AW (odds ratio, 95% confidence interval) (1.10, 1.00 to 1.22) (De Jonghe et al., 2002). This finding could reflect the negative effect of immobilisation on neuromuscular function. In a prospective study of 222 survivors of acute lung injury (Fan, Dowdy, et al., 2014), the duration of bed rest was independently predictive of muscle weakness 3 – 24 months post ICU discharge, but the incidence of ICU-AW in this cohort was not measured. The association between sedation practice and risk of ICU-AW has not been investigated, and it may be difficult to separate the effect of sedation from the impact of immobility.

The combination of sedation and immobilisation of patients results in “mechanical silencing” that is unique to critically ill patients (Friedrich et al., 2015). This is different from immobilisation resulting from bed rest or casting, where weight bearing has been removed, but there is still internal strain from the activation of contractile proteins.

Other risk factors

Several other risk factors were independently associated with the development of ICU-AW. For example, low serum albumin (Witt et al., 1991), high peak lactate (odds ratio, 95% confidence interval) (2.18, 1.39 to 3.43) (Wieske et al., 2014), hyperosmolarity (odds ratio, 95% confidence interval) (4.8, 1.05 to 24.38) (Garnacho-Montero et al., 2001), and electrolyte disturbances (odds ratio, 95% confidence interval) (2.48, 1.02 to 6.01) (Nguyen The & Nguyen Huu, 2015) were independent risk factors for ICU-AW in prospective studies. These risk factors may contribute to ICU-AW development via pathways listed in the next section, such as decreased protein synthesis, mitochondria dysfunction, and reduced excitability of nerve and muscle cells due to electrolyte disturbances.

2.7.4. Pathophysiology and molecular mechanisms

The proposed pathophysiological mechanisms of ICU-AW are multifactorial and complex. Numerous independent or interacting pathways could contribute to functional and structural changes to muscles and nerves. Furthermore, both the critical illness and its treatment are likely to contribute to the development of ICU-AW in these mechanistic models. The following section will summarise the normal physiology of the skeletal motor unit and present the mechanisms that contribute to the development of ICU-AW.

2.6.4.1 Physiology of the skeletal motor unit.

The physiology of the motor neuron and the motor unit is described in detail in Chapter 34 of Principles of Neural Science (Erie & Kandel, 2000). This section is a summary of this work.

A motor unit consists of a motor neuron in the ventral horn of the spinal cord, its axon, and the muscle fibres that the axon innervates (Liddell & Sherrington, 1925). A single muscle fibre consists of many myofibrils encapsulated by the muscle fibre membrane, the sarcolemma. A myofibril is made up of many sarcomeres arranged in series. The sarcomere is the most basic functional unit of the muscle, which contains contractile proteins. The contractile proteins actin and myosin are arranged in a regular interdigitated matrix (Figure 2.3).

The activation of a motor unit begins with an action potential, which moves down the axon in a depolarising wave, propagated by voltage-gated sodium ion channels. When the action potential reaches the axon terminal, it activates voltage-gated calcium ion channels. The influx of calcium ions into the axon terminal causes acetylcholine to be released into the synaptic cleft. As this occurs, voltage-gated potassium channels open to repolarise the axon terminal, transitioning the axon terminal into the rest phase.

The acetylcholine binds to nicotinic receptors on the sarcolemma. As a result, the nicotinic receptor is activated, and the muscle cell starts to depolarise. When the depolarisation reaches a membrane threshold potential, further rapid depolarisation is caused by voltage-gated sodium ion channels, forming an action potential. The

action potential moves along the sarcolemma and results in the release of calcium ions from the sarcoplasmic reticulum into the cytosol.

The calcium ions bind to troponin proteins on the contractile protein matrix, results in the exposure of the myosin-binding site on actin. Myosin attaches to actin, and using energy in the form of adenosine triphosphate, pulls along the actin filament, shortening the muscle sarcomere (Smith, 2018). As the muscle cell reaches its peak actin potential, voltage-gated potassium ion channels open, repolarising the sarcolemma and transitioning the muscle cell into the rest phase.

The muscle strength generated is dependent on both muscle mass (number of motor units available), number of motor units activated, and the force-generating capacity of the motor units (Schefold et al., 2020).

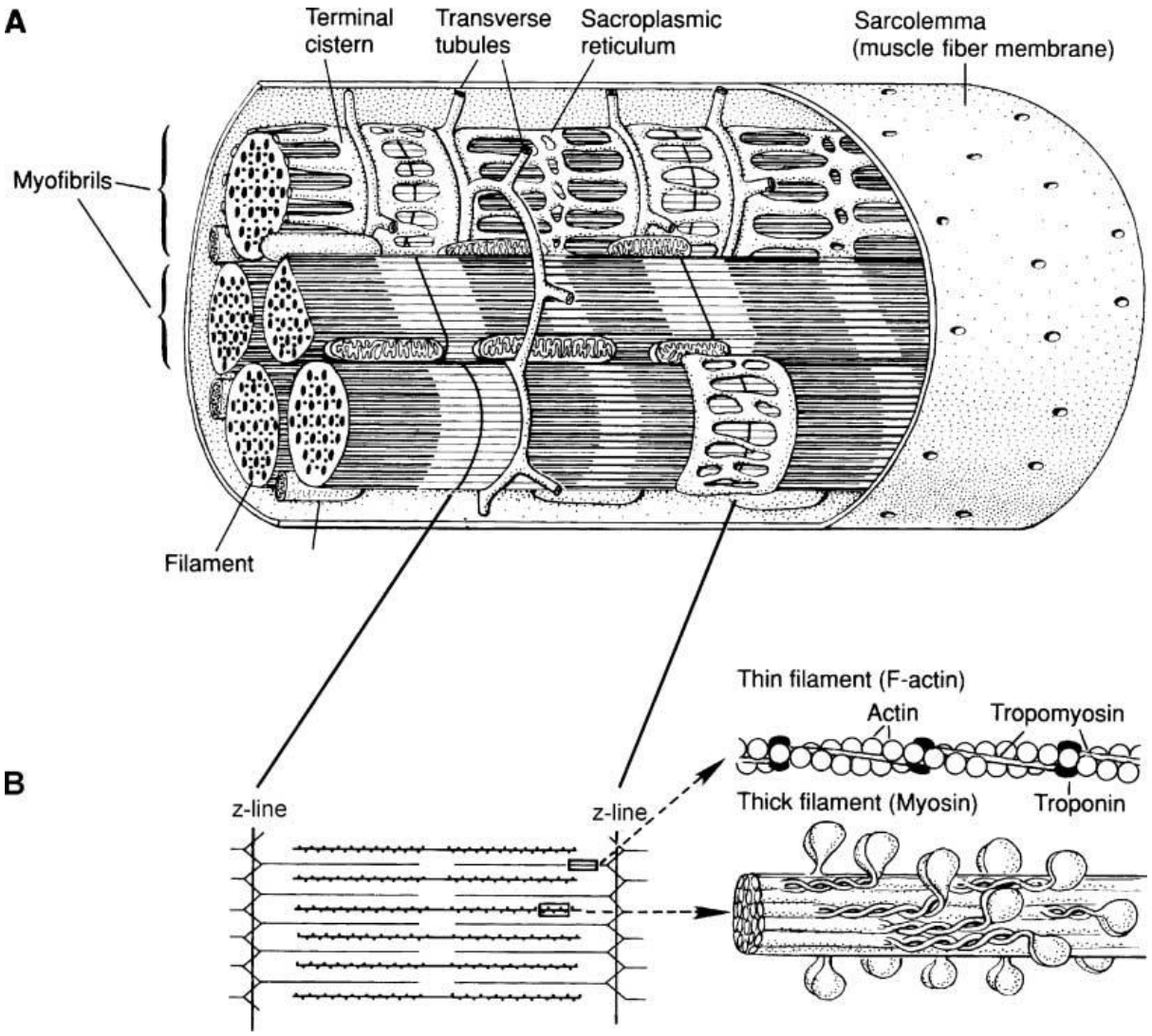


Figure 2.3 Structure of a single muscle fibre. A. This is a three-dimensional reconstruction of a section of muscle fibre, showing the relationship of the myofibrils to the membrane, transverse tubule system, and sarcoplasmic reticulum. B. The arrangement of contractile proteins in sarcomeres and details of the contractile proteins. Figure reproduced with permission from (Heckman & Enoka, 2004).

2.7.4.2 Pathophysiological changes in critical illness

Numerous mechanisms and pathways are implicated in the development of ICU-AW. The combination of inactivity and inflammation in critical illness act synergistically to influence muscle atrophy and dysfunction (Ferrando et al., 1999; Fink et al., 2008). Pathophysiological processes include pro-inflammatory cytokines, decreased protein synthesis, increased protein degradation, oxidative injury, impaired excitability of neurons and muscle cells, and direct injury to the motor unit (Callahan & Supinski, 2009; Chambers et al., 2009; Siu, 2009; Siu & Alway, 2009; Spate & Schulze, 2004; Winkelman, 2004). These observed or potential mechanisms will be discussed in the next section.

Failure of neuromuscular transmission

Neuromuscular blocking agents may be used in critical illness to facilitate mechanical ventilation (Papazian et al., 2010) but have been associated with the development of persistent weakness (Price et al., 2016). The underlying mechanism has been identified as prolonged neuromuscular blockade due to slow clearance of blocking agents and denervation atrophy after prolonged use (Barohn et al., 1994; Lagasse et al., 1990; Partridge et al., 1990).

Disturbances in microcirculation such as tissue oedema and hypoperfusion are commonly observed in sepsis and critical illness (Kara et al., 2016). These changes predispose nerves to ischemia because blood vessels supplying the peripheral nervous system lacks autoregulation (Bolton, 2005; Smith et al., 1977). Sepsis evokes changes in the endoneurium that increases vascular permeability and allows penetration of toxic factors into the nerve ends (Bolton, 2005; Fenzi et al., 2003).

This may result in endoneurial oedema, impair energy delivery to the axon and cause axonal death. Skeletal muscles samples from critically ill patients with weakness showed similar findings of capillary occlusion, oedema, atrophy, and segmental necrosis (N. Diaz et al., 1998). Tissue hypoperfusion is also associated with membrane depolarisation of terminal motor axons and reduced nerve excitability (Z'Graggen et al., 2006).

Reduced excitability of muscle and nerve

In critically ill patients with severe weakness, the muscle can become electrically unexcitable (Rich et al., 1997; Rich et al., 1996). Further studies reveal this may be due to reduced muscle fibre conduction velocity, increased refractory period, and reduced excitability of fibres in response to direct muscle stimulation (Allen et al., 2008; Bierbrauer et al., 2012; Lefaucheur et al., 2006).

Voltage-gated sodium ion channels determine membrane excitability of the sarcolemma and are especially sensitive to cell injury. Critical illness directly cause acquired channelopathy in both skeletal muscle and motor axons, resulting in reduced excitability (Boucher et al., 2012; Filatov et al., 2009).

Plasma ionic imbalance associated with critical illness may affect the steady-state inactivation or activation of sodium ion channels. For example, raised extracellular potassium found in critically ill patients can cause substantial resting membrane

depolarisation and limit the excitability of muscles and nerves (Cunningham et al., 1971; Z'Graggen et al., 2006).

Calcium ion has crucial roles in neuromuscular transmission and the activation of the contractile proteins in muscles. Voltage-gated calcium ion channels and global muscle calcium ion homeostasis are impaired in animal models of critical illness. However, data on human subjects are lacking. Thus, further studies are required to confirm this mechanism in patients with critical illness.

Proinflammatory cytokines

Proinflammatory cytokines such as tumour necrosis factor-alpha and interleukin-1 can promote muscle atrophy and weakness in critically ill patients (Winkelman, 2004).

Tumour necrosis factor-alpha is a proinflammatory cytokine commonly elevated in critically ill patients (Damas et al., 1992; Puthucheary et al., 2018). At the cellular level, tumour necrosis factor-alpha stimulates protein loss via the ubiquitin-proteasome pathway in animal models (García-Martínez et al., 1994; LI et al., 2003). Tumour necrosis factor-alpha also depresses the force of muscle contraction in the absence of atrophy in animal models (Wilcox et al., 1996) via muscle-derived oxidants (Reid et al., 1992).

Interleukin-1 is also elevated in critically ill patients (Damas et al., 1992). It is a potential stimulus for protein loss and muscle atrophy seen in critical illness.

Elevated interleukin-1 levels promote muscle atrophy in experimental animals (Cooney et al., 1999). Studies of underlying mechanisms suggest that interleukin-1 affects protein degradation and protein synthesis (Baracos et al., 1983; Zamir et al., 1991).

Myosin loss following mechanical silencing

In mechanically ventilated and sedated ICU patients, there is complete mechanical silencing to the muscles due to the removal of external (weight-bearing, passive movements induced by activation of agonists and antagonists) and internal (activation of contractile proteins) mechanical load. Mechanical load influences immediate signalling events in muscle, such as calcium ion release from the sarcoplasmic reticulum, and influences protein synthesis and degradation (Rennie et al., 2004). Clinical studies confirm that long-term mechanical ventilation and mechanical silencing induce preferential myosin loss in patients (Larsson, 2008; Llano-Diez et al., 2012). Furthermore, in an animal ICU model, mechanical silencing induces oxidative stress, downregulation of myosin synthesis, and protein degradation via the E3 ligase MuRF1 pathway (Renaud et al., 2013). However, data on human subjects are lacking and require further research.

Bioenergetic failure

Muscle fatigue in patients with sepsis may be due to mitochondrial alterations and ATP depletion (Fredriksson & Rooyackers, 2007). Mitochondrial dysfunction is driven by a vicious cycle of increased free oxygen radical generation, which inhibits

mitochondrial enzymes, resulting in further oxidative stress and disruption to the production of adenosine triphosphate (Friedrich et al., 2015). In patients with severe sepsis, mitochondria functional alterations were evident in muscle biopsies taken within 24 hours of ICU admission (Brealey et al., 2002), with a reduction in adenosine triphosphate (Fredriksson et al., 2006).

Decreased protein synthesis

The primary pathway involved in muscle protein synthesis is the IGF1-PI3K-Akt-mTOR pathway (Schiaffino et al., 2013). The components of this pathway are considerably down-regulated in patients with CIM (Weber-Carstens et al., 2013). Protein synthesis is depressed on the first day after ICU admission (Puthucheary et al., 2013), with depressed mRNA expression levels for myosin heavy chains (Derde et al., 2012; Hermans et al., 2013; Wollersheim et al., 2014). Reduced protein synthesis and inhibited uptake of amino acids contribute to the catabolic response in skeletal muscle in critical illness (Hasselgren et al., 1986).

Increased protein degradation

Several processes during critical illness may promote the loss of muscle protein, selectively involving myosin (Derde et al., 2012; Wollersheim et al., 2014). These include inflammation, immobilisation, endocrine stress responses, nutritional deficit, impaired microcirculation, and denervation (Batt et al., 2013; Bloch et al., 2012; Weber-Carstens et al., 2013). Muscle atrophy involves the shrinkage of myofibers due to a net loss of proteins, organelles, and cytoplasm. The ubiquitin-proteasome

system and the autophagy-lysosome pathway are the degradation systems involved in this process.

Myofibrillar proteins constitute 55% to 60% of the total protein in muscle tissue by weight. These are the proteins that constitute the myofibril or contractile structure in skeletal muscle. Muscle atrophy in critical illness results predominately from the degradation of myofibrillar proteins (Hasselgren et al., 1989; Long et al., 1981). Subsequently, the loss of contractile machinery during atrophy accounts for the reduction in muscle strength (Cohen et al., 2015).

The Ubiquitin-proteasome system

The Ubiquitin-proteasome system (UPS) is thought to be the primary cause of protein degradation (Lecker, 2003), with key components of the pathway upregulated in critical illness (Constantin et al., 2011). Most, but not all, intracellular proteins are degraded by the UPS (Jagoe & Goldberg, 2001; Lecker et al., 1999; Rock et al., 1994). Most muscle proteins, particularly myofibrillar components, are mainly degraded by the UPS (Russell, 2010; Solomon & Goldberg, 1996).

Proteins that form the contractile unit are broken down in a specific order (Figure 2.4), and the E3 ubiquitin ligases have prominent roles. The E3 ubiquitin ligase MuRF1 disassemble the layer of cytoskeletal proteins that binds the myofilaments into myofibrils, releasing the myofilaments. These free myofilaments can subsequently be degraded by the 26S proteasome (Clarke et al., 2007; Cohen et al.,

2009; Fielitz et al., 2007). The breakdown of actin and other thin filaments involves another E3 ubiquitin ligase, TRIM32 (Cohen et al., 2012).

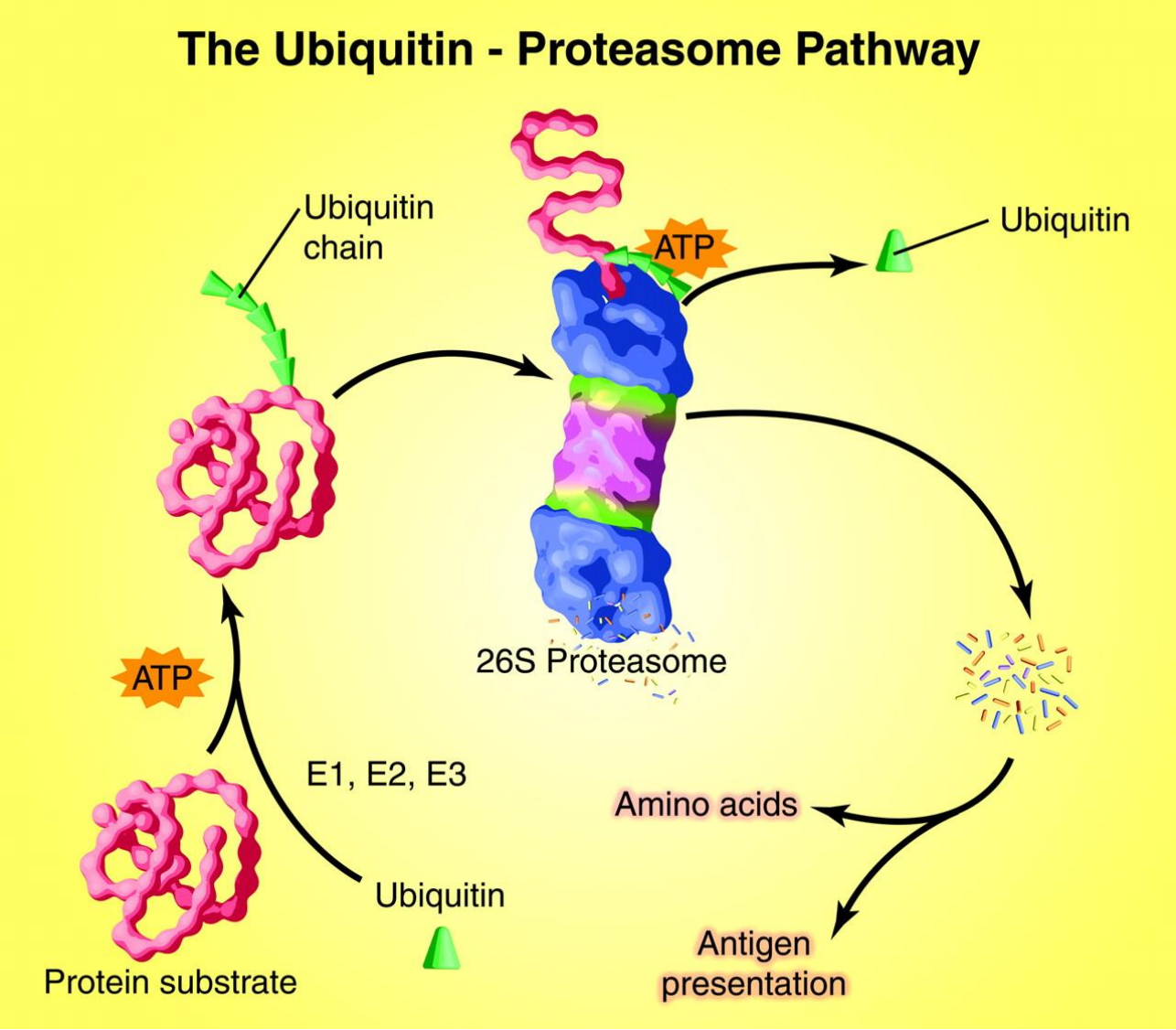


Figure 2.4 Simplified scheme of the ubiquitin-proteasome pathway. Reproduced with permission from (Lecker et al., 2006).

In early critical illness, expression of transcriptional mediators FoxO1 and FoxO3 are induced (Sander et al., 2002; Wollersheim et al., 2014), which directly generates two essential muscle-specific E3 ligases, atrogin-1 and MuFf1 (Kamei et al., 2004; Llano-Diez et al., 2011; Sandri et al., 2004). Atrogin-1 and MuFf1 are higher at mRNA and

protein levels in critically ill patients (Constantin et al., 2011; Hooijman et al., 2015; Hussain et al., 2010; Levine et al., 2008; Llano-Diez et al., 2019; Tiao et al., 1997). Their upregulation occurs early in critical illness and is sustained (Kamei et al., 2004; Sandri et al., 2004). Elevated levels of E3 ligases TRIM32 and TRIM62 have been found in patients with ICU-AW (Llano-Diez et al., 2019; Schmidt et al., 2014). In addition, increased activity of the 20S proteasome, a subunit of the larger, more complex 26S, can be observed in critical illness (Hussain et al., 2010; Tiao et al., 1997) and up to 6 months after ICU discharge (Dos Santos et al., 2016). Consequently, there is an increased concentration of ubiquitinated proteins in the atrophied muscle of critically ill patients (Helliwell et al., 1998; Jaber et al., 2011; Rabuel et al., 2004).

Upstream activation of the UPS is a potential area to target for therapy in muscle atrophy in critical illness. While still a controversial factor in ICU-AW, glucocorticoids induce muscle atrophy via atrogin-1 and MuRF1 (Bodine et al., 2001; Clarke et al., 2007; Shimizu et al., 2011). Activities of the activin receptor type 2B (ActRIIB) pathway also lead to muscle wasting and cachexia via the autophagy-lysosome system and are discussed below.

Autophagy-lysosome system

Autophagy is used to degrade and recycle, through the lysosomal machinery, long-lived proteins, mitochondria, and organelles (Mizushima & Komatsu, 2011). The loss of mitochondria accounts for the decreased endurance capacity of the atrophied muscles. Autophagy is also crucial for maintaining muscle mass and integrity

(Masiero et al., 2009). The role of the Autophagy-lysosome system (ALS) system in the development of muscle atrophy and weakness in the critically ill is more complex, with parts of the system activated at different times (Llano-Diez et al., 2011).

Muscle mass loss in critical illness patients has been associated with the upregulation of ALS (Constantin et al., 2011; Helliwell et al., 1998; Levine et al., 2008; Llano-Diez et al., 2019; Mofarrahi et al., 2012). In addition, the cathepsins (CTSS, CTSB, CTSA, CTSD, CTSZ, and LGMN), which are lysosomal proteases, are upregulated in critical illness (Constantin et al., 2011; Llano-Diez et al., 2019) and are associated with muscle fibre atrophy in this population (Helliwell et al., 1998).

However, despite upregulation of the system, successful activation of autophagy may be impaired in critical illness (Vanhorebeek et al., 2011), and successful activation of autophagy can be associated with faster recovery from muscle weakness (Hermans et al., 2013). These findings are consistent in the animal model, where inhibition of ALS caused more severe muscle loss instead of protecting against atrophy (Masiero et al., 2009). Furthermore, deficient autophagy results in sarcomere disorganisation, and debris accumulation may have a crucial role in the development of CIM (Masiero et al., 2009) and other myopathies (Levine & Kroemer, 2008; Mammucari et al., 2007; Zhao et al., 2007). Thus, the activity of the ALS system must be well balanced. While its activation can induce muscle atrophy, its impaired activity may play an essential role in CIM development.

Calpain system

Calpains are a family of nonlysosomal, calcium-dependent cysteine proteases. Calpains can also release myofilaments from myofibrils for ubiquitination, by the cleavage of myofibrillar cytoskeletal proteins (47, 52, 93, 94).

Calpain levels were markedly elevated in atrophied muscle fibres in patients with CIM (Di Giovanni et al., 2000; Showalter & Engel, 1997). Currently, the specific roles of different isoforms of caplains are not fully understood, but gene expression for calpain-1, -2, -4, and -10 are upregulated in patients with CIM (Llano-Diez et al., 2019), and calpain-1 and -2 levels are found to be elevated in mechanically ventilated patients (Zhu et al., 2017).

Certain calpains are also downregulated in patients with CIM, such as calpain -3 -6, and -8 (Constantin et al., 2011; Llano-Diez et al., 2019). The muscle-specific isoform, calpain-3, is required for the regenerative process during sarcomere remodelling. The lack of functional calpain-3 is associated with muscle wasting in myopathies (Hauerslev et al., 2012).

Activin signalling

Activin A is a potent negative regulator of muscle mass, belonging to the TGF-β ligands family. Activin A binds to ActRIIB, a high-affinity activin type-2 receptor in muscle. The activin A-Smad3 pathway is the primary negative regulator of protein synthesis (Schiaffino et al., 2013), its activation directly inhibiting the IGF1-PI3K-Akt-mTOR pathway (Gumucio et al., 2015). The activin pathway also initiates a signalling

cascade (Figure 2.5), leading to increased expression of genes involved in the UPS and ALS to induce muscle protein degradation (Lokireddy et al., 2011; Marino et al., 2015; Tisdale, 2010; Zhou et al., 2010). In animal models, activin A plays a dominant role in the development and progression of muscle wasting (Lach-Trifilieff et al., 2014; Lee & McPherron, 2001; Lee et al., 2005; Lokireddy et al., 2011; Matzuk et al., 1994; Souza et al., 2008; Tisdale, 2010; Zhou et al., 2010). Elevated levels of activin A induce loss of muscle mass, endomysial fibrosis, decreased peak force-generating capacity, and reduced fatigue resistance (Chen et al., 2014), features commonly observed in CIM (Eikermann et al., 2006; Herridge et al., 2003).

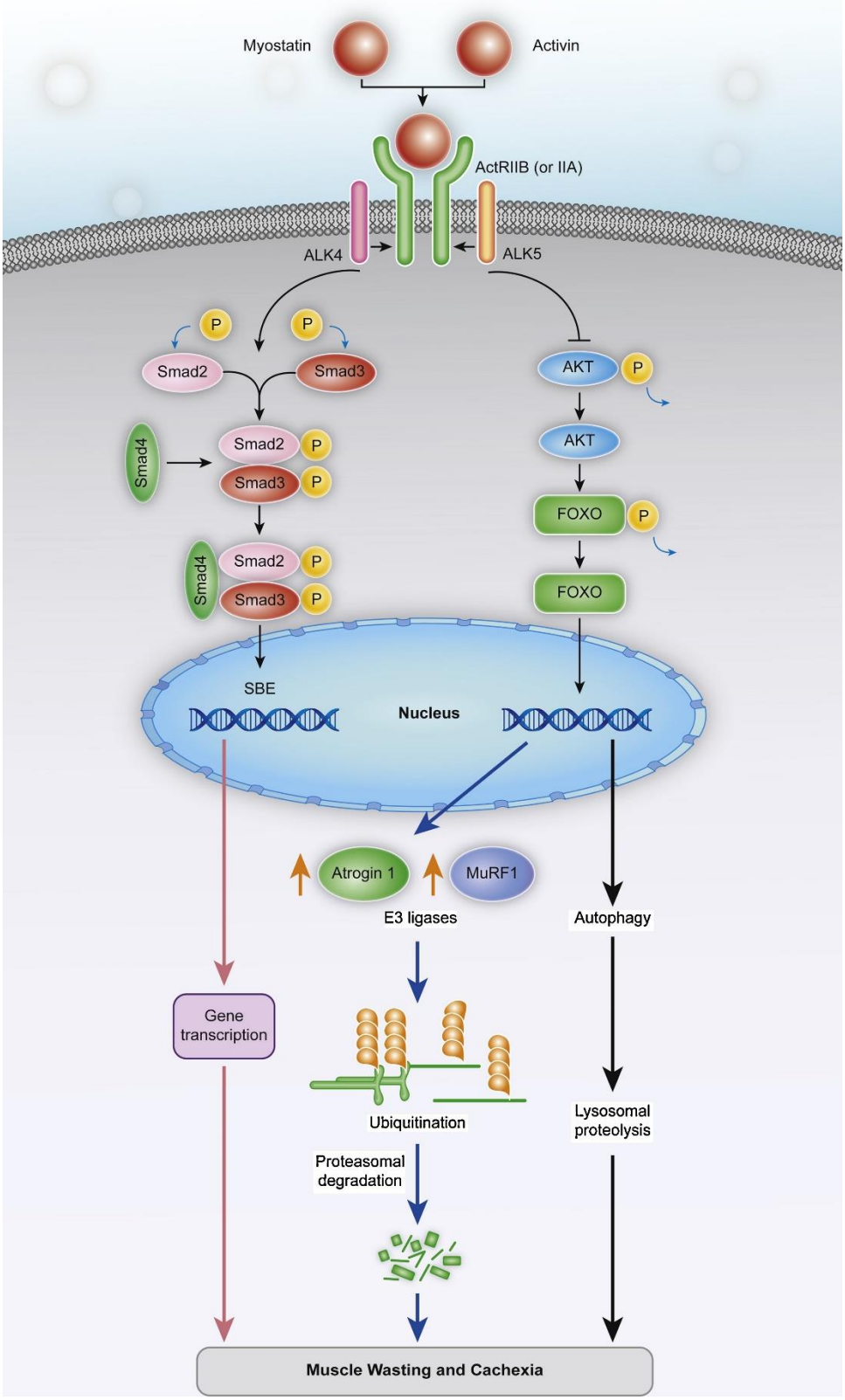


Figure 2.5 Activin signalling in muscle. Activin binds to activin receptor type IIB, which leads to the recruitment of the ubiquitin-proteasome and autophagy-lysosome pathways and suppressing protein synthesis via the Smad pathway. Reproduced with permission from (Han et al., 2013).

Summary of pathophysiologic changes

Microvascular changes that occur during critical illness result in axonal injury and death. In addition, acquired channelopathy and plasma ion imbalance reduce the excitability of neurons as well as muscles. These changes may explain the clinical features of critical illness polyneuropathy.

Several processes can cause a reduction in the force-generating capacity of muscle. First, proinflammatory cytokines can reduce the force generated by muscle and induce muscle atrophy. Second, mechanical silencing induces preferential myosin loss. Third, muscle membrane inexcitability is caused by sodium ion channel dysfunction. Fourth, muscle fatigue in critically ill patients may be explained by bioenergetic failure. Finally, microvascular dysregulation may directly result in muscle cell injury and death.

Muscle atrophy in critical illness is brought about by decreased muscle protein synthesis and increased protein degradation. Activin A potentially facilitates multiple pathways that lead to loss of muscle mass.

2.7.5. Short and long-term outcomes of ICU-AW

ICU-AW is associated with prolonged weaning from mechanical ventilation (De Jonghe et al., 2007; De Jonghe, Bastuji-Garin, et al., 2004; De Jonghe et al., 2002), and increased ICU (De Jonghe et al., 2002; Garnacho-Montero et al., 2005) and hospital length of stay (Garnacho-Montero et al., 2005). ICU-AW is also associated with increased mortality in-ICU (Sharshar et al., 2009), in-hospital (Ali et al., 2008;

Sharshar et al., 2009), and in the first year after ICU admission (Hermans et al., 2014). In one prospective study, the incidence of CIM was more frequent (68%) than CIP (38%), while patients with CIP had a significantly longer ICU length of stay and had a higher degree of weakness (Koch et al., 2011). This persists beyond ICU and hospital stay, with long-term follow-up demonstrating a worse CIP prognosis than CIM (Guarneri et al., 2008; Intiso et al., 2011; Koch et al., 2014).

In a recent prospective study, physical functioning was significantly more impaired in patients with ICU-AW compared to ICU survivors without ICU-AW at 3 and 12 months (Dettling-Ihnenfeldt et al., 2017). Recovery from weakness takes weeks to months. In a prospective study of patients with acute lung injury, 36% had ICU-AW at hospital discharge, 22% at three months, 15% at six months, 14% of patients at one year, and 9% at two years (Fan, Dowdy, et al., 2014). Even at five years after discharge from ICU, the diagnosis of ICU-AW has longer-term associations with an increased physical disability (Herridge et al., 2011) and increased mortality (Dinglas et al., 2017).

2.7.6. Prevention and treatment

Limited treatment or prevention with proven efficacy has been identified to date (Latronico et al., 2017). Proposed treatments to date have focused on minimising or preventing risk factor exposure and facilitating the resolution of the underlying critical illness.

<u>Corticosteroids management</u>

Corticosteroids are an essential treatment in certain critically ill patients, such as severe sepsis, ARDS, and severe COVID-19 disease. In systematic reviews and meta-analyses of randomised controlled trials investigating prolonged corticosteroid use in sepsis (Annane et al., 2015) and ARDS (Tang et al., 2009), the incidence of ICU-AW was similar between the control and the treated groups. Thus, in patients with sepsis and ARDS, glucocorticoids' potential direct harmful neuromuscular effect may be balanced by the overall clinical improvement and reduced duration of organ failure, in particular ventilator dependency and associated immobilisation, which are key risk factors for ICU-AW (Meduri et al., 2016).

Management of neuromuscular blockade

A randomised controlled trial comparing the early use of a neuromuscular blocking agent to a placebo in patients with ARDS did not change the incidence of ICU-AW (Papazian et al., 2010). In this study, the duration of neuromuscular blocking was 48 hours in duration, which may not be long enough to induce denervation atrophy. This study suggests that an early and short period of neuromuscular blockade does not increase the incidence of ICU-AW.

Management of hyperglycaemia

Intensive glucose control (target of 4.4 to 6.1 mmol/litre) in surgical and medical patients decreased the risk of developing electrophysiological signs of ICU-AW compared with conventional glucose control target between 10.0 and 11.1 mmol/litre (Hermans et al., 2007; Van den Berghe et al., 2005). While it is generally accepted

that hyperglycaemia should be avoided (Dellinger et al., 2013), the optimal glucose target remains controversial. The safety of intensive glucose control (4.5 to 6.0 mmol/litre) has come under question when it increased all-cause 90-day mortality among adults in the ICU, compared to conventional glucose control of less than 10.0 mmol/litre in a large randomised controlled trial (Finfer et al., 2009). The incidence of ICU-AW was not examined in this trial.

Physical rehabilitation

Physical rehabilitation is an integral part of the management of the physical sequelae of critical illness (Davidson et al., 2013; Needham et al., 2011; Schweickert et al., 2009). Early mobilisation and rehabilitation have been shown to reduce the likelihood of developing ICU-AW in recent systematic reviews with meta-analyses (D. E. Anekwe et al., 2020; Zang et al., 2020). Interventions investigated consisted of neuromuscular electrical stimulation (NMES), passive range of movements, and progressive functional activities such as sitting up, standing, and walking. These interventions are safe and feasible in the ICU environment (K. P. Mayer et al., 2020; Stiller, 2013).

In patients that are not awake or clinically stable enough to participate in early mobilisation, NMES has been proposed as an alternative (Parry et al., 2013). However, in a meta-analysis of six randomised controlled trials specifically investigating NMES, the intervention did not improve global muscle strength (Zayed et al., 2020). Thus, currently, the use of NMES is not standard practice in ICUs across the world.

Inspiratory muscle training is a promising therapy that targets the respiratory muscle weakness of patients with ICU-AW. Systematic reviews and meta-analyses have shown that inspiratory muscle training improves respiratory muscle strength (Elkins & Dentice, 2015), shorten the duration of mechanical ventilation (Vorona et al., 2018), duration of weaning (Vorona et al., 2018; Worraphan et al., 2020), and the length of stay in the ICU and hospital (Elkins & Dentice, 2015). Currently, the practice of inspiratory muscle training is heterogeneous, with variable methods, time of initiation, and target populations (Vorona et al., 2018). Thus, despite the increasing amounts of evidence to supports its use, inspiratory muscle training is not yet standard practice in ICUs.

Avoiding early parenteral nutrition

Early parental nutrition has been identified as an independent risk factor for the development of ICU-AW in the post hoc analysis of a large randomised controlled trial (n= 4640) comparing early vs. late parenteral nutrition (Hermans et al., 2013). Other randomised controlled trials have also shown that early initiation of supplemental parenteral nutrition is not beneficial and may be harmful (Doig et al., 2013; Fivez et al., 2016; Heidegger et al., 2013). However, none of these studies have investigated ICU-AW as an outcome. Therefore, further prospective trials are needed to investigate when parenteral nutrition can be safely and effectively initiated.

Pharmacological interventions

A systematic review of drug therapies found no evidence to support the use of oxandrolone, human growth hormone, propranolol, immunoglobulin, and glutamine in the prevention and treatment of ICU-AW (Shepherd et al., 2016).

2.8 Chapter summary

The critically ill patient is frequently subject to physical inactivity and immobilisation. This, in combination with their severity of illness and exposure to other risk factors unique to the ICU, place them at risk of developing ICU-AW. ICU-AW is a well-defined and widely recognised clinical syndrome. However, there are gaps in our understanding of its pathophysiology. As a result, there are limited treatment or prevention strategies with proven efficacy. Currently, physical rehabilitation is the only safe, feasible, and effective intervention in the treatment and prevention of ICU-AW. However, the practice of physical rehabilitation in ICU is heterogeneous, and certain types of exercises may be more effective than others. Therefore, we must further our understanding of the pathophysiology of this condition and identify new potential targets for treatment.

Chapter 3. Activin A level is associated with muscle strength and physical function in critically ill patients

3.1. Introduction

Muscle wasting is a frequent complication in patients with critical illness. Several pathways have been implicated in its pathogenesis. However, no treatment to date aims to affect these pathways directly. Activin A is a potent negative regulator of muscle mass that is elevated in critical illness. It is implicated in several pathways that result in the loss of muscle mass in animal models of critical illness. The potential role of activin A in muscle wasting and functional decline in critically ill patients has not been investigated. If activin A is proven to be a crucial facilitator of muscle wasting in critically ill patients, therapies that target activin A activity can be explored.

This chapter presents a prospective cohort study of thirty-six critically ill patients from two ICUs. It explored the relationship between serum activin A concentration, muscle strength, and physical function outcomes.

3.2. Activin A level is associated with muscle strength and physical function in critically ill patients

Wang YT, Harrison CA, Skinner EH, Haines KJ, Holdsworth C, Lang JK, Hibbert E, Scott D, Eynon N, Tiruvoipati R, French CJ, Stepto NK, Bates S, Walton KL, Crozier TM, Haines TP (under review). Activin A level is associated with muscle strength and physical function in critically ill patients.

Abstract

Introduction: Activin A is a potent negative regulator of muscle mass elevated in critical illness. It is unclear whether muscle strength and physical function in critically ill humans are associated with elevated activin A levels.

Objective: To investigate the relationship between serum activin A levels, muscle strength, and physical function at discharge from intensive care unit (ICU) and hospital.

Design, Setting, and Participants: Thirty-six participants were recruited from two tertiary ICUs in Melbourne, Australia. Participants were included if they were mechanically ventilated > 48 hours and expected to have a total ICU stay of > 5 days.

Main Outcomes and Measures: Total serum activin A levels were measured daily in ICU. Handgrip strength, Medical Research Council Sum Score, Physical Function ICU Test Scored, Six-Minute Walk Test, and Timed Up and Go Test were assessed throughout the hospital admission.

Main Results: Higher Medical Research Council Sum Score at first time sitting out of bed (ordered log-odds regression coefficient, 95% confidence interval, p-value) (-0.07, -0.13 to -0.01, p = 0.029), improved Physical Function ICU Test score at ICU discharge (ordered log-odds regression coefficient, 95% confidence interval, p-value) (-0.27, -0.52 to -0.01, p = 0.041), and higher Six-Minute Walk Test distance at hospital discharge (ordered log-odds regression coefficient, 95% confidence interval, p-value) (-0.01, -0.01 to -0.00, p = 0.007) were associated with lower peak serum activin A.

Conclusions: Higher peak activin A is associated with the functional decline of critically ill patients. Further research is indicated to examine its potential as a therapeutic target and a prospective predictor for muscle wasting in critical illness.

Introduction

Acute skeletal muscle wasting is a frequent complication in critical illness (Dos Santos et al., 2016; Hayes et al., 2018; Kirby P. Mayer et al., 2020; Puthucheary et al., 2013; Sheean et al., 2014), occurring early in the intensive care unit admission and lasting up to 6 months after ICU discharge (Dos Santos et al., 2016). Lower limb muscle cross-sectional area can decrease by up to 18.5% in the first 7 to 10 days of ICU admission (Hayes et al., 2018; Kirby P. Mayer et al., 2020; Puthucheary et al., 2013). Muscle wasting is associated with muscle weakness and physical function in ICU (Hayes et al., 2018), at hospital discharge (Kirby P. Mayer et al., 2020), and in the 12 months after ICU admission (Chan et al., 2018).

Muscle wasting in critical illness occurs via decreased muscle protein synthesis (Puthucheary et al., 2013) and increased protein degradation (Derde et al., 2012; Puthucheary et al., 2013), in particular the degradation of myofibrillar proteins (Derde et al., 2012). Protein degradation in critical illness is due to the upregulation of the two major protein degradation pathways (Helliwell et al., 1998; Levine et al., 2008) - the ubiquitin-proteasome system (UPS) (Constantin et al., 2011; Schmidt et al., 2014; Tiao et al., 1997) and autophagic-lysosomal system (ALS) (Constantin et al., 2011; Mofarrahi et al., 2012).

Activin A is a potent negative regulator of muscle mass, belonging to the TGF-β ligands family. Activin A binds to Activin receptor type 2B (ActRIIB), a high-affinity activin A receptor in muscle. Thus, Activin A initiates signalling cascades that inhibit protein synthesis (Schiaffino et al., 2013) and muscle protein degradation via the UPS and ALS pathways (Lokireddy et al., 2011; Marino et al., 2015; Zhou et al., 2010).

While muscle mass and architecture are important outcomes, the measurement of total skeletal muscle mass is problematic. Estimating lean body mass using whole-body plethysmography, total body water, magnetic resonance imaging, computed tomography, dual-energy X-ray absorptiometry, or bioelectric impedance analysis as surrogate measures for muscle mass can be inaccurate (Evans et al., 2019) and impractical in the critically ill population. Meanwhile, muscle strength and physical function have been included in a core set of patient-important outcomes after critical illness by an international consensus of critical illness survivors, their families, researchers, and clinicians (D. M. Needham et al., 2017).

Serum Activin A is elevated in critically ill patients with sepsis (Lee et al., 2016; Michel et al., 2003), acute respiratory distress syndrome (ARDS) (Kim et al., 2019), coronavirus disease 2019 (COVID-19) (Synolaki et al., 2021), H1N1 (Linko et al., 2014) and acute respiratory failure (de Kretser et al., 2013) but associations between activin A levels with muscle strength and physical function in critically ill humans have not been investigated. There are also multiple methods via which measurement of activin levels can be conceptualised, and these levels may vary over an ICU admission. For example, one could look at the first measurement taken within an ICU, the mean or median of several measurements, or the highest value of all measurements taken. It is unknown which approach yields the strongest associations with clinical outcomes. While several studies have investigated the functional sequelae of ICU-AW (Dettling-Ihnenfeldt et al., 2017; Guarneri et al., 2008; Intiso et al., 2011; Koch et al., 2014), few have investigated the extent to which bench-top and clinical physiological findings are linked. Such evaluations are critical given that data suggest

that patients surviving ICU may have normal long-term physical function despite abnormalities in neurophysiology studies (Fletcher et al., 2003). We aim to investigate the relationship between serum activin A levels, muscle strength, and physical function at ICU and hospital discharge.

Materials and methods

This prospective observational cohort study (Australian and New Zealand Clinical Trials Registry Number ACTRN12615000047594) was conducted between February 2017 and December 2018 in the 14-bed tertiary ICU at Frankston Hospital and the 14-bed tertiary ICU at Sunshine Hospital, Melbourne, Australia. Institutional ethical approval was granted for both sites by respective local ethical review boards (Reference Numbers: HREC/14/SHA/26; SSA/15/PH/14). Informed consent was obtained from participants or their surrogate decision-makers. The reporting of this study conforms to the STROBE statement for observational cohort studies (Von Elm et al., 2007).

Participants

The treating ICU physiotherapist screened participants on weekdays. Adult participants >18 years old were eligible if they had received invasive mechanical ventilation for more than 48 hours and were expected to remain in the ICU for at least 120 hours. Exclusion criteria are listed in detail in supplemental digital content. In the absence of empirical data on which to base the sample size, we aimed to recruit 20 participants who could complete outcome measures to ICU discharge.

Participant age, sex, Acute Physiology and Chronic Health Evaluation (APACHE II) (Knaus et al., 1985), admission diagnosis (APACHE III diagnostic codes (Australian and New Zealand Intensive Care Society Modified)) (Australian and New Zealand Intensive Care Society, 2020), Sequential Organ Failure Assessment (SOFA) (J.-L. Vincent et al., 1996), time on mechanical ventilation, length of ICU and hospital stay, and ICU and hospital mortality were recorded.

Activin A measurements

Blood samples were collected on the day of enrolment and daily after that for 21 days until the patient was discharged from the ICU or no longer had indwelling arterial vascular access, whichever occurred first. A (two-site) enzyme-linked immunosorbent assay (Ansh Labs, Webster, TX, USA) was used to quantify the activin A concentration in serum samples. The intra-assay coefficients of variation for activin A were 5.7%, inter-assay coefficients of variation of 7.7%, and the lower level of detection was 24 pg/ml. Measurement of activin A level was performed by an investigator blinded to the clinical records and outcomes of the patients. Results of the activin A levels were not available to the outcome assessors until all assessments were completed.

Outcome measures

A range of standardised muscle strength and physical function outcome measures were used (appendix 3.1, 3.2, and 3.3), drawn from an international consensus of core outcome measures (D. M. Needham et al., 2017). These measures have been used

feasibly in ICU cohorts, with established clinometric properties (Denehy, Skinner, et al., 2013). Daily assessments included the overall muscle strength using the Medical Research Council Sum Score (MRC-SS) (Kleyweg et al., 1991) and handgrip strength of dominant hand using dynamometers (Jamar hydraulic dynamometer, JLW Instruments, Chicago, USA, and Exacta™ Hydraulic Hand Dynamometer, North Coast Medical, Gilroy California, USA), with a standardised protocol (Baldwin et al., 2013). The Physical Function ICU Test (Scored) (PFIT-s) (Denehy, de Morton, et al., 2013) was performed at the first time sitting out of bed (SOOB) and on ICU discharge. The Timed Up and Go Test (TUG) (Podsiadlo & Richardson, 1991) and the 6-minute walk test (6MWT) (ATS, 2002) were measured on ICU discharge and acute hospital discharge.

Statistical analysis

Three different measures of activin A concentration were examined: i) the first measurement taken between 48-72 hours of commencement of mechanical ventilation, ii) the peak measurement across the duration of ICU stay, and iii) the median measurement across the duration of ICU stay. Relationships between these values and study outcomes were analysed using ordered logistic regression, with serum activin A denoted the ordinal dependent variable in each case. This was because low-level measurements of activin A taken using the assay approach return a result of "<24 pg/ml", meaning this variable could not be treated as continuous. In our analyses, treating these values as ordinal dependent variables was the most appropriate solution to this analytic problem. Patient measures of function and strength were treated as independent variables. Where univariate analysis demonstrated a

statistically significant association, multivariable analysis including plausible confounders (severity of illness, age, and sex) was performed to check the sensitivity of the univariate association to the inclusion of these variables. Missing data were excluded listwise from analyses. Statistical analysis was performed using STATA/SE version 13 (StataCorp LP, Austin, TX, USA). $P < 0.05$ was accepted as the level of statistical significance.

Results

Demographics

Thirty-six participants were included in the study. Twenty-seven participants (75%) survived to ICU discharge. Of these, nineteen participants were able to complete outcome measures up to and including ICU discharge. Twenty-two participants (61%) survived to hospital discharge. Of these, seventeen participants were able to complete outcome measures at hospital discharge. A detailed description of the flow of participants from screening to final follow-up is outlined in Figure 3.1. The sample had a mean age of 60.7 years, was mostly male (61.1%), and the primary diagnoses were bacterial pneumonia, sepsis, and septic shock (Table 3.1).

Activin levels

Serum activin A was measured in all 36 participants at least once. The median number of measurements per participant was 5, with an interquartile range of 2.5 to 7.5. The peak activin A, median activin A and initial activin A concentrations (Table 3.1) in our

cohort were all significantly elevated compared to reference levels (de Kretser et al., 2013), wherein the serum activin A concentration was 110 ± five pg/ml among a cohort of 52 healthy volunteers aged 51 to 65.

Peak activin A and strength and function measures

Univariate analyses of the relationship between activin A concentrations and patient outcomes are presented in Figures 3.2 and 3.3. Higher MRS-SS at the first time sitting out of bed was associated with lower peak serum activin A level, a one-unit increase in MRC-SS was associated with a 0.06 unit (ordered log-odds regression coefficient, 95% confidence interval, p-value) (-0.07, -0.13 to -0.01, p = 0.029) decrease in the ordered log-odds of being in a higher peak activin category. Better PFIT-s score at ICU discharge and 6MWT distance at hospital discharge were also associated with lower peak serum activin A level (ordered log-odds regression coefficient, 95% confidence interval, p-value) (-0.27, -0.52 to -0.01, p = 0.041) and (-0.01, -0.01 to -0.00, p = 0.007), respectively.

Multivariate sensitivity analysis (Table 3.2) demonstrated that further 6MWT distance at hospital discharge was independently associated with lower peak activin concentration (Figure 3.4) after adjusting for the possible confounding effects of severity of illness, age, and sex. A one-metre increase in 6MWT distance was associated with a 0.01 unit (ordered log-odds regression coefficient, 95% confidence interval, p-value) (-0.01, -0.01 to -0.00, p = 0.029) decrease in the ordered log-odds of being in a higher peak activin category, while the other independent variables were

held constant. However, MRC-SS and PFIT-s scores were not associated with peak activin A concentration in the sensitivity analysis.

ICU and hospital mortality were associated with higher peak activin A concentrations (univariate analysis presented in Table 3.3; data presented in Figure 3.5). In patients who died in the ICU, their odds of having a higher peak activin concentration was 7.54 times higher than patients who survived (proportional odds ratio, 95% confidence interval, p-value) (7.54, 1.65 to 34.43, p = 0.009). In patients who did not survive to hospital discharge, their odds of having a higher peak activin concentration was 15.24 times higher than patients who did (proportional odds ratio, 95% confidence interval, p-value) (15.24, 3.48 to 66.76, $p < 0.0005$). Multivariate sensitivity analysis (Table 3.4) demonstrated that ICU and hospital mortality were independently associated with higher peak activin A concentrations, after adjusting for the severity of illness, age, and sex (proportional odds ratio, 95% confidence interval, p-value) (8.56, 1.85 to 39.59, p = 0.006) and (16.60, 3.39 to 81.18, p = 0.001), respectively. Thus, peak activin A concentration was the best method of activin measurement at predicting hospital mortality (Figure 3.6).

Initial activin A and outcomes

A higher 6MWT distance at hospital discharge was associated with a lower initial activin A level (ordered log-odds regression coefficient, 95% confidence interval, p-value) (-0.01, -0.01 to -0.00, p = 0.048). Multivariate sensitivity analysis (Table 3.2) demonstrated that higher 6MWT distance at hospital discharge was independently associated with lower initial activin concentration, after adjusting for the possible

confounding effects of severity of illness, age, and sex (ordered log-odds regression coefficient, 95% confidence interval, p-value) (-0.01, -0.02 to -0.00, p = 0.035).

ICU mortality was not associated with increased initial activin A concentration in univariate analysis (proportional odds ratio, 95% confidence interval, p-value) (3.97, 0.96 to 16.35, p = 0.056). Hospital mortality was associated with higher initial activin A concentration (proportional odds ratio, 95% confidence interval, p-value) (4.74, 1.30 to 17.24, p = 0.018). Multivariate sensitivity analysis (Table 3.4) showed that ICU and hospital mortality were both independently associated with higher initial activin A concentrations, after adjusting for the severity of illness, age, and sex (proportional odds ratio, 95% confidence interval, p-value) (5.95, 1.25 to 28.40, p = 0.025) and (6.26, 1.38 to 28.41, p = 0.017), respectively.

Median activin A and outcomes

None of the muscle strength or physical function outcome measures were associated with median activin A concentrations (Figure 3.2 and 3.3). ICU and hospital mortality were associated with higher median activin A concentrations (proportional odds ratio, 95% confidence interval, p-value) (6.34, 1.52 to 26.40, p = 0.011) and (8.21, 2.14 to 31.47, p = 0.002), respectively. Multivariate sensitivity analysis (Table 3.4) demonstrated that ICU and hospital mortality were independently associated with higher median activin A concentrations, after adjusting for severity of illness, age, and sex (proportional odds ratio, 95% confidence interval, p-value) (6.75, 1.54 to 29.54, p = 0.011) and (9.97, 2.22 to 44.91, p = 0.003), respectively.

Discussion

Clinical significance

This novel study has explored and demonstrated the relationship between activin A concentration, muscle strength, and physical function in the critically ill. Peak activin A concentration was the most promising measure of activin A in the intensive care setting. There was excellent concordance of the direction of the ordered log-odds regression coefficient across the outcome measures and time points. Elevated peak activin A concentration was associated with worse muscle strength and physical function at different time points in the patient's ICU and hospital stay.

One of the main clinical and histological features of ICU-AW is muscle fibre atrophy (Batt et al., 2013; García-Martínez et al., 2019). In critically ill patients, the upregulation of the UPS (Constantin et al., 2011; Schmidt et al., 2014; Tiao et al., 1997) and ALS (Constantin et al., 2011; Mofarrahi et al., 2012) protein degradation pathways are responsible for muscle catabolism (Helliwell et al., 1998; Levine et al., 2008). Both these pathways are upregulated by activin A and its receptor, ActRIIB, in animal models (Lokireddy et al., 2011; Marino et al., 2015; Zhou et al., 2010). While activin A concentrations are elevated in critically ill humans (de Kretser et al., 2013; Michel et al., 2003), this is the first study to demonstrate that elevated activin A concentrations are associated with worse muscle strength and physical function. This is of particular significance because inhibition of ActRIIB has been shown to increase muscle mass in healthy volunteers (Attie et al., 2013) and patients with chronic obstructive pulmonary disease. Our data suggest activin A is an influential factor in the muscle catabolism observed in critical illness survivors, and a potential therapeutic target.

Importantly, pharmacological agents such as bimagrumab (Polkey et al., 2019) and muscle regulator ACE-031 (Attie et al., 2013) target the activin A pathway and have been used safely in human subjects. These reagents may slow muscle catabolism in critically ill patients.

Activin A and mortality

In our study, ICU and hospital mortality were independently associated with increased activin A concentrations. This finding is consistent with similar observational studies in the critically ill population. For example, in a prospective observational study of 518 critically ill patients with acute respiratory failure, a higher admission activin A concentration was associated with higher 12-month mortality (de Kretser et al., 2013). In another observational study of 130 critically ill patients with suspected sepsis, the serum activin A level at ICU admission was a predictor of sepsis severity, ICU and hospital mortality (Lee et al., 2016). The proposed mechanism for this relationship is attributed to activin's role as a major controller of the systemic inflammatory response in humans (Hedger et al., 2011; Jones et al., 2004; Jones et al., 2007). Activin A has been implicated in several acute inflammatory syndromes such as acute respiratory distress syndrome (Kim et al., 2019), COVID-19 (Synolaki et al., 2021), sepsis, acute food poisoning, acute coronary syndromes, asthma, meningitis, burns, and traumatic brain injury (Phillips et al., 2009).

Elevated activin A levels in critical illness

The levels of activin A observed in our cohort are consistent with larger cohorts of critically ill patients. In a study of 518 critically ill patients with acute respiratory failure, the median admission serum activin A concentration was 270 (interquartile range (IQR) 310) pg/mL in those that died at 1-year, 210 (IQR = 330) pg/ml in those that were alive at 1-year (de Kretser et al., 2013). In 130 critically ill patients with suspected sepsis, mean serum activin A concentration was 251.6 (standard deviation (SD) 126.3) pg/mL in patients without sepsis, 595.5 (SD 527.8) pg/ml in severe sepsis, and 937.1 (SD 792.2) pg/ml in those with septic shock (Lee et al., 2016). Our participants' activin A levels were significantly elevated compared to normal values, where a mean concentration of 110 (SD 41) pg/mL was measured in 138 healthy volunteers (de Kretser et al., 2013). This study further confirms that activin A activity is increased in patients with critical illness.

Limitations

As a proof-of-concept study with a small consecutive sample, we were underpowered to investigate the relationship between activin A and patient outcomes thoroughly. Several of our measures were not found to have significant associations with activin measures. While the directions of coefficients were consistent with our hypothesis, the confidence intervals were wide. We therefore cannot be sure that a clinically meaningful association with these variables does not exist due to our small sample size. A consecutive sample also meant there was heterogeneity in the participant cohort, with a mixture of medical and surgical patients, and different admission diagnoses. The effect of activin A could have been variable across this cohort. At the time of the study, we lacked a feasible and accurate method to measure total skeletal

muscle mass. Therefore we did not include muscle mass as an outcome. We need to consider the possibility that activin A impacts muscle strength and physical function through mechanisms other than muscle mass. We also did not have the opportunity to investigate the expression of key genes involved in the UPS and ALS, which would have provided further insight into the role of activin A in muscle catabolism in the critically ill.

We could not treat activin A concentration as a continuous variable because low-level measurements of activin A taken using the assay approach return "<24 pg/ml". We accommodated this by using ordered logistical regression, treating activin level as the ordinal dependent variable. While this was the most appropriate way to analyse our data, it meant that we could not investigate the accuracy of activin as a predictor variable while adjusting other possible confounders with patient outcomes.

We also noted floor and ceiling effects with some of the outcome measures. For example, only one participant had an MRC-SS of 48 or more at first awakening, while on hospital discharge, all surviving participants had an MRC-SS of 48 or more. In addition, only four out of 21 participants could walk any distance at all for the 6MWT and TUG at ICU discharge. These ceiling and floor effects mean that these measures may not be sensitive to clinically meaningful change in these outcome constructs that occur at the extreme ends of these scales. This would reduce the statistical power to find associations between these outcomes and patient Activin levels.

Future directions

A single physical function outcome measure responsive to change across the continuum of care needs to be developed to support future observational and interventional studies in this population. An accurate and practical method to measure total skeletal mass in critically ill patients is also needed. A recent review on measures of body composition (Evans et al., 2019) identified D3-creatine dilution as a promising method to measure muscle mass and should be validated in this population. We recommend future research take serial measurements of activin A so the peak value can be identified. This will allow activin A to be investigated as an independent continuous variable, alongside other predictors of physical function and mortality. A larger study in a more homogenous patient cohort such as sepsis or acute respiratory failure is warranted to explore further the relationship between activin receptor agonists and patient outcomes, including measurements of muscle mass and gene expression. Phase I clinical trials involving activin receptor antagonists, such as bimagrumab (Polkey et al., 2019) and ACE-031 (Attie et al., 2013), should be planned in the critically ill populations susceptible to muscle wasting.

Conclusion

Serum activin A concentration was elevated in our cohort of critically ill patients. Higher peak activin A concentrations were associated with worse muscle strength and physical function. High activin A concentrations were also associated with increased

ICU and hospital mortality. Activin A appears to be a promising pharmacological target for physical disability in critical illness.

References

References have been incorporated into the thesis bibliography.

Tables

Table 3.1 Participant characteristics. Data are presented in n (%) and median [IQR] unless otherwise specified.

Characteristics of participants		N=36
Age (years), Mean (SD)		60.7 (14.9)
Male sex, *n* (%)		22 (61.1%)
Admission diagnosis, *n* (%) *		
Non-operative		
Bacterial pneumonia		7 (19%)
Sepsis with shock, other than urinary		6 (17%)
Sepsis, other than urinary		5 (14%)
Pancreatitis		3 (8%)
COPD		3 (8%)
Coma		1 (3%)
Metabolic coma		1 (3%)
Aspiration pneumonia		1 (3%)
Other respiratory diseases		1 (3%)
Cardiogenic shock		1 (3%)
Asthma		1 (3%)
Cardiac arrest		1 (3%)
Post-operative		
Other GI diseases		3 (8%)
Ruptured aortic aneurysm		1 (3%)
Other respiratory diseases		1 (3%)
Admission APACHE II score†	Mean (SD)	20.8 (8.0)
	Median [IQR]	19.5 [15.75 – 27]
SOFA score on enrolment ‡	Mean (SD)	9.5 (3.4)
	Median [IQR]	9 [7 – 12]
Initial Activin A concentration, pg/ml§		182.4 [94.0 – 384.6]
Median Activin A concentration, pg/ml‖		177.1 [107.4 – 344.4]
Peak Activin A concentration, pg/ml¶		321.0 [190.8 – 603.7]
Duration of mechanical ventilation, hours		165.6 [88.8 – 255.8]
Length of stay in ICU, days		8.2 [5.8 - 15.5]

Length of stay in hospital, days	17 [10.5 - 26.5]
Survived to ICU discharge, *n* (%)	27 (75%)
Survived to Hospital discharge, *n* (%)	22 (61%)

*Acute Physiology and Chronic Health Evaluation III diagnostic codes (Australian and New Zealand Intensive Care Society Modified)

†Acute Physiology and Chronic Health Evaluation II

‡Sequential Organ Failure Assessment score

§Initial Activin A concentration is measured from a blood sample taken between 48 to 72 hours of the ICU admission

‖peak activin A concentration for the duration of ICU stay

¶median activin A concentration for the duration of the ICU stay

Table 3.2 Multivariate sensitivity analysis of activin A concentrations vs. muscle strength and physical function outcomes.

Dependent variables	Independent variables	Ordered log-odds regression coefficient	95% CI	p-value
Initial activin A	6MWT distance at hospital discharge	-0.01	-0.02 to -0.00	0.035*
	APACHE II score	-0.08	-0.24 to 0.08	0.353
	Age	-0.01	-0.10 to 0.08	0.867
	Sex (Male)	-1.56	-4.59 to 1.47	0.313
Peak activin A	MRC-SS when first SOOB	-0.03	-0.11 to 0.04	0.419
	APACHE II score	0.09	-0.04 to 0.22	0.172
	Age	-0.01	-0.06 to 0.05	0.831
	Sex (Male)	-1.66	-3.63 to 0.30	0.096
Peak activin A	PFIT-s on ICU discharge	-0.26	-0.58 to 0.06	0.114
	APACHE II score	0.07	-0.08 to 0.22	0.368
	Age	-0.01	-0.06 to 0.05	0.861
	Sex (Male)	-1.83	-3.96 to 0.30	0.092
Peak activin A	6MWT distance at hospital discharge	-0.01	-0.01 to -0.00	0.029*
	APACHE II score	0.09	-0.06 to 0.24	0.258
	Age	-0.03	-0.10 to 0.05	0.504
	Sex (Male)	-0.58	-3.15 to 1.99	0.660

*indicates a statistically significant association after adjusting for plausible confounders

Table 3.3 Univariate analysis of different measures of activin A concentration vs. mortality outcomes.

Dependent variable	Independent variable	Proportional odds ratio	95% CI	p-value
Initial activin A	ICU mortality	3.97	0.96 to 16.35	0.056
Initial activin A	Hospital mortality	4.74	1.30 to 17.24	0.018*
Median activin A	ICU mortality	6.34	1.52 to 26.40	0.011*
Median activin A	Hospital mortality	8.21	2.14 to 31.47	0.002*
Peak activin A	ICU mortality	7.54	1.65 to 34.43	0.009*
Peak activin A	Hospital mortality	15.24	3.48 to 66.76	< 0.0005*

*indicates a statistically significant association

Table 3.4 Multivariate sensitivity analysis of activin A concentrations and mortality outcomes.

Dependent variable	Independent variable	Proportional odds ratio	95% CI	p-value
Initial activin A	ICU mortality	5.95	1.25 to 28.40	0.025*
	APACHE II score	0.98	0.90 to 1.06	0.610
	Age	1.00	0.95 to 1.05	0.937
	Sex (Male)	0.22	0.05 to 0.87	0.031*
Initial activin A	Hospital mortality	6.26	1.38 to 28.41	0.017*
	APACHE II score	0.96	0.89 to 1.04	0.362
	Age	0.98	0.93 to 1.04	0.567
	Sex (Male)	0.38	0.10 to 1.46	0.160
Median activin A	ICU mortality	6.75	1.54 to 29.54	0.011*
	APACHE II score	0.98	0.91 to 1.06	0.670
	Age	1.01	0.97 to 1.05	0.754
	Sex (Male)	0.48	0.14 to 1.64	0.243
Median activin A	Hospital mortality	9.97	2.22 to 44.91	0.003*
	APACHE II score	0.98	0.90 to 1.05	0.537
	Age	0.99	0.94 to 1.04	0.666
	Sex (Male)	0.75	0.22 to 2.59	0.650
Peak activin A	ICU mortality	8.56	1.85 to 39.59	0.006*
	APACHE II score	1.05	0.97 to 1.13	0.209
	Age	1.00	0.96 to 1.05	0.937
	Sex (Male)	0.29	0.09 to 0.98	0.046*
Peak activin A	Hospital mortality	16.60	3.39 to 81.18	0.001*
	APACHE II score	1.04	0.96 to 1.12	0.354
	Age	0.98	0.94 to 1.03	0.480
	Sex (Male)	0.41	0.12 to 1.46	0.168

*indicates a statistically significant association after adjusting for plausible confounders

FIGURES

Figure 3.1 The flow of participants through the study

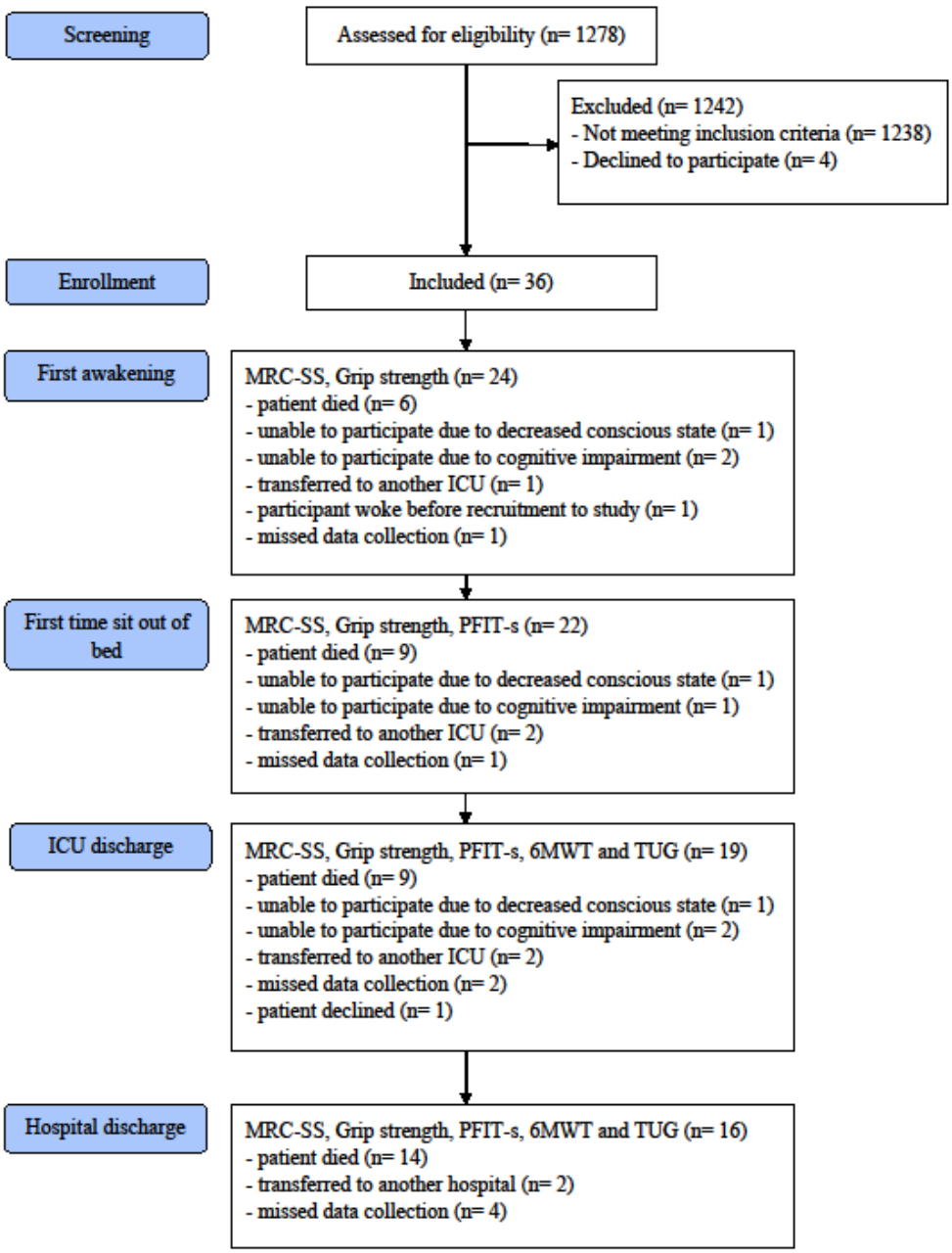


Figure 3.2 Univariate analysis of different measures of activin A concentration vs. muscle strength and physical function outcomes.

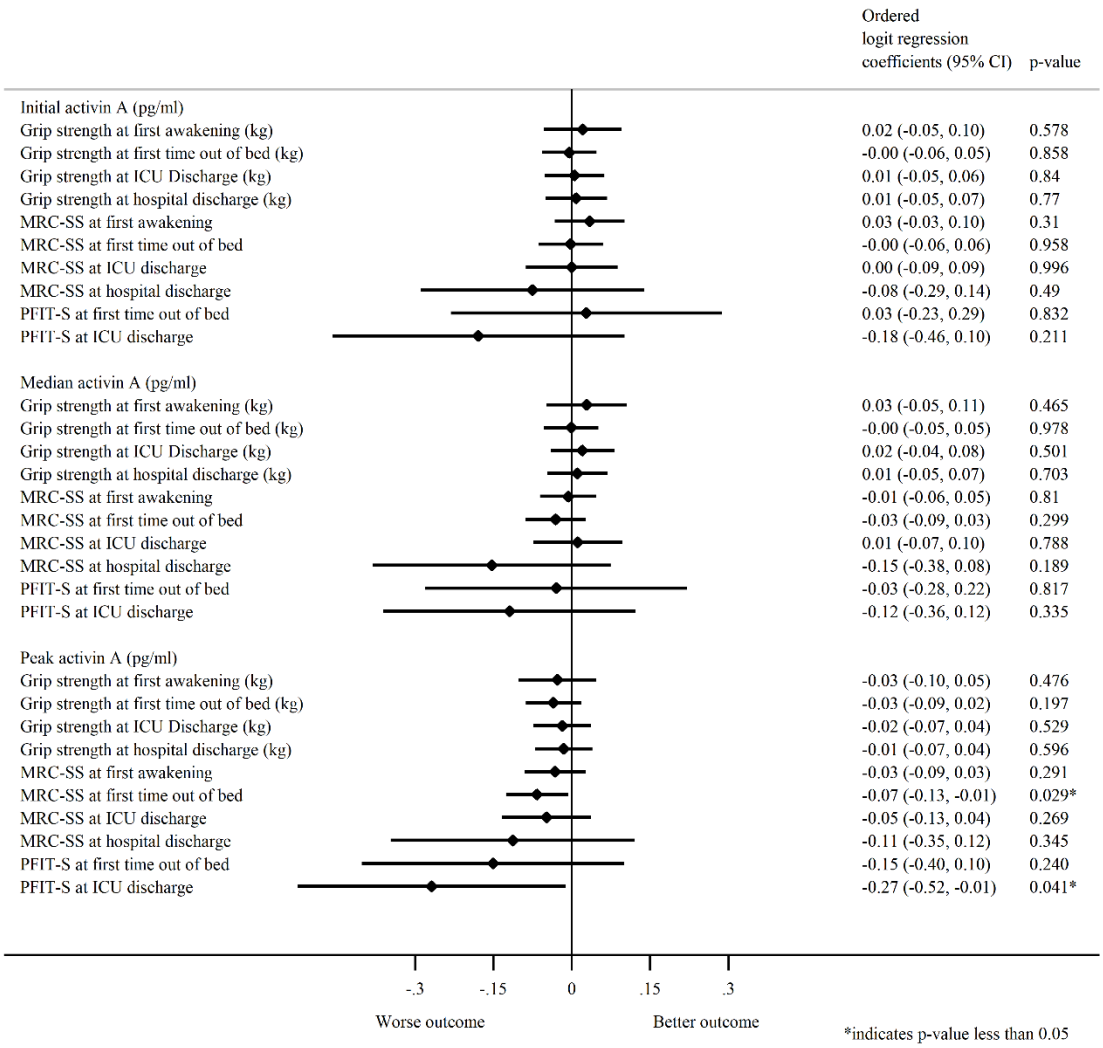


Figure 3.3 Univariate analysis of different methods of measuring activin A concentration vs. physical function outcomes.

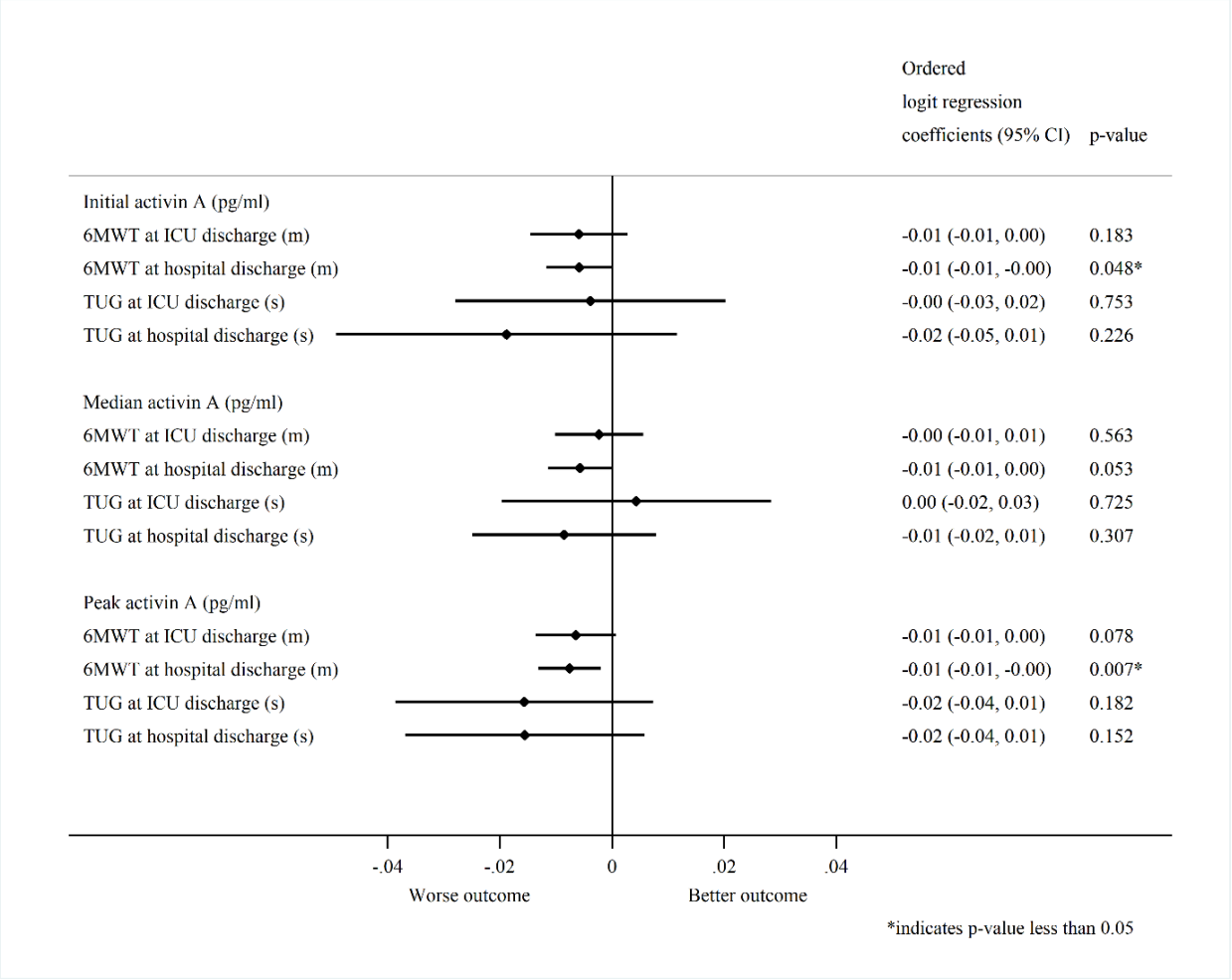


Figure 3.4 Peak activin A concentration vs. Six-Minute Walk Test distance at hospital discharge.

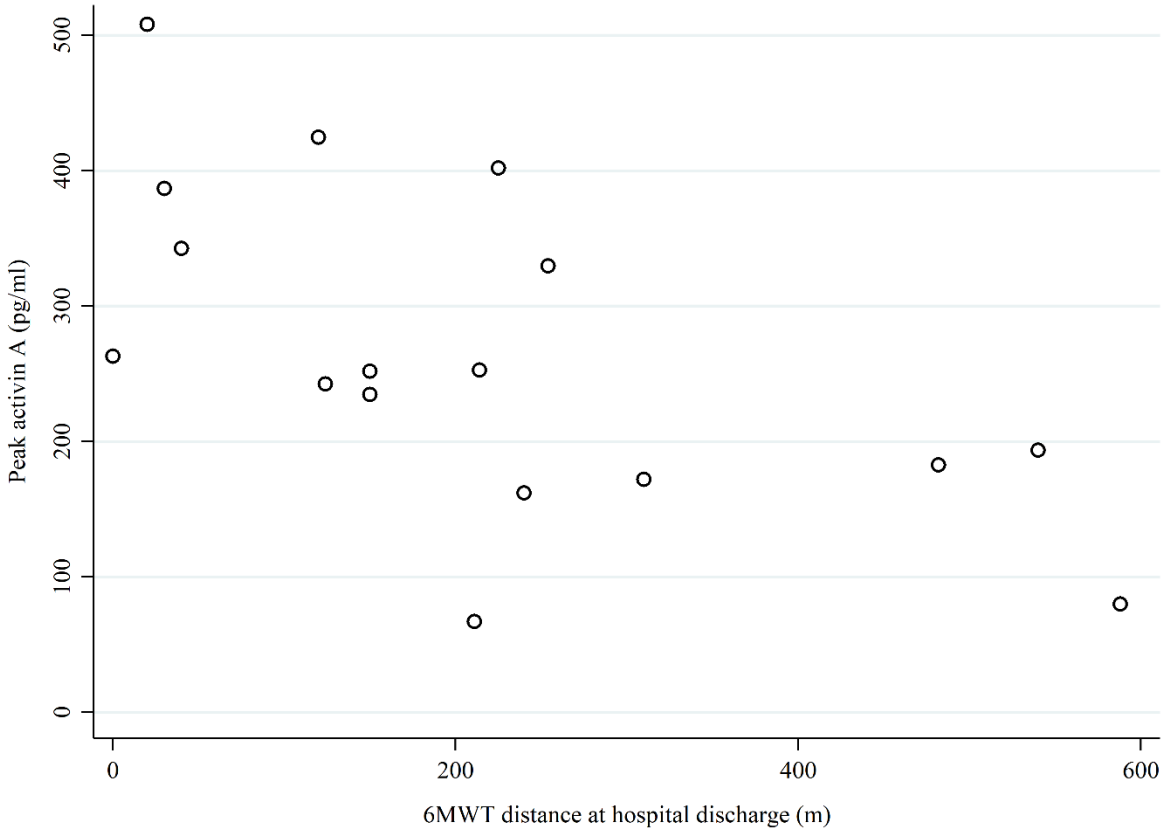


Figure 3.5 Peak activin A concentration vs. mortality outcomes.

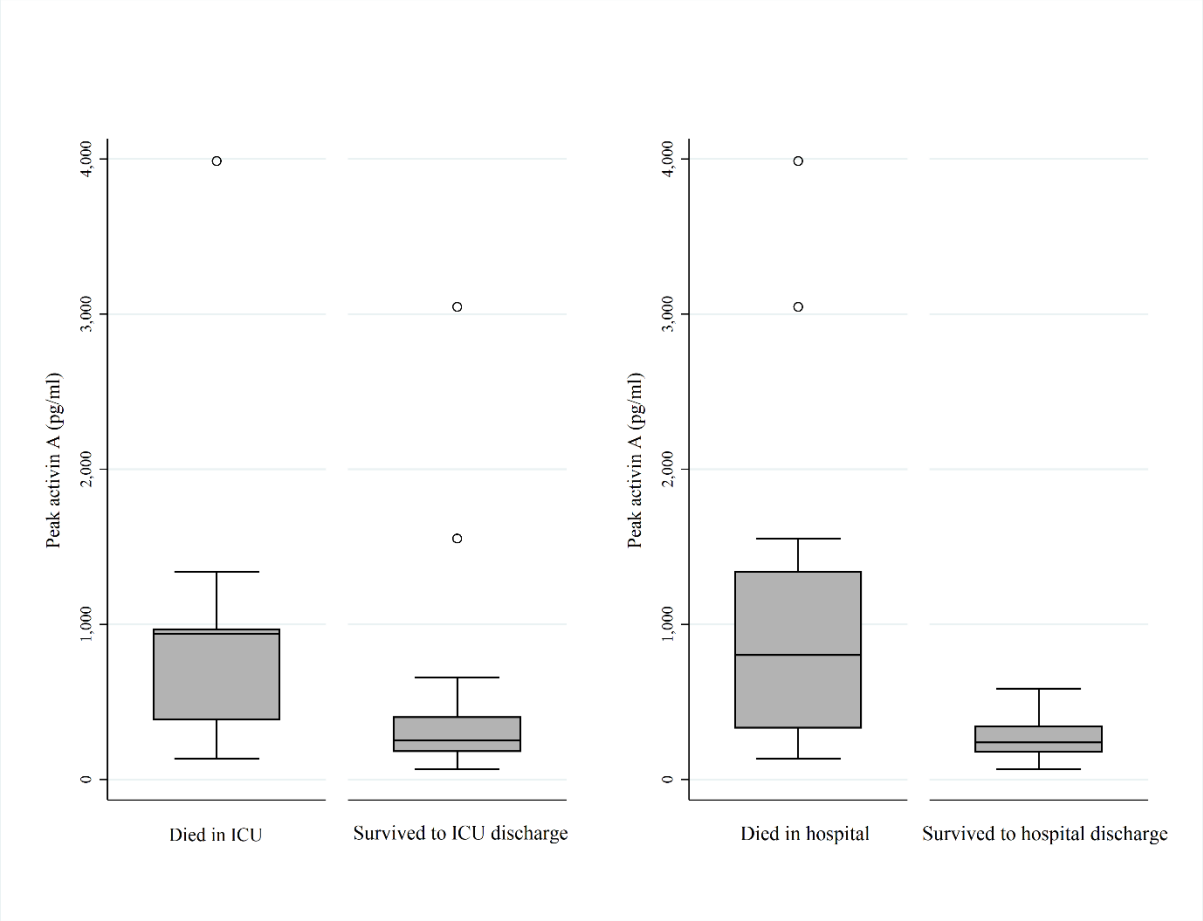
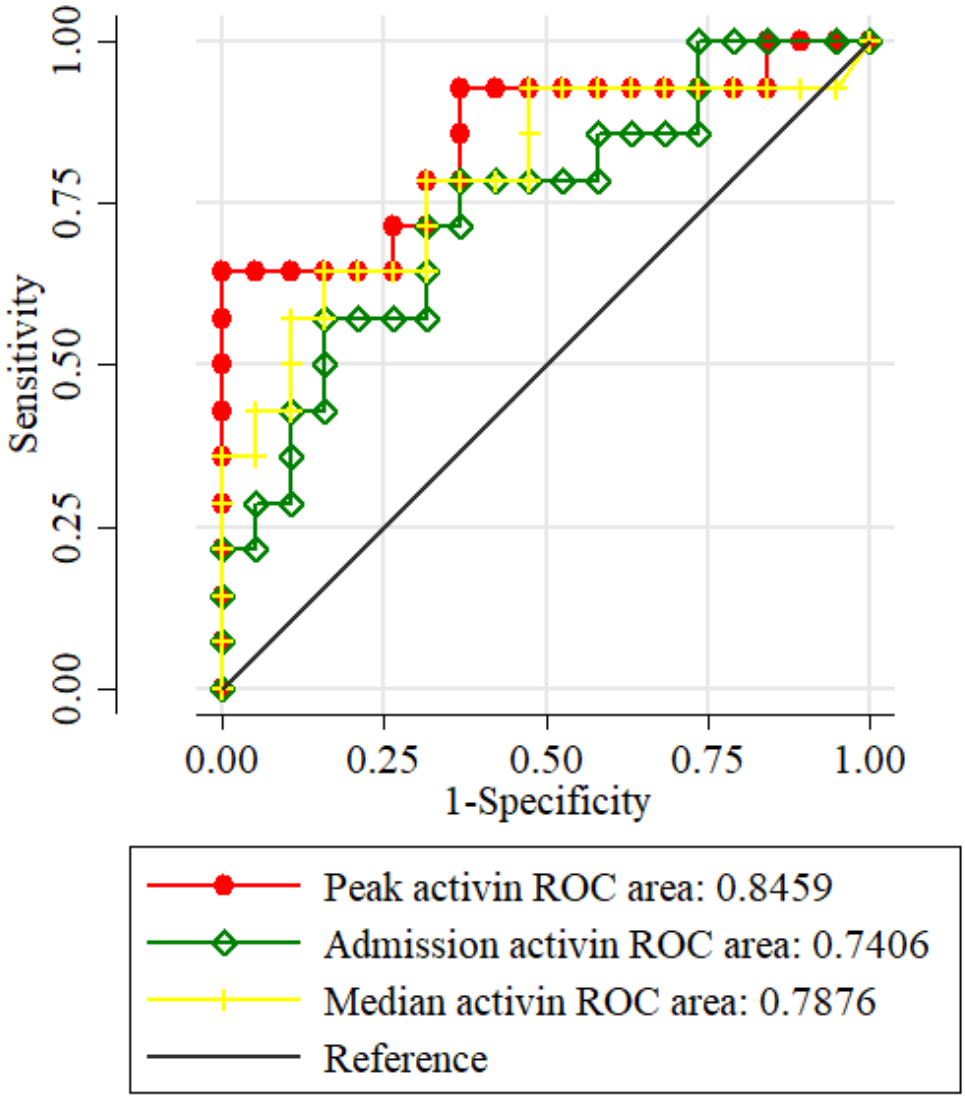


Figure 3.6 Receiver operating characteristic curve for the sensitivity and specificity of the three different methods of activin measurement at predicting hospital mortality



SUPPLEMENTAL DIGITAL CONTENT

Supplemental methods

Participants were excluded from enrolment if death was deemed imminent or inevitable; they were mechanically ventilated for more than 72 hours; had been intubated and ventilated previously in the same episode of hospital admission, or they met pre-specified criteria of proven or suspected medical conditions that precluded participation in the physical outcome measures:

- Head injuries
- Burns
- Central nervous system injury, including spinal cord
- Orthopaedic, plastic, or vascular surgeries resulting in restrictions to limb movement or weight-bearing
- Open abdomen
- Limb amputation
- Neuromuscular disease
- Poor premorbid mobility limiting the ability to ambulate independently

3.3. Chapter summary

This novel study has explored and demonstrated the relationship between activin A concentration, muscle strength, and physical function in the critically ill. Elevated peak activin A concentration was associated with worse muscle strength and physical function at different time points in the patient's ICU and hospital stay.

Phase I clinical trials involving activin receptor antagonists should be planned in the critically ill populations susceptible to muscle wasting.

While activin A may contribute to the functional decline of critically ill patients, the bedrest and immobilisation associated with the monitoring and management of these patients also have real and deleterious consequences. The next chapter will investigate the safety and feasibility of early mobilisation in a cohort of patients traditionally subject to long periods of immobility.

Chapter 4. Early mobilisation on continuous renal replacement therapy is safe and may improve filter life

4.1. Introduction

Historically, patients with acute renal failure undergoing continuous renal replacement therapy have been restricted to bed rest. This is due to concerns regarding catheter dislodgement, infection, thrombosis, premature disconnection, and reduced filter life.

Patients undergoing continuous renal replacement therapy may be at risk of the development of ICU-AW due to their higher severity of illness, long periods of immobilisation, and electrolyte disturbances associated with acute renal failure.

While early mobilisation has been shown to reduce the likelihood of ICU-AW, the safety and feasibility of early mobilisation have not been established in patients with acute renal failure undergoing continuous renal replacement therapy.

This chapter presents a novel prospective, quasi-experimental study that investigated the safety and feasibility of a physical activity program conducted with thirty-three patients on continuous renal replacement therapy in the ICU.

4.2. Early mobilisation on continuous renal replacement therapy is safe and may improve filter life

Published manuscript: Wang, Y. T., Haines, T. P., Ritchie, P., Walker, C., Ansell, T. A., Ryan, D. T., ... & Skinner, E. H. (2014). Early mobilization on continuous renal replacement therapy is safe and may improve filter life. Critical Care, 18(4), 1-10.

Wang et al. Critical Care 2014, 18:R161
http://ccforum.com/content/18/4/R161

CRITICAL CARE

RESEARCH Open Access

Early mobilization on continuous renal replacement therapy is safe and may improve filter life

Yi Tian Wang[1], Terry P Haines[2,3], Paul Ritchie[4], Craig Walker[4], Teri A Ansell[4], Danielle T Ryan[1], Phaik-Sim Lim[5], Sanjiv Vij[6], Rebecca Acs[6], Nigel Fealy[7] and Elizabeth H Skinner[1,2,3,4,8*]

Abstract

Introduction: Despite studies demonstrating benefit, patients with femoral vascular catheters placed for continuous renal replacement therapy are frequently restricted from mobilization. No researchers have reported filter pressures during mobilization, and it is unknown whether mobilization is safe or affects filter lifespan. Our objective in this study was to test the safety and feasibility of mobilization in this population.

Methods: A total of 33 patients undergoing continuous renal replacement therapy via femoral, subclavian or internal jugular vascular access catheters at two general medical-surgical intensive care units in Australia were enrolled. Patients underwent one of three levels of mobilization intervention as appropriate: (1) passive bed exercises, (2) sitting on the bed edge or (3) standing and/or marching. Catheter dislodgement, haematoma and bleeding during and following interventions were evaluated. Filter pressure parameters and lifespan (hours), nursing workload and concern were also measured.

Results: No episodes of filter occlusion or failure occurred during any of the interventions. No adverse events were detected. The intervention filters lasted longer than the nonintervention filters (regression coefficient = 13.8 (robust 95% confidence interval (CI) = 5.0 to 22.6), $P = 0.003$). In sensitivity analyses, we found that filter life was longer in patients who had more position changes (regression coefficient = 2.0 (robust 95% CI = 0.6 to 3.5), $P = 0.007$). The nursing workloads between the intervention shift and the following shift were similar.

Conclusions: Mobilization during renal replacement therapy via a vascular catheter in patients who are critically ill is safe and may increase filter life. These findings have significant implications for the current mobility restrictions imposed on patients with femoral vascular catheters for renal replacement therapy.

Trial registration: Australian and New Zealand Clinical Trials Registry ACTRN12611000733976 (registered 13 July 2011)

Introduction

Acute renal failure occurs in 5.5% to 6.0% of patients admitted to the intensive care unit (ICU), with almost three-fourths of these patients requiring the institution of continuous renal replacement therapy (CRRT) via temporary double-lumen vascular catheters [1]. Historically, patients with femoral vascular catheters have been restricted to bed rest [2,3] to avoid catheter dislodgement, infection and thrombosis [4]. Patient movement may alter fluid dynamics, pressures and blood flow of the CRRT circuit [5]. In contrast, immobilization protocols may increase the risk of thrombosis and embolism [6]. Early mobilization in the ICU is generally safe [7] on the basis of an increasing evidence base [8-12]; in the context of evolved understanding of post-ICU syndrome [13-16], however, there are still specific clinical scenarios in which the safety and feasibility of mobilization has not been established. Moreover, CRRT is frequently present (in up to 9% of sessions) [3] in patients most likely to benefit (for example, those on mechanical ventilation for more than 48 hours).

* Correspondence: elizabeth.skinner@wh.org.au
[1]Department of Physiotherapy, Monash Health, 246 Clayton Road, Clayton, Victoria 3168, Australia
[2]Allied Health Research Unit, Monash Health, 400 Warrigal Road, Cheltenham, Victoria 3192, Australia
Full list of author information is available at the end of the article

The presence of femoral catheters is a considerable barrier to early mobilization [17]. Although mobilization in the presence of femoral arterial catheters is safe [18,19], delivery of CRRT via femoral catheters precludes hip flexion in practice and research [3]. Researchers in several recent studies have reported data on the safety and feasibility of mobilization in patients with femoral catheters (including arterial, venous and haemodialysis) [5,18-20], but none have reported CRRT data specifically during mobilization. Maintenance of the filter circuit is important, as premature disconnection results in loss of blood, increased nursing workload and increased costs [21]. Filter life is also an important indicator of CRRT efficacy [22]. The specific effects of mobilization on the vascular catheter, circuit pressures, fluid dynamics and blood flow in patients receiving CRRT via dual-lumen femoral vascular catheters are uncertain. Therefore, our objective in this study was to test the safety and feasibility of mobilization in ICU patients with femoral vascular catheter placement during CRRT.

Material and methods

Design, setting and participants

This prospective cohort study (Australian and New Zealand Clinical Trials Registry Number ACTRN12611000733976) was conducted between August 2011 and August 2012 in the 21-bed tertiary ICU at Monash Medical Centre and the 14-bed tertiary ICU at Dandenong Hospital, both of which are in Victoria, Australia. In the absence of empirical data on which to base the sample size, a convenience sample of 40 participants was selected. The institutional ethical review board responsible for both sites (Monash Health, Melbourne, Australia) approved the study at both sites. Informed consent was obtained from participants or their surrogate decision-makers. Participants were eligible if admitted to the ICU with the insertion of a vascular catheter for CRRT. Patients were excluded if they were receiving sustained low-efficiency dialysis or CRRT via permanent vascular access.

Exclusion and cessation criteria

Passive group patients were ineligible to participate in the intervention if they met any of the following criteria:

- Extreme agitation or confusion (Richmond Agitation–Sedation Scale +3 or +4 [23])
- Heart rate >160 or <40 beats/min or new arrhythmia
- Limb movement restricted for reasons other than the presence of the vascular catheter

Low-level or high-level group patients were ineligible for the reasons listed above or if they met any of the following criteria:

- Mean arterial blood pressure <60 mmHg or >120 mmHg
- >10 μg/min noradrenaline (or equivalent)
- Fraction of inspired oxygen >0.6 and/or partial pressure of oxygen <65 mmHg
- Peripheral oxygen saturation <85% or drop >10% from resting level
- Respiratory rate >35 breaths/min
- Temperature >38.5°C
- Drowsy, unable to follow commands
- New-onset chest pain with suspected cardiac cause

The intervention was ceased if these criteria were met without recovery in 2 minutes. Any CRRT alarms during the intervention were assessed and responded to by the bedside nurses. The intervention was then continued in consultation with the nurse after troubleshooting of the machine alarms was complete. If the CRRT alarms could not be resolved by the bedside nurse within 2 minutes and were thought to be associated with the intervention, mobilization was ceased.

Procedure

Routine baseline data on the primary outcomes were recorded prior to study recruitment for 19 additional patients to monitor the Hawthorne effect. Participants were screened by treating ICU physiotherapists daily on weekdays. CRRT was generally delivered via continuous veno-venous haemodiafiltration (CVVHDF) using Prismaflex ST100 filters (Gambro Lundia AB, Lund, Sweden) at a dialysate rate of 20 ml/kg/h, a replacement fluid rate of 15 ml/kg/h (delivered after the filter) and an effluent fluid removal rate of 50 to 100 ml/h with primarily Lactasol™ or Hemosol™ (Gambro Lundia AB).

Intervention

The movement on vascular catheter evaluation (MOVE) intervention was delivered by senior treating ICU physiotherapist(s) at three different levels (passive, low-level physical function, high-level physical function), depending on the participant's ability. No training of staff was required to deliver the intervention, as mobilization activities formed part of usual care in the study sites. A single intervention of 20 minutes (five positions for 4 minutes each) was delivered to reflect an effective clinical treatment dosage [9]. Prior to the intervention, investigators checked vascular catheter security and suturing. The following were the three intervention levels and details:

1. *Passive:* (a) Unable to participate (for example, sedation, low Glasgow Coma Scale score, severe weakness); (b) supine, sustained hip flexion (45°), supine, repeated-movement hip flexion (45°), supine.
2. *Low-level*: (a) Able to participate, assessed as likely unable to stand; (b) supine, repeated hip flexion (45°), supine, sitting on the edge of the bed, supine.

3. *High-level*: (a) Able to participate, assessed as likely being able to stand (with or without assistance); (b) supine, standing, marching on the spot, sitting on the edge of the bed, supine.

Measurement

The following data were recorded on the day of intervention and daily thereafter for at least three further filters, until the intervention vascular catheter was removed or the patient was discharged from the ICU, whichever occurred first: age, sex, severity of illness (based on Acute Physiology and Chronic Health Evaluation (APACHE II and III) scores), mechanical ventilation, vascular catheter type, site, daily pathology (for example, platelets, international normalized ratio (INR), activated partial thromboplastin time (aPTT)), non-intervention-related position changes (daily) and sedation and delirium scores. Sedation and delirium were assessed using the Richmond Agitation–Sedation Scale [23] and the Confusion Assessment Method for the ICU [24,25].

The primary outcome measure was the occurrence of adverse events during or after interventions, defined *a priori* as the following:

- Vascular catheter dislodgement (assessed by visual inspection)
- Filter circuit clotting or disruption (assessed by circuit disconnection)
- Bleeding, haematoma at the vascular catheter site (assessed by visual inspection and medical and nursing documentation)
- Clinical suspicion of thrombosis (vascular observations recorded every 2 hours postintervention, medical documentation, radiology for ultrasound referral)
- Arrhythmia (assessed by visual inspection of electrocardiogram and medical documentation)

The following secondary outcome measures were used:

- Filter life (measured from filter commencement to disconnection as documented by nursing staff (1:1 ratio))
- Intervention feasibility (measured by filter alarm rates, pressures (access, return, transmembrane), blood flow recorded each minute from the digital output screen (Prismaflex))

Additional secondary measures included nursing workload and nurses' concerns about filter disconnection (see Additional file 1 for more details on methods and results).

Data analysis

The reason for cessation of filtration was recorded (either elective or not), and elective cessation filters were excluded from the filter life analyses. Descriptive statistics (median (IQR) or mean (SD)) were calculated as appropriate (Kolmogorov-Smirnov test). Linear regression analyses clustered by individual participant (to account for multiple filters within individual participants) and robust variance estimates were used to compare filter lifespan for filters where the participant was exposed to an intervention as opposed to filters where no intervention was provided. The number of filters that participants received was adjusted for by including the filter numbers (first filter = 1, second filter = 2 and so forth) in an interaction term with the intervention term in the analysis. Subgroup analyses separating data on the basis of vascular catheter site (femoral vs nonfemoral) and intervention group (passive vs low-level vs high-level) were performed. Sensitivity analyses were conducted to determine whether differences in aPTT, INR, platelets, non-intervention-related position changes (frequency), APACHE III scores and number of CRRT alarms during intervention influenced the primary analyses. In these sensitivity analyses, covariates were added to the regression models to examine their influence on the statistical significance of the MOVE intervention. Missing data were excluded listwise from analyses. Statistical analysis was performed using IBM SPSS Statistics™ 20 version 20.0.0 (SPSS, Chicago, IL, USA) and STATA/SE version 12 (StataCorp LP, Austin, TX, USA). $P < 0.05$ was accepted as the level of statistical significance.

Results

In the analyses, 34 patients were included and 1 was excluded (Figure 1). Recruitment was ceased without six high-level intervention participants, as those meeting the relevant inclusion criteria were present in much lower than anticipated numbers. No patients died in the ICU. Twenty-three (17.2%) of one hundred thirty-four femoral filters and fourteen (23.0%) of sixty-one nonfemoral filters were excluded from filter life analyses (elective cessation). The sample was broadly representative of a general ICU cohort (Table 1). None of the filters were planned for disconnection on the intervention day. The vascular catheter was sutured upon site check prior to the intervention in all patients. Eleven, sixteen and six patients received a single passive, low-level or high-level intervention, respectively (Figure 1), with mean (SD) treatment duration of 19 (±3) minutes. The median (IQR) days of follow-up was 4 (2 to 6).

Safety

No adverse events occurred during or following the interventions. One participant had a pulmonary artery catheter placed (in the low-level group), and no arrhythmias were associated with the interventions.

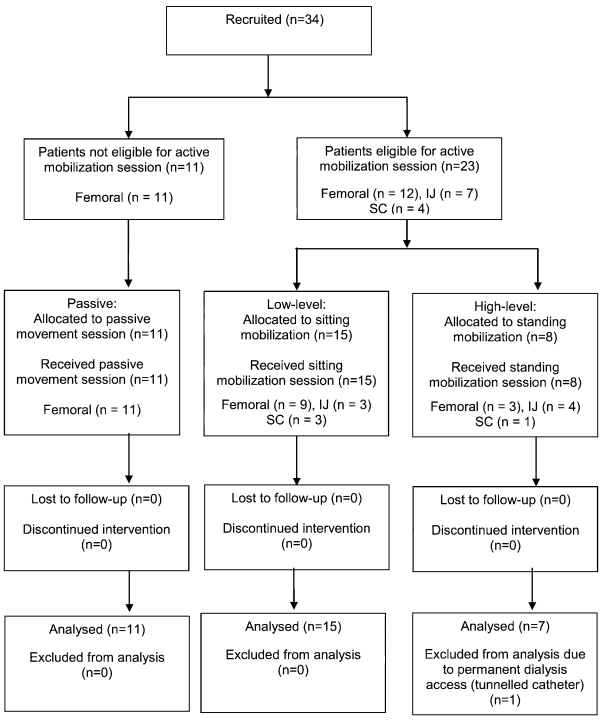


Figure 1 Flowchart of participants through the study. IJ: Internal jugular; SC: Subclavian.

Filter life

Mean filter life at the time of the intervention was 19.5 hours (SD ±13.8), with no difference observed between femoral and nonfemoral filters (21.6 (15.1) hours vs 15.3 (9.9) hours, $P = 0.45$). Filters lasted for a mean of 17.4 (SD 12.7) hours after intervention. Intervention filters lasted longer than nonintervention filters (regression coefficient = 13.8, robust 95% confidence interval (CI) = 5.0 to 22.6, $P = 0.003$). A difference was also found in the femoral filter subgroup (regression coefficient = 15.7, robust 95% CI = 4.6 to 26.7, $P = 0.008$), but not in the nonfemoral access filter subgroup (regression coefficient = 9.2, robust 95% CI = –6.0 to 24.4, $P = 0.20$) (Figure 2).

An increasing effect of the MOVE intervention on filter life was evident in the higher the number of previous filters at the time of intervention (filter number × MOVE interaction effect: regression coefficient = 3.5, robust 95% CI = 0.3 to 6.6, $P = 0.03$). The effect of MOVE was approximately a 3-hour increase in filter life per filter already placed in the patient.

A higher number of daily position changes was associated with higher filter life in the overall cohort (regression coefficient = 2.0, robust 95% CI = 0.6 to 3.5, $P = 0.007$) and the femoral filter subgroup (regression coefficient = 2.0, robust 95% CI = 0.5 to 3.6, $P = 0.01$), but not in the nonfemoral filter subgroup (regression coefficient = 1.9, robust 95% CI = –1.7 to 5.4, $P = 0.27$) (Table 2). Alarm frequency during interventions was associated with a shorter filter life in the overall cohort (regression coefficient = –3.1, robust 95% CI = –5.0 to –1.2, $P = 0.003$) and the femoral filter subgroup (regression coefficient = –7.4, robust 95% CI = –13.0 to –1.8, $P = 0.01$), but, again, not in the nonfemoral filter subgroup (regression coefficient = –2.3, robust 95% CI = –4.6 to 0.0, $P = 0.05$). The passive intervention had a significant role in increasing filter life in the femoral filter subgroup, but only INR and aPTT were associated with filter life in the nonfemoral filter subgroup (Table 2). There were no significant differences in aPTT, INR, platelet count or rate of non-intervention-related position changes between the femoral filter intervention and nonintervention groups (Additional file 2). Addition of these covariates to the sensitivity analyses did not influence the effect of the MOVE intervention.

Table 1 Demographic and clinical details of the sample at the time of the intervention[a]

Variable	Baseline group (*n* = 19)	Intervention group (*n* = 33)	Femoral (*n* = 23)	Nonfemoral (*n* = 10)
Age, yr	63.6 (13.6)	63.7 (14.8)	63.7 (14.1)	63.6 (17.2)
Sex, % male	79%	61%	65%	50%
BMI	28.0 (5.1)	29.3 (10.6)	31.7 (11.2)	23.9 (7.0)
Diagnosis, %				
Cardiogenic shock/cardiac	26%	33%	30%	40%
Septic shock/sepsis/MOF	47%	43%	44%	40%
Renal/metabolic/electrolyte	21%	15%	17%	10%
Haemorrhagic shock/haematoma	0%	9%	9%	10%
Vascular surgery	5%	0%	0%	0%
APACHE II score	–	26.1 (7.2)	25.7 (6.8)	26.9 (8.2)
APACHE III score	98.3 (26.9)	93.8 (24.9)	91.1 (23.1)	100.0 (29.1)
ICU length of stay, days	10.2 (6.9)	15.0 (10.0)	15.4 (9.3)	14.1 (11.8)
MV, %	74%	76%	74%	80%
MV hours, median (IQR)	78 (0 to 153)	76 (0 to 267)	89 (0 to 295)	63 (30 to 190)
Site[b], %				
Femoral	63%	70%	100%	0%
Internal jugular	37%	21%	0%	70%
Subclavian	0%	9%	0%	30%
Catheter type[c], *n* (%)				
Dolphin Protect	13 (68%)	19 (58%)	13 (57%)	6 (55%)
Niagara™	5 (26%)	9 (27%)	7 (30%)	2 (18%)
Arrow-Howes™	1 (5%)	5 (15%)	3 (13%)	1 (9%)
Intervention filter type, %				
Prismaflex ST100	N/A	94%	91%	100%
Intervention filter anticoagulation, %				
Heparin	N/A	27%	26%	30%
Citrate	N/A	6%	4%	10%
Saline	N/A	0%	0%	0%
Regional circuit	N/A	52	48%	60%
Other	N/A	3%	4%	0%
Nil	N/A	12%	17%	0%
FBE on intervention filter, median (IQR)				
Hb, g/dl	N/A	89 (85 to 94)	88 (81 to 91)	93 (90 to 103)
Platelets, 10^3 U/L	N/A	125 (60 to 200)	121 (59 to 174)	179 (60 to 252)
INR	N/A	1.1 (1.1 to 1.4)	1.2 (1.1 to 1.4)	1.1 (1.1 to 1.3)
aPTT	N/A	39 (34 to 52)	40 (34 to 55)	34 (33 to 44)
RASS, median (IQR)	N/A	−1 (−4 to 0)	−2 (−4 to 0)	−1 (−1 to 0)
CAM-ICU positive, %	N/A	42%	39%	50%
Hospital LOS in days, median (IQR)	23 (9 to 31)	31 (21 to 57)	29 (21 to 57)	37 (15 to 57)
Hospital mortality, %	42%	15%	17%	10%

[a]aPTT, Activated thromboplastin time; BMI: Body mass index; CAM-ICU: Confusion Assessment Method for the ICU; FBE: Full blood examination; Hb: Haemoglobin; ICU: Intensive care unit; INR: International normalized ratio; IQR: Interquartile range; LOS: Length of stay; MOF: Multiorgan failure; MV: Mechanical ventilation; N/A: Not applicable; RASS: Richmond Agitation–Sedation Scale. [b]Femoral (14 in right, 9 in left), intrajugular (6 in right, 1 in left) and subclavian (3 in left, 1 in right). [c]Dolphin Protect (13-French gauge, 25 cm; Gambro, Hechingen, Germany), Niagara™ (13.5-French gauge; Bard Access Systems, Salt Lake City, UT, USA), Arrow-Howes™ triple-lumen (13-French, 20 cm; Teleflex, Research Triangle Park, NC, USA). Data are mean (SD) unless otherwise specified. Percentages may not add up to 100% due to rounding.

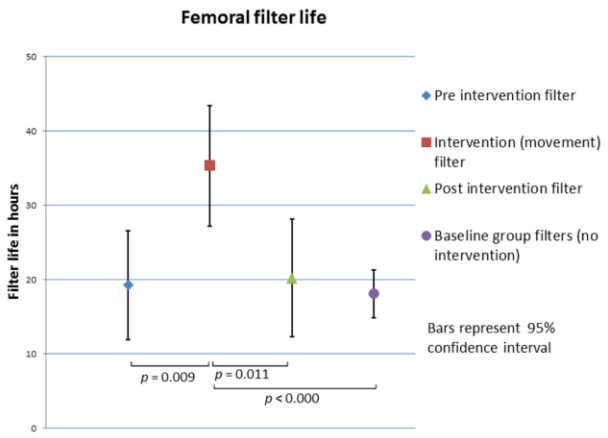


Figure 2 Comparison of femoral filter life. Preintervention filters are those that patients had prior to recruitment and intervention. Intervention filters are those in place during the time the intervention took place. Postintervention filters are those placed after the intervention filter.

Feasibility

No filter alarms sounded during interventions on 20 occasions (61% of the time). The machine alarmed a median of 0.0 (interquartile range = 0 to 2, range = 0 to 10) times during interventions. No differences in access, return or transmembrane (TM) pressures were observed in any group between the final and first phases (Additional file 3). There was a drop in access pressure during the sitting on edge of bed phase accompanied by a rise in TM pressure in the low-level group. There was an increase in access, return and TM pressures during the standing and marching phases in the high-level group, which returned to preintervention pressures during the final period (Additional file 3).

Discussion

Mobilization of patients with femoral vascular catheters receiving CRRT in the ICU was safe and feasible. The intervention did not result in vascular catheter dislodgement, haematoma or bleeding, and there were no detectable clinical sequelae, including suspected thrombosis or filter circuit disruption. Average pressures did not approach circuit failure definitions (TM pressure >250 mmHg and access pressure >200 mmHg [26]) in any intervention group. These findings have significant implications for clinical practice situations where patients on CRRT are unnecessarily restrained from movement because of the perceived importance of these restrictions to maintaining filter patency and filter life and reducing mortality [27]. Interruptions in CRRT impact the dose of therapy delivered as well as clinical outcomes [27]. Testing mobilization during CRRT is critical, given that the opportunity to mobilize off CRRT can be minimal (minimum 16 hours required to maintain urea and creatinine, with a median time of 3 hours daily off filtration [22]), whereas time off CRRT can occur when it is impractical to mobilize (for example, overnight). Historically, contraindications to mobilization arose during an era of rigid medical plastics, which were associated with greater potential for vascular damage with movement. Although advances in materials [28] have resulted in more malleable catheters, manufacturers do not provide mobility specifications. These findings underscore the importance of empirically testing practices that have been accepted for many years. The presence of femoral vascular catheters for CRRT is a significant barrier to the delivery of early mobilization in the ICU [3,17], as demonstrated in this study, where nurses' concerns about circuit disconnection rose significantly when they were informed that mobilization was to occur. Few researchers have reported mobilization data regarding patients with femoral catheters [5,18,29,30]. Although no catheter-related adverse events occurred during mobilization with femoral catheters in two of these previous studies [18,30], only six patients in one cohort received an intervention with CRRT femoral catheters *in situ* [18] and the mobility intervention delivered to patients with femoral dialysis catheters was not specified in the other [30]. In neither study did the investigators report filter life or whether the intervention occurred during CRRT. Our present study is the first in which the safety and feasibility of mobilizing patients undergoing CRRT were prospectively evaluated.

It was important to test the safety of hip flexion, as key early mobilization trials have included passive range of motion [8] and cycle ergometry [9] as rehabilitation

Table 2 Subgroup and sensitivity analyses of filter life and possible confounders[a]

Group	Factors	Regression coefficient (robust 95% CI)	*P* value
Baseline ($n = 19$)	INR	0.8 (−1.4 to 3.0)	0.44
	aPTT	0.1 (−0.3 to 0.5)	0.63
	Platelets	0.0 (0.0 to 0.1)	0.09
	Positional changes	1.2 (−0.4 to 2.9)	0.13
	APACHE III	−0.1 (−0.3 to 0.0)	0.09
Overall cohort (MOVE intervention) ($n = 33$)	MOVE intervention	13.8 (5.0 to 22.6)	0.003[b]
Overall subgroup and sensitivity analyses	Passive movements	20.0 (5.4 to 34.6)	0.01[b]
	SOEOB	5.8 (−10.7 to 22.3)	0.46
	MOS	18.3 (−1.3 to 37.9)	0.06
	INR	9.3 (−2.0 to 20.5)	0.10
	aPTT	0.0 (−0.2 to 0.2)	0.86
	Platelets	0.0 (−0.1 to 0.0)	0.10
	Positional changes	2.0 (0.6 to 3.5)	0.007[b]
	APACHE III	0.1 (0.0 to 0.3)	0.02[b]
	Alarms	−3.1 (−5.0 to −1.2)	0.003[b]
Femoral subgroup ($n = 23$)	MOVE intervention	15.7 (4.6 to 26.9)	0.008[b]
Femoral subgroup and sensitivity analyses	Passive movements	20.0 (5.4 to 34.6)	0.01[b]
	SOEOB	8.5 (−20.6 to 37.7)	0.51
	MOS	20.5 (−19.9 to 60.9)	0.16
	INR	7.6 (−4.9 to 20.0)	0.22
	aPTT	−0.1 (−0.2 to 0.1)	0.38
	Platelets	0.0 (−0.1 to 0.0)	0.29
	Positional changes	2.0 (0.5 to 3.6)	0.01[b]
	APACHE III	0.6 (−0.1 to 0.2)	0.42
	Alarms	−7.4 (−13.0 to −1.8)	0.01[b]
Nonfemoral subgroup ($n = 10$)	MOVE intervention	9.2 (−6.0 to 24.4)	0.20
Nonfemoral subgroup and sensitivity analyses	Passive movements	N/A	–
	SOEOB	1.0 (−12.8 to 14.8)	0.86
	MOS	20.6 (−23.3 to 64.4)	0.23
	INR	26.4 (7.5 to 45.3)	0.01[b]
	aPTT	0.5 (0.1 to 0.9)	0.03[b]
	Platelets	−0.1 (−0.1 to 0.0)	0.08
	Positional changes	1.9 (−1.7 to 5.4)	0.27
	APACHE III	0.2 (0.0 to 0.5)	0.05
	Alarms	−2.3 (−4.6 to 0.0)	0.05

[a]APACHE III: Acute Physiology and Chronic Health Evaluation III; aPTT: Activated partial thromboplastin time; CI: Confidence interval; INR: International normalized ratio; MOS: Marching on the spot; MOVE: Movement on vascular catheter evaluation intervention; N/A: Not applicable; SOEOB: Sitting on edge of bed. Electively ceased filters were excluded from analysis. Twenty-three (17.2%) of one hundred thirty-four femoral filters and fourteen (23.0%) of sixty-one nonfemoral filters were excluded from the filter life analyses, as they were electively ceased. Units of measurement for filter life are hours. Position changes are measured as number per day. Alarms are the number of alarms during the intervention session. [b]Statistically significant difference.

components. Patients undergoing CRRT should no longer be precluded from early mobilization on the basis that a vascular catheter or CRRT is *in situ*. It should be noted that the ability of patients undergoing CRRT to stand and march appears to be limited. In this study, we were able to recruit only three participants *with femoral catheters* who were able to perform these activities in 12 months in two ICUs. Talley and colleagues found that only 1.8% of their cohort were able to stand and/or ambulate with assistance [5], although the functional benefit of walking in the ICU compared to standing, marching on the spot or sitting on the edge of the bed is unclear. This is likely due to high

hospital mortality, which is reported to range from 55% to 51% [5,31], with 28-day mortality of 41% [32], though few studies have investigated functional and quality-of-life outcomes in this population [33].

Another key finding, which requires further empirical testing given the small sample size in this study, is that mobilization extended filter life, which has clinical, cost and potential survival implications. Increasing filter life could reduce nursing workload, costs, blood loss and infection risk [5]. Reducing flow stasis has been suggested to improve filter life [20], and, as exercise increases blood volume flow in healthy individuals [34,35], the mechanism of mobilization is plausible. Although few researchers have investigated blood flow and immobilization in critical illness, it has been hypothesized that inactivity-related vascular injury, venous pooling and microvascular dysfunction increase thromboembolism risk [36,37]. There are published data demonstrating that exercise increases blood volume flow in healthy individuals [34,35]. It is therefore plausible that increasing blood flow could reduce thrombosis in critically ill patients who are undergoing continuous renal replacement therapy. The results of the sensitivity analyses in our present study support this hypothesis, as passive hip flexion and positional changes improved filter life in the femoral subgroup, but not in the nonfemoral subgroup. Because mean peak blood flow is usually higher in the subclavian and internal jugular veins than in the femoral veins [38,39], we hypothesize that catheters sited in the femoral veins may be more susceptible to the effects of stasis with immobility. This hypothesis is supported by the results of our sensitivity analyses, which demonstrate that the MOVE intervention and position changes were not significantly associated with filter life (but that INR and aPTT were) in the nonfemoral subgroup. There are also potential trends in the data that may be more thoroughly explored with larger sample sizes; for example, large regression coefficients that were not statistically significant were seen for marching on the spot and INR in the overall cohort sensitivity analyses. It is possible that different results would be found in patients undergoing continuous venovenous haemofiltration rather than CVVHDF, although in Australia the majority of CRRT delivery is via CVVHDF [31]. Generalizability of the results to other ICUs may be influenced by variation in CRRT practices, although filtration practices in the two centres in this study were largely reflective of Australasian ICUs.

Limitations

This study is limited by its single-health-service design, although it was conducted at two sites. The sample size was small (albeit one of the largest to date in this field reported in the literature). The results may have been influenced by sampling error; however, it should be noted that the characteristics of the study sample were largely consistent with characteristics of the routine baseline sample. Large multicentre studies are warranted to confirm our findings and further strengthen our conclusions, in particular those pertaining to filter life. Delivery of CRRT was not standardized, and the filter failure criteria were not specified *a priori*. The reason for filter cessation was not always recorded and could have been biased by nursing staff, although the average filter life of the nonintervention filters during the study period was the same as that of the baseline filters and less than half the nursing staff knew that their patients had mobilized during CRRT. Despite this, the main previously reported determinants of filter life were comparable between femoral and nonfemoral filters. A single intervention session was delivered to each patient, and it was not possible to examine possible dose–response relationships between duration of mobilization and filter life, because the intervention duration was standardized. In future studies, researchers could investigate a possible dose–response relationship between mobilization and filter life.

Conclusions

Mobilization during CRRT via a vascular catheter in patients who are critically ill is safe and may increase filter life. Given the established benefit of early mobilization in the critical care population, early mobilization should be considered as part of the management of patients undergoing CRRT. Stasis secondary to immobility may contribute to the life of the haemodiafiltration circuit. Large multicentre studies are warranted to confirm the findings of our study and further strengthen our conclusions, particularly those pertaining to filter life.

Key messages

- Early mobilization improves health outcomes following admission to the ICU, including ventilation duration, length of stay and delirium. However, patients undergoing CRRT are frequently precluded from participation in early mobilization because of concerns about catheter safety and filter circuit patency. There are no previous studies in which researchers have reported data on filter circuit patency and filter life associated with early mobilization.
- This study is the first in which filter life data were recorded for patients undergoing CRRT via a vascular catheter in the ICU. Mobilization was found to be safe and associated with no adverse events, and we found an increase in filter life in the group with femoral catheters.

- Our presently reported work will have a significant impact on clinical medicine, as it provides empirical data suggesting that restrictions on mobilization imposed on patients undergoing CRRT are detrimental to filter life, which has a direct impact on the success of the therapy.
- Our present research suggests that stasis of blood influences filter life, which may be a significant contributor to ICU morbidity and mortality in this population. This concept remains unexplored in the ICU literature.
- Our findings have significant implications for the clinical management and morbidity of patients undergoing CRRT in critical care.

Additional files

Additional file 1: Nursing workload and nursing concern about filter disconnection. Includes methods and results of the effect of the intervention on nursing workload and nursing perception of likelihood of filter circuit discontinuation.

Additional file 2: Characteristics of filters by intervention group and access site. Includes clinical data of baseline, intervention and nonintervention filters (femoral and nonfemoral).

Additional file 3: Mean CVVHDF filter parameters during intervention in patients with femoral catheters. Includes variations in access and transmembrane pressure during the three levels of intervention: passive (hip flexion), low-level (hip flexion and sitting on edge of bed) and high-level (sitting on edge of bed, standing and marching on spot).

Abbreviations

aPTT: Activated partial thromboplastin time; CI: Confidence interval; CRRT: Continuous renal replacement therapy; CVVHDF: Continuous venovenous haemodiafiltration; ICU: Intensive care unit; IJ: Internal jugular; INR: International normalized ratio; IQR: Interquartile range; MOS: Marching on the spot; MOVE: Movement on vascular catheter evaluation; SC: Subclavian; SOEOB: Sitting on the edge of the bed; TM: Transmembrane.

Competing interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/conflicts-of-interest/ (available on request from the corresponding author) and declare that they have no competing interests.

Authors' contributions

YTW (guarantor) was involved in the conception and design of the study; led patient recruitment, data collection, data analysis and interpretation of the study; completed the first draft of the manuscript; and reviewed the manuscript for intellectually important content. TPH was involved in the data analyses and interpretation of the study and reviewed the manuscript for intellectually important content. PR was involved in the design of the study and data collection, data analysis and interpretation of the study, and provided intellectual input into the writing of the manuscript. CW, TAA, PSL, SV and RA were involved in the design of the study and data collection, data analysis and interpretation of the study, and reviewed the manuscript for intellectually important content. DTR was involved in the conception of the study and data analysis and interpretation of the study, and reviewed the manuscript for intellectually important content. NF was involved in the data analyses and interpretation of the study and reviewed the manuscript for intellectually important content. EHS led the conception and design of the study; was involved in patient recruitment, data collection, data analysis and interpretation of the study; and reviewed the manuscript for intellectually important content. EHS had full access to all of the data (including statistical reports and tables) in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis and had final responsibility for the decision to submit the manuscript for publication. All authors read and approved the final manuscript.

Acknowledgements

The authors acknowledge Rosalie Russo for her contribution to conception of the study. No formal funding was received for this study. This research was completed with in-kind support from the Allied Health Research Unit, Monash Health, and the physiotherapy departments of Monash Medical Centre and Dandenong Hospital (Monash Health). TPH is supported by a National Health and Medical Research Council (Australia) Career Development Award. YTW was previously employed by Monash Health and is employed by Peninsula Health. PR, CW, TAA, DTR, PSL, SV and RA are employed by Monash Health. NF is employed by Austin Health. EHS was previously employed by Monash Health and is employed by Western Health.

Author details

[1]Department of Physiotherapy, Monash Health, 246 Clayton Road, Clayton, Victoria 3168, Australia. [2]Allied Health Research Unit, Monash Health, 400 Warrigal Road, Cheltenham, Victoria 3192, Australia. [3]Department of Physiotherapy, Faculty of Medicine, Nursing and Health Science, Monash University, McMahons Road, Frankston, Victoria 3199, Australia. [4]Department of Intensive Care, Monash Health, 246 Clayton Road, Clayton, Victoria 3168, Australia. [5]Department of Physiotherapy, Monash Health, 135 David Street, Dandenong 3175, Victoria, Australia. [6]Department of Intensive Care, Monash Health, 135 David Street, Dandenong 3175, Victoria, Australia. [7]Department of Intensive Care, Austin Health, Studley Road, Heidelberg, Victoria 3084, Australia. [8]Department of Physiotherapy, Western Health, Gordon Street, Footscray, Victoria 3011, Australia.

Received: 26 February 2014 Accepted: 30 June 2014
Published: 28 July 2014

References

1. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Ronco C, Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators: **Acute renal failure in critically ill patients: a multinational, multicentre study.** *JAMA* 2005, **294:**813–818.
2. Berney S, Haines K, Skinner EH, Denehy L: **Safety and feasibility of an exercise prescription approach to rehabilitation across the continuum of care for survivors of critical illness.** *Phys Ther* 2012, **92:**1524–1535.
3. Pohlman MC, Schweickert WD, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D, Schmidt GA, Bowman A, Barr R, McCallister KE, Hall JB, Kress JP: **Feasibility of physical and occupational therapy beginning from initiation of mechanical ventilation.** *Crit Care Med* 2010, **38:**2089–2094.
4. Schwab SJ, Beathard G: **The hemodialysis catheter conundrum: hate living with them, can't live without them.** *Kidney Int* 1999, **56:**1–17.
5. Talley CL, Wonnacott RO, Schuette JK, Jamieson J, Heung M: **Extending the benefits of early mobility to critically ill patients undergoing continuous renal replacement therapy: the Michigan experience.** *Crit Care Nurs Q* 2013, **36:**89–100.
6. Hsieh H, Liao H, Wei C, Tarng D: **Indwelled femoral vein non-cuffed, double-lumen haemodialysis catheter complicated by pulmonary thromboembolism.** *Clin Nephrol* 2004, **62:**162–164.
7. Adler J, Malone D: **Early mobilization in the intensive care unit: a systematic review.** *Cardiopulm Phys Ther J* 2012, **23:**5–13.
8. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D, Schmidt GA, Bowman A, Barr R, McCalliste KE, Hall JB, Kress JP: **Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial.** *Lancet* 2009, **373:**1874–1882.
9. Burtin C, Clerckx B, Robbeets C, Ferdinande P, Langer D, Troosters T, Hermans G, Decramer M, Gosselink R: **Early exercise in critically ill patients enhances short-term functional recovery.** *Crit Care Med* 2009, **37:**2499–2505.
10. Morris PE, Goad A, Thompson C, Taylor K, Harry B, Passmore L, Ross A, Anderson L, Baker S, Sanchez M, Penley L, Howard A, Dixon L, Leach S, Small R, Hite RD, Haponik E: **Early intensive care unit mobility therapy in the treatment of acute respiratory failure.** *Crit Care Med* 2008, **36:**2238–2243.

11. Stiller K: **Physiotherapy in intensive care: an updated systematic review.** *Chest* 2013, **144:**825–847.
12. Kayambu G, Boots R, Paratz J: **Physical therapy for the critically ill in the ICU: a systematic review and meta-analysis.** *Crit Care Med* 2013, **41:**1543–1554.
13. Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, Guest CB, Mazer CD, Mehta S, Stewart TE, Kudlow P, Cook D, Slutsky AS, Cheung AM, Canadian Critical Care Trials Group: **Functional disability 5 years after acute respiratory distress syndrome.** *N Engl J Med* 2011, **364:**1293–1304.
14. Iwashyna TJ, Ely EW, Smith DM, Langa KM: **Long-term cognitive impairment and functional disability among survivors of severe sepsis.** *JAMA* 2010, **304:**1787–1794.
15. Skinner EH, Warrillow S, Denehy L: **Health-related quality of life in Australian survivors of critical illness.** *Crit Care Med* 2011, **39:**1896–1905.
16. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, Zawistowski C, Bemis-Dougherty A, Berney SC, Bienvenu OJ, Brady SL, Brodsky MB, Denehy L, Elliott D, Flatley C, Harabin AL, Jones C, Louis D, Meltzer W, Muldoon SR, Palmer JB, Perme C, Robinson M, Schmidt DM, Scruth E, Spill GR, Storey CP, Render M, Votto J, Harvey MA: **Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference.** *Crit Care Med* 2012, **40:**502–509.
17. Leditschke IA, Green M, Irvine J, Bissett B, Mitchell IA: **What are the barriers to mobilizing intensive care patients?** *Cardiopulm Phys Ther J* 2012, **23:**26–29.
18. Damluji A, Zanni JM, Mantheiy E, Colantuoni E, Kho ME, Needham DM: **Safety and feasibility of femoral catheters during physical rehabilitation in the intensive care unit.** *J Crit Care* 2013, **28:**535. e9–535.e15.
19. Perme C, Lettvin C, Throckmorton TA, Mitchell K, Masud F: **Early mobility and walking for patients with femoral arterial catheters in intensive care unit: a case series.** *J Acute Care Phys Ther* 2011, **2:**32–36.
20. Al-Wakeel J, Milwalli A, Malik G, Huraib S, Al-Mohaya S, Abu-Aisha H, Memon N: **Dual-lumen femoral vein catheterization as vascular access for haemodialysis.** *Angiology* 1998, **49:**557–562.
21. Joannidis M, Oudemans-van Straaten HM: **Clinical review: patency of the circuit in continuous renal replacement therapy.** *Crit Care* 2007, **11:**218.
22. Uchino S, Fealy N, Baldwin I, Morimatsu H, Bellomo R: **Continuous is not continuous: the incidence and impact of circuit "down-time" on uraemic control during continuous veno-venous haemofiltration.** *Intensive Care Med* 2003, **29:**575–578.
23. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK: **The Richmond Agitation–Sedation Scale: validity and reliability in adult intensive care unit patients.** *Am J Respir Crit Care Med* 2002, **166:**1338–1344.
24. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, Truman B, Speroff T, Gautam S, Margolin R, Hart RP, Dittus R: **Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU).** *JAMA* 2001, **286:**2703–2710.
25. Ely EW, Pun BT: *Confusion Assessment Method for the ICU (CAM-ICU): The Complete Training Manual.* Nashville TN: Vanderbilt University Medical Center; 2002. Available at http://www.icudelirium.org/docs/CAM_ICU_training.pdf. (accessed 5 August 2014).
26. Fealy N, Kim I, Baldwin I, Schneider A, Bellomo R: **A comparison of the Niagara and Medcomp catheters for continuous renal replacement therapy.** *Ren Fail* 2013, **35:**308–313.
27. Schiffl H, Lang SM, Fischer R: **Daily hemodialysis and the outcome of acute renal failure.** *N Engl J Med* 2002, **346:**305–310.
28. Rivera AM, Strauss KW, van Zundert A, Mortier E: **The history of peripheral intravenous catheters: how little plastic tubes revolutionized medicine.** *Acta Anaesthesiol Belg* 2005, **56:**271–282.
29. Zanni JM, Korupolu R, Fan E, Pradhan P, Janjua K, Palmer JB, Brower RG, Needham DM: **Rehabilitation therapy and outcomes in acute respiratory failure: an observational pilot project.** *J Crit Care* 2010, **25:**254–262.
30. Perme C, Nalty T, Winkelman C, Kenji Nawa R, Masud F: **Safety and efficacy of mobility interventions in patients with femoral catheters in the ICU: a prospective observational study.** *Cardiopulm Phys Ther J* 2013, **24:**12–17.
31. Cole L, Bellomo R, Silvester W, Reeves JH: **A prospective, multicenter study of the epidemiology, management, and outcome of severe acute renal failure in a "closed" ICU system.** *Am J Respir Crit Care Med* 2000, **162:**191–196.
32. Ahlström A, Tallgren M, Peltonen S, Räsänen P, Pettilä V: **Survival and quality of life of patients requiring acute renal replacement therapy.** *Intensive Care Med* 2005, **31:**1222–1228.
33. Bagshaw SM: **The long-term outcome after acute renal failure.** *Curr Opin Crit Care* 2006, **12:**561–566.
34. Hitos K, Cannon M, Cannon S, Garth S, Fletcher JP: **Effect of leg exercises on popliteal venous blood flow during prolonged immobility of seated subjects: implications for prevention of travel-related deep vein thrombosis.** *J Thromb Haemost* 2007, **5:**1890–1895.
35. Jorfeldt L, Wahren J: **Leg blood flow during exercise in man.** *Clin Sci* 1971, **41:**459–473.
36. Brower RG: **Consequences of bed rest.** *Crit Care Med* 2009, **37**(10 Suppl):S422–S428.
37. Winkelman C: **Bed rest in health and critical illness: a body systems approach.** *AACN Adv Crit Care* 2009, **20:**254–266.
38. Kwon OY, Jung DY, Kim Y, Cho SH, Yi CH: **Effects of ankle exercise combined with deep breathing on blood flow velocity in the femoral vein.** *Aust J Physiother* 2003, **49:**253–258.
39. Pucheu A, Evans J, Thomas D, Scheuble C, Pucheu M: **Doppler ultrasonography of normal neck veins.** *J Clin Ultrasound* 1994, **22:**367–373.

doi:10.1186/cc14001
Cite this article as: Wang *et al.*: Early mobilization on continuous renal replacement therapy is safe and may improve filter life. *Critical Care* 2014 **18**:R161.

Additional File 1: Nursing workload and nursing concern about filter disconnection.

Methods

The nursing workload was measured using the NASA Task Load Index (NASA-TLX) and the Nine Equivalents of Nursing Manpower use score (NEMS) during the intervention shift and on the subsequent shift. Originally developed to measure workload in aviation (Hart & Staveland, 1988), the NASA-TLX is reliable, valid and easy to administer measurement of subjective workload perception in ICU nurses (Hoonakker et al., 2011). The NEMS measures the objective nursing workload and is easy to administer, reliable and valid (Reis Miranda et al., 1997; Rothen et al., 1999).

Nursing concern about filter disconnection was measured using a Likert scale of 1 = extremely concerned, 2 = very concerned, 3 = moderately concerned, 4 = mildly concerned and 5 = not at all concerned. Nurses rated their concern about filter disconnection prior to being informed of the mobilisation plan and again once informed of the specific details of the intervention by the treating therapist.

Analysis

Nursing workload and concern were analyzed using paired t-tests and Fisher's Exact Test. For analyses, the Likert categories of nursing concern were collapsed to

concerned (rating = 1, 2, 3 or 4) vs. Unconcerned (rating = 5). Statistical analysis was performed using IBM SPSS Statistics™ 20 Version 20.0.0 (SPSS Inc., Chicago, IL, USA) and $p < 0.05$ was accepted as statistical significance.

Results

No differences in nursing workload were seen between the intervention and following shifts, as measured by either the NASA-TLX (mean (SD) 13.1 (3.1) vs. 12.2 (4.9), mean difference (95% CI) -0.93 (-3.6, 1.7), $p = 0.46$) or the NEMS (mean (SD) 33.4 (10.7) vs. 33.9 (10.6), mean difference (95% CI) 0.45 (-6.9, 6.0). A NASA-TLX score of 32.8 is equivalent to administering injections (Burford, 2012) and the mean scores for both shifts were considerably lower, although the mean NEMS was higher than usual (mean 26.2, SD 9.4) (Reis Miranda et al., 1997). Nursing concern about the likelihood of the filter circuit clotting was heightened by informing nurses that the intervention was going to occur (61% vs. 76%, $p < 0.001$). The day following the intervention, only 48% of nurses knew their patient had been mobilized on the filter the preceding day.

References

References have been integrated into the thesis bibliography.

Additional File 2: Characteristics of filters by intervention group and access site

Characteristics of filters by intervention group and access site (median (IQR) unless otherwise indicated).

	Baseline filters n=69	Baseline femoral filters n=46	Baseline non-femoral filters n=23	All intervention filters n=33	Femoral intervention filters n=23	Non-femoral intervention filters n=10	All non-intervention filters n=93	Femoral non-intervention filters n=65	Non-femoral non-intervention filters n=28
Filter life[a] (hours)	22.3 (15.2)	18.0 (11.1)	32.6 (18.8)	35.2 (17.2)	35.3 (17.6)	34.9 (17.4)	21.4 (18.3)	19.5 (16.3)	25.8 (22.1)
Hb (g/dL)	94 (87-103)	95 (88-104)	92 (84-99)	89 (85-94)	88 (81-91)	93 (90-103)	91 (85-96)	89 (85-95)	94 (82-99)
INR	1.2 (1.0-1.6)	1.2 (1.0-1.7)	1.2 (1.1-1.6)	1.1 (1.1-1.4)	1.2 (1.1-1.4)	1.1 (1.1-1.3)	1.2 (1.1-1.4)	1.2 (1.1-1.4)	1.1 (1.0-1.2)
Platelets, $x10^3$/UL	145 (88-216)	133 (85-212)	149 (116-226)	125 (60-200)	121 (59-174)	179 (60-252)	111 (60-171)	108 (59-149)	137 (73-288)
APTT (seconds)	36 (31-50)	34 (30-48)	38 (34-54)	39 (34-52)	40 (34-55)	34 (33 – 44)	37 (30 – 53)	38 (30 – 52)	37 (30 – 53)
Position changes/Day	6 (3-7)	6 (3-7)	6 (4-7)	6 (5-7)	5 (4-7)	8 (6-9)*	5 (4-7)	5 (3-7)	6 (4-7)*

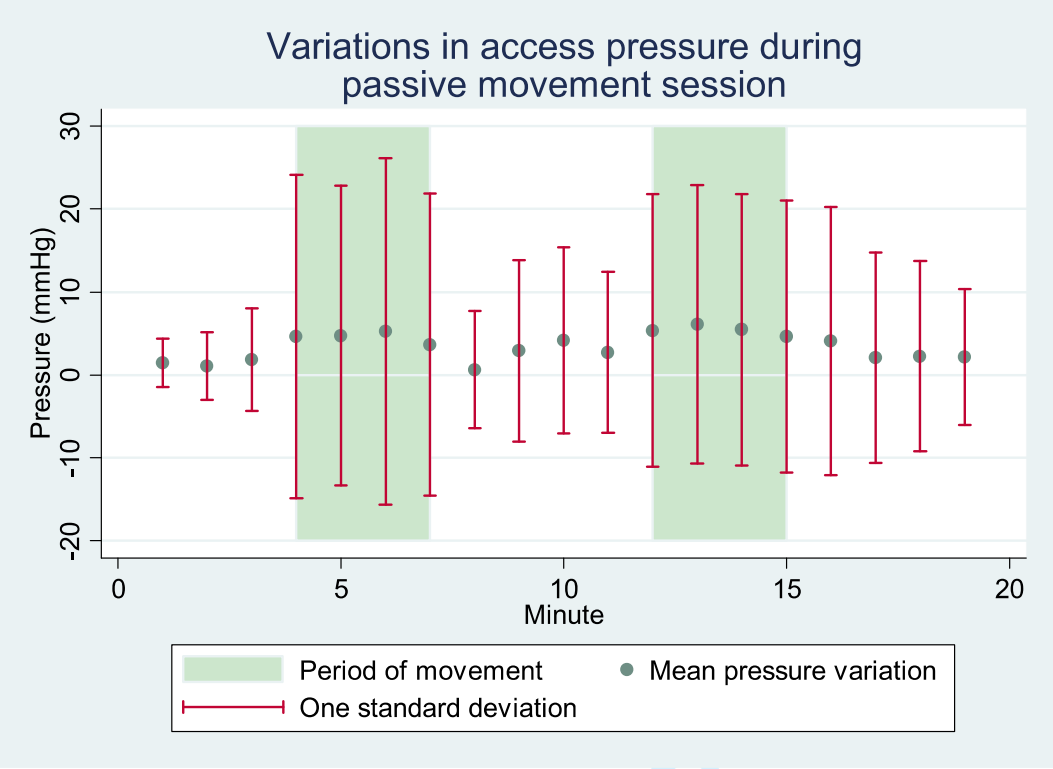
Anticoagulation method[b]									
Heparin	13%	15%	9%	27%	26%	30%	24%	24%	25%
Citrate	14%	17%	9%	6%	4%	10%	3%	5%	0%
Regional heparinisation	32%	37%	22%	52%	48%	60%	38%	35%	46%
Other	3%	0%	9%	3%	4%	0%	10%	5%	21%
Nil	25%	24%	26%	12%	17%	0%	26%	35%	7%

[a]Mean (SD), [b]percentage. Percentages may not add up to 100% due to rounding. Hb, haemoglobin. Heparin, unfractioned heparin. INR, International Normalized Ratio. APTT, Activated Partial Thromboplastin Time. Regional Heparinization, unfractioned heparin infusion combined with protamine infusion. *Significant difference between groups, regression co-efficient [95% CI] 2 [1, 3], p=0.002.

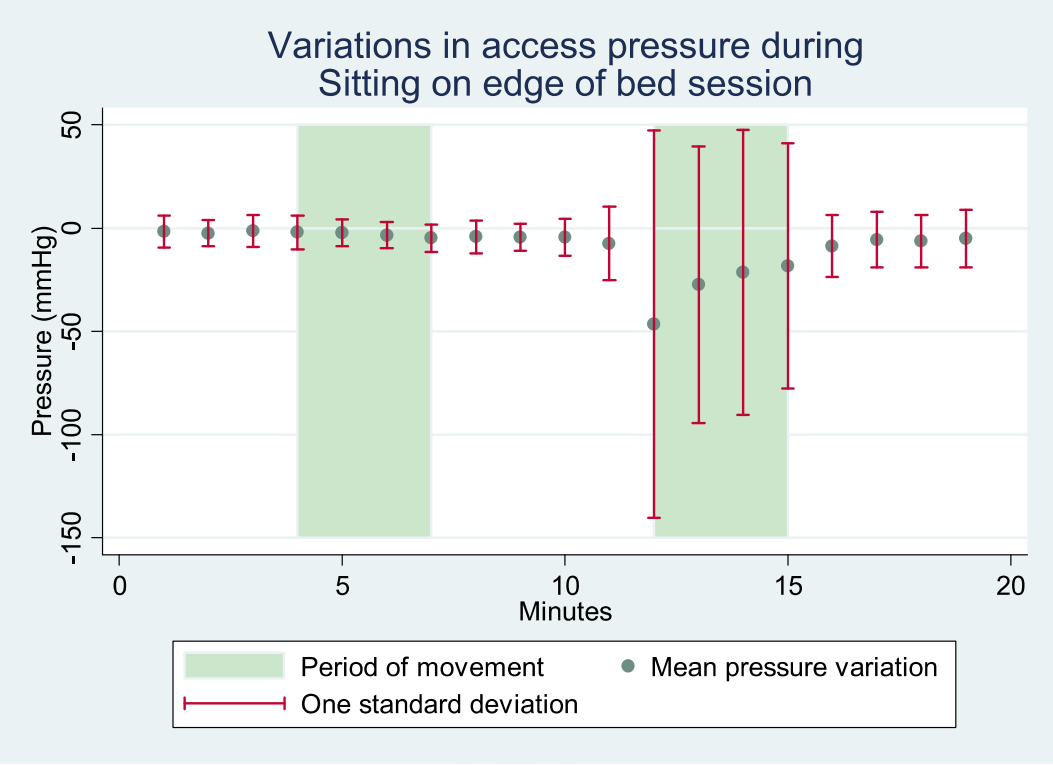
Additional File 3: Mean CVVHDF filter parameters during intervention in patients with femoral catheters.

Data presented as variations to the pre-intervention filter pressure measured at the beginning of the intervention session. Pressure parameters are compared within each filter to the pre-intervention parameters at time 0. The shaded region represent period of movement or mobilisation, non-shaded region represent periods of rest or recovery. Error bars represent one standard deviation on either side of the mean. Each bar (95% confidence interval) represents the average pressures of all participants calculated each minute.

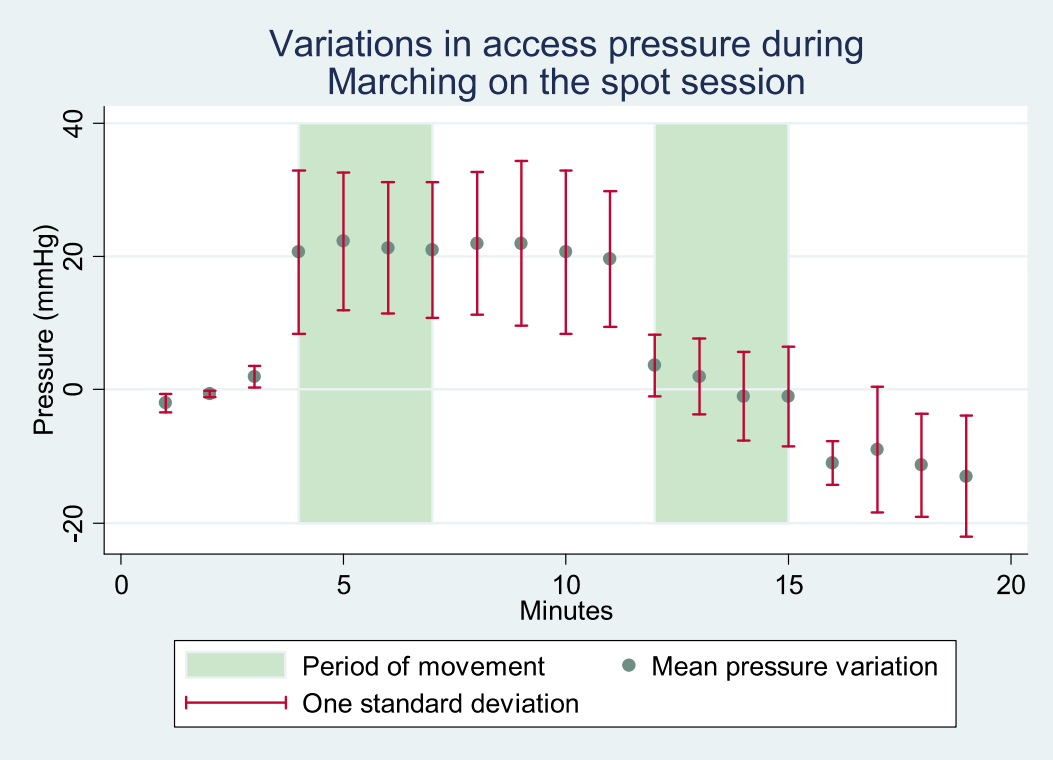
Access pressure during passive intervention



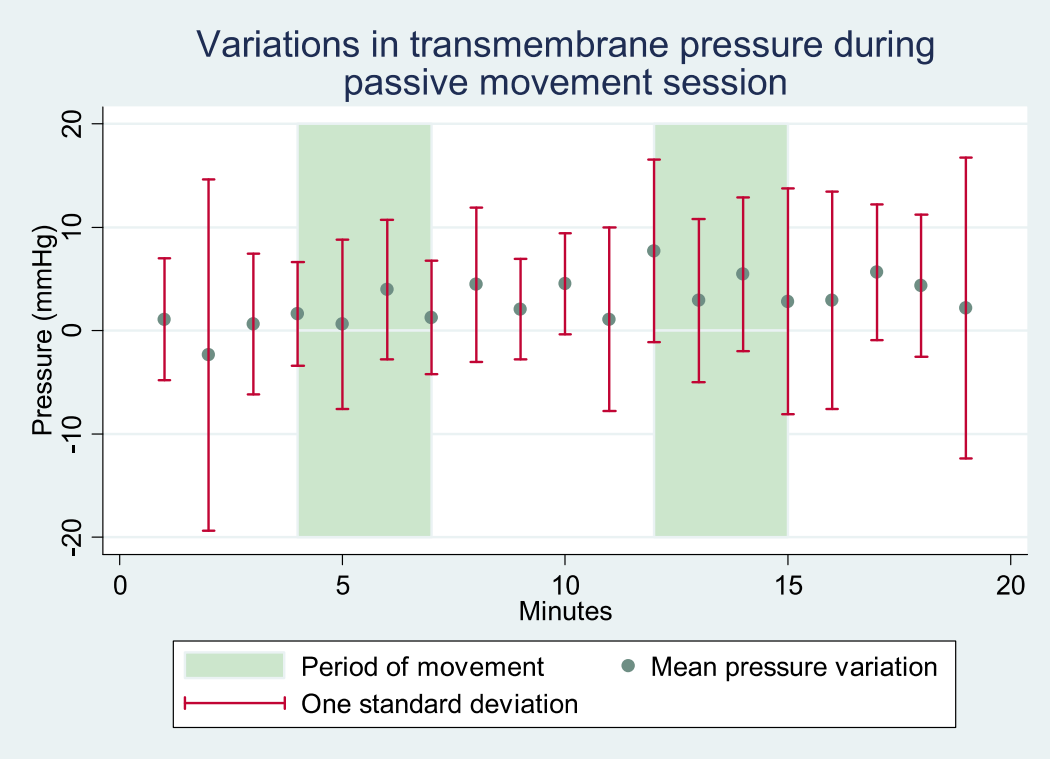
Access pressure during low-level intervention



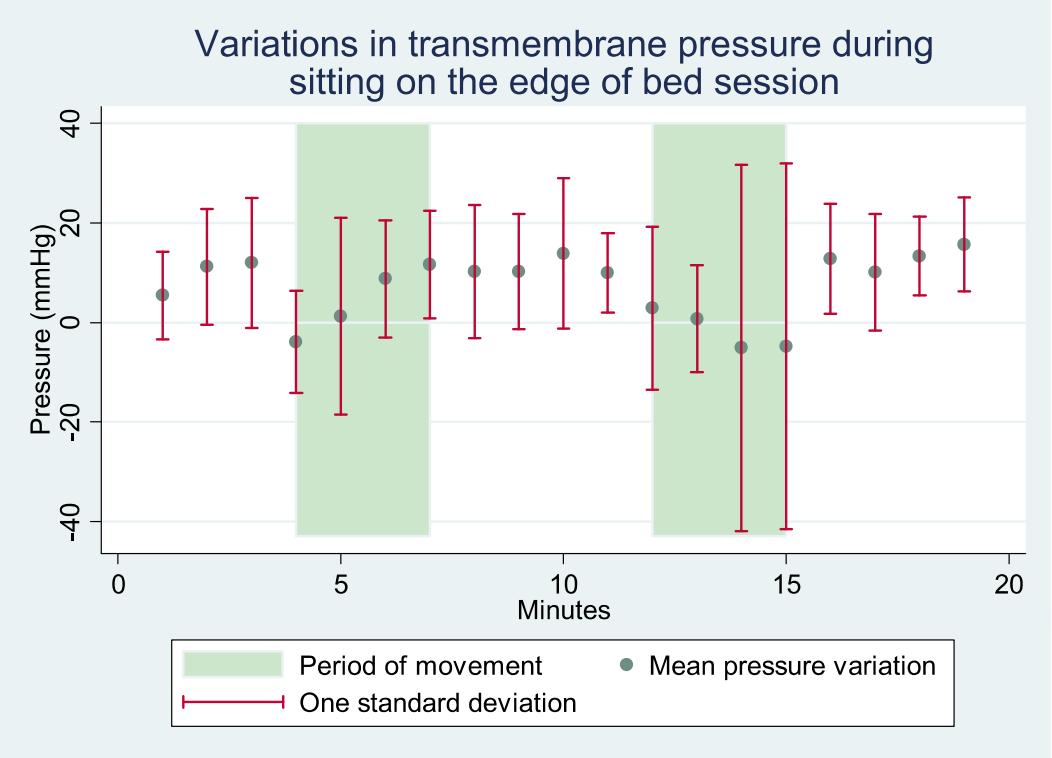
Access pressure during high-level intervention



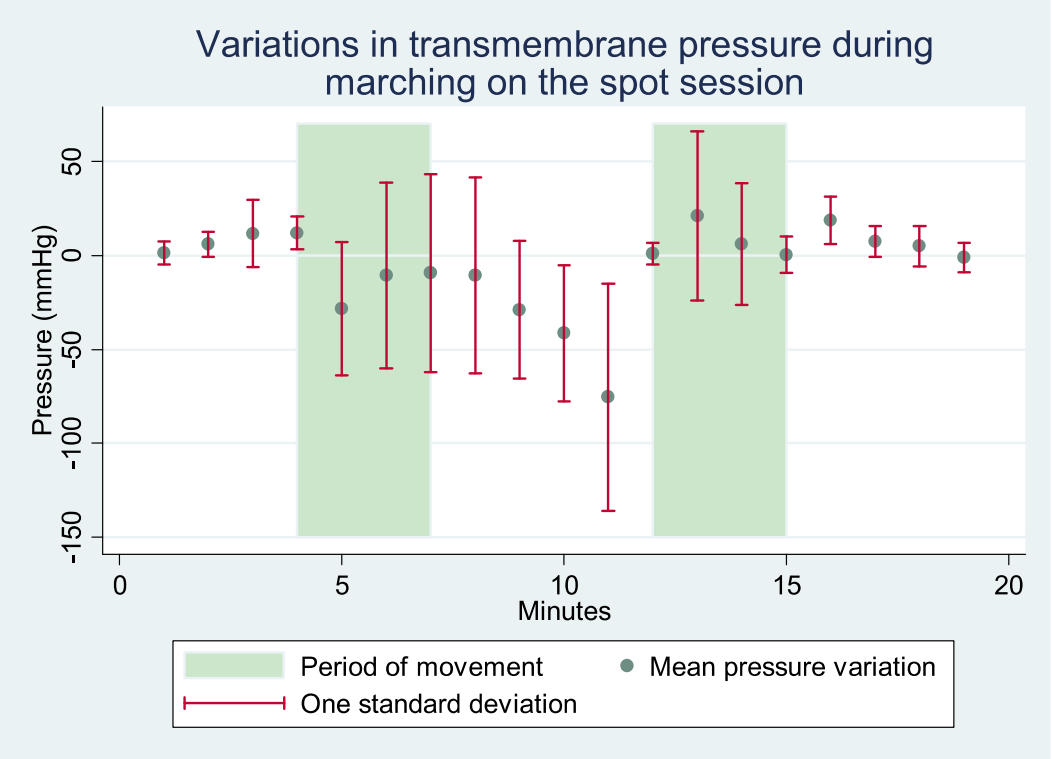
Transmembrane pressure during passive intervention



Transmembrane pressure during low-level intervention



Transmembrane pressure during high-level intervention



4.5. Chapter summary

This study was the first to prospectively evaluated the safety and feasibility of mobilising patients undergoing CRRT. This study demonstrated an extremely low incidence of adverse events in critically ill patients requiring CRRT participating in functional and bed-based physical rehabilitation.

Findings of this study also suggest that stasis of blood influences filter life, which may be a significant contributor to ICU morbidity and mortality in this population. This finding needs to be evaluated in a larger multicentred study, as discussed in our response to a letter to the editor (appendix 4.1).

Since the publication of this research, international expert consensus and recommendations no longer consider CRRT or femoral dialysis catheters as barriers to early rehabilitation.

Findings of this study further support that physical rehabilitation in critically ill patients is safe and feasible. However, the effectiveness of physical rehabilitation in the ICU remains uncertain. The next chapter will investigate the efficacy of physical rehabilitation that begins in the ICU.

Chapter 5. Physical rehabilitation in the intensive care unit, a systematic review and meta-analysis

5.1. Introduction

The systematic review presented in this chapter examines the relationship between physical rehabilitation and patient outcomes. Previous systematic reviews and meta-analyses have been more restricted in scope to reduce heterogeneity in the confidence intervals of the reported results. For example, reviews have focused on specific types of interventions, such as active mobilisation (Tipping et al., 2017), early initiation of rehabilitation (Fuke et al., 2018; Worraphan et al., 2020), inspiratory muscle training (Vorona et al., 2018), and electrical neuromuscular stimulation (Zayed et al., 2020).

However, in some of these reviews, heterogeneity in the confidence intervals of the reported results remained high, while the results and conclusions across these meta-analyses have been inconsistent.

Significant variability exists in the routine physical rehabilitation practices in intensive care units across the world. The use of task-specific exercises and the frequency of rehabilitation services are important factors that may impact outcomes. However, reviews to date have not thoroughly examined these variables as possible confounders and sources of heterogeneity.

This chapter presents a systematic review and meta-analysis of 60 trials that investigated the effect of physical rehabilitation on patient outcomes in the ICU, focusing on the impact of task-specific training and the dose-response profile of the intervention. The unique study design and statistical method have been reviewed and supported by an independent statistician (appendix 5.1).

5.2. Physical rehabilitation in the intensive care unit, a systematic review and meta-analysis

Manuscript in press: Wang, Y.T., Lang, J.K., Haines, K.J., Skinner, E.H., Haines, T.P. (2021). Physical rehabilitation in the intensive care unit, a systematic review and meta-analysis. *Critical Care Medicine, in press*

Abstract

Objective: Significant variability exists in physical rehabilitation modalities and dosage used in the intensive care unit (ICU). Our objective was to investigate the effect of physical rehabilitation on patient outcomes, the impact of task-specific training, and the dose-response profile in the ICU.

Data Sources: A systematic search of Ovid MEDLINE, Cochrane Library, EMBASE, and CINAHL plus databases were undertaken on the 28th of May 2020.

Study Selection: Randomised controlled trials and controlled clinical trials investigating physical rehabilitation commencing in the ICU in adults were included. Outcomes included muscle strength, physical function, duration of mechanical ventilation, ICU and hospital length of stay, mortality, and health-related quality of life. Two independent reviewers assessed titles, abstracts, and full texts against eligibility criteria.

Data Extraction: Details on intervention for all groups were extracted using the template for intervention description and replication checklist.

Data Synthesis: Sixty trials were included, with a total of 5352 participants. Random-effects pooled analysis showed that physical rehabilitation improved physical function at hospital discharge (standardised mean difference, 95% confidence interval (0.22, 0.00 to 0.44), reduced ICU of stay by 0.8 days (mean difference, 95% confidence interval) (-0.80, -1.37 to -0.23) and hospital length of stay by 1.75 days (mean difference, 95% confidence interval) (-1.75, -3.03 to -0.48). Physical rehabilitation had no impact on the other outcomes. The intervention was more effective in trials where the control group received low-dose physical rehabilitation and in trials that investigated functional exercises.

Conclusion: Physical rehabilitation in the ICU improves physical function, reduces ICU and hospital length of stay. However, it does not appear to impact other outcomes.

Introduction

Up to 65% of critical illness survivors suffer clinically detectable weakness from a combination of muscle mass loss, myopathy (Derde et al., 2012; Puthucheary et al., 2013), and polyneuropathy (Bolton et al., 1984). These changes occur early in ICU admission and are associated with prolonged weaning from mechanical ventilation (MV) (De Jonghe et al., 2007; De Jonghe, Bastuji-Garin, et al., 2004; De Jonghe et al., 2002) and increased ICU (De Jonghe et al., 2002; Garnacho-Montero et al., 2005) and hospital length of stay (LOS) (Garnacho-Montero et al., 2005). Clinical weakness is also associated with increased mortality in ICU (Sharshar et al., 2009), in-hospital (Ali et al., 2008; Sharshar et al., 2009), and over the first year after ICU discharge (Hermans et al., 2014).

Physical rehabilitation is a commonly adopted approach to manage the physical sequelae of critical illness following a signal in clinical trials (Davidson et al., 2013; Needham et al., 2011; Schweickert et al., 2009). Rehabilitation begins in the ICU, with the intent to reverse muscle catabolism, mitigate neuropathy, and minimise the effects of immobility (Truong et al., 2009). Early systematic reviews have demonstrated the safety and feasibility of physical rehabilitation in the ICU (Stiller, 2013), improved physical function (Adler & Malone, 2012; Kayambu et al., 2013), health-related quality of life (HRQoL), muscle strength, ventilator-free days, and ICU LOS (Kayambu et al., 2013). However, recent systematic reviews with meta-analyses (Castro-Avila et al., 2015; Menges et al., 2021; Okada et al., 2019; Tipping et al., 2017) have not consistently supported these findings.

Considerable heterogeneity in routine physical rehabilitation practices in ICUs exist globally (Bakhru et al., 2016; Harrold et al., 2015; Skinner et al., 2008), and previous reviews have not considered the amount of physical rehabilitation available to the control group as a confounding factor and source of heterogeneity. Moreover, investigation of the effectiveness of task-specific training in the ICU is clinically important. Functional exercises such as sitting on the side of the bed, standing, and walking involve more complex decision-making incorporating sedation management, feasibility, and safety.

This review aimed to determine:

1. Does physical rehabilitation in ICU improve patient outcomes?
2. Are functional exercise interventions more effective?
3. How does the dose of control therapy impact the effectiveness of experimental interventions?

Materials and methods

Study Design

This protocol was registered on the PROSPERO International Prospective Register of Systematic Reviews (CRD42017074228). Reporting conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2015) guidelines and The Cochrane Handbook (Higgins, 2019).

Study selection and databases

Ovid MEDLINE, EMBASE, CINAHL plus, and the Cochrane Library were electronically searched for randomised controlled trials (RCT) and Controlled Clinical Trials (CCT) evaluating physical rehabilitation in critically ill patients (supplemental methods details the search strategy). Publications available from the 1st of January 2000 - 28th of May 2020 were screened against eligibility criteria (Table 5.1) by two independent reviewers (YW, JL). Full-text articles were obtained if titles and abstracts were insufficient. Conflicts were discussed between the two reviewers and adjudicated by a third reviewer (TH) if required.

Data Extraction

Data extraction included study design, participant, intervention delivered using the template for intervention description and replication (Hoffmann et al., 2014), and predefined outcomes (details listed in supplemental methods).

Risk of bias

Two reviewers (YW, JL) independently assessed the risk of bias at the outcome level. Conflicts were discussed between the two reviewers and adjudicated by a third reviewer (TH) if required. The Cochrane risk-of-bias tool for randomized trials (Sterne et al., 2019) was used to assess the RCTs. The Risk Of Bias In Non-randomized Studies – of

Interventions assessment tool (Sterne et al., 2016) was used to assess the CCTs. The visualization tool for risk of bias assessments in a systematic review (McGuinness & Higgins, 2020) was used to present results.

Summary of measures

Principal summary measures were the pooled standardised mean difference, mean difference, or risk difference with 95% confidence intervals. For outcomes in which multiple heterogeneous outcome measures were used, results were summarised as a standardised mean difference to facilitate their inclusion (a key limitation in research synthesis) by standardising the results of the individual studies to a uniform scale. A standardised mean difference expresses the size of the intervention effect relative to the variability observed in each study (Higgins, 2019). Interpretation of the magnitude of a standardised mean difference is based on previous guidelines (Cohen, 2013). Where a single outcome measure was used, the mean difference was used. Mortality outcomes were summarised using the risk difference.

Synthesis of results

Random-effects meta-analysis was performed with STATA/SE version 13 (StataCorp LP, Austin, TX, USA) to quantify the effect of the intervention. Studies with more than two groups were included. Studies that presented data in alternate methods than mean and

standard deviation were attempted to be included, and these methods are described in detail in supplemental methods.

Subgroup and sensitivity analyses

Subgroup analyses and meta-regression of studies included in the primary pooled analysis were pre-planned according to PROSPERO registration.

Stratifications occurred posthoc because it was unknown how much detail regarding intervention type and dosage would be available. Subgroup analyses by individual intervention components were unable to be performed due to insufficient reporting, and many trials combined multiple interventions. Meta-regression analysis by delivered dosage was also not possible due to insufficient reporting of intervention delivery, for both intervention and control groups.

Subgroup analyses were conducted to compare the type of experimental intervention: functional exercise(s) (defined as lifting head, rolling, sitting up, sitting balance, standing, transferring, walking) vs. non-functional exercise (defined as passive or active range of motion (ROM), neuromuscular electrical stimulation (NMES), and cycle ergometry). These subgroups were based on evidence that task-specific exercises may be more effective than impairment-based training in non-ICU patients (de Vreede et al., 2005; Di Monaco et al., 2009; Lowe et al., 2009; Nadeau et al., 2013).

Subgroup analyses were also conducted by stratifying the amount of physical rehabilitation available to control group participants as a part of routine care. High-dose control therapy was defined as the control group receiving or being assessed for physical rehabilitation ≥ 5 days per week. Low-dose control therapy was defined as the control group receiving or being assessed for physical rehabilitation < 5 days per week. These subgroups were determined by surveys of mobilisation practices in Canada (Koo et al., 2016) and the US (Bakhru et al., 2015) and the standard care delivered by recent trials investigating the efficacy of physical therapy rehabilitation in the ICU. Standard practice has likely evolved over time since the earliest trials found significant benefits (Burtin et al., 2009; Morris et al., 2008; Schweickert et al., 2009). In the 23 trials published since 2017 (Abu-Khaber et al., 2019; Amundadottir et al., 2019; Bianchi et al., 2018; dos Santos et al., 2020; Eggmann et al., 2018; Fontes Cerqueira et al., 2018; Fossat et al., 2018; Gama Lordello et al., 2020; Hickmann et al., 2018; Hodgson et al., 2020; Kho et al., 2019; Koutsioumpa et al., 2018; Leite et al., 2018; McCaughey et al., 2019; McWilliams et al., 2018; Nakamura et al., 2019; M. R. Nickels et al., 2020; Nydahl et al., 2019; Sarfati et al., 2018; Seo & Shin, 2019; Winkelman et al., 2018; Wollersheim et al., 2019; Wright et al., 2018), 19 (Amundadottir et al., 2019; Bianchi et al., 2018; dos Santos et al., 2020; Eggmann et al., 2018; Fontes Cerqueira et al., 2018; Fossat et al., 2018; Gama Lordello et al., 2020; Hickmann et al., 2018; Kho et al., 2019; Koutsioumpa et al., 2018; Leite et al., 2018; McWilliams et al., 2018; Nakamura et al., 2019; M. R. Nickels et al., 2020; Sarfati et al., 2018; Seo & Shin, 2019; Winkelman et al., 2018; Wollersheim et al., 2019; Wright et al., 2018) reported that physical rehabilitation was available to the control group ≥ 5 days per week. In contrast, out of 19 trials published before 2015 (Brummel et al.,

2014; Burtin et al., 2009; Cader et al., 2010; Caruso et al., 2005; Chang et al., 2011; Condessa et al., 2013; Dantas et al., 2012; Denehy, Skinner, et al., 2013; Dong et al., 2014; Elbouhy et al., 2014; Hanekom et al., 2012; Martin et al., 2011; Morris et al., 2008; Pandey et al., 2013; Patman et al., 2001; Routsi et al., 2010; Savci et al., 2011; Schweickert et al., 2009; Winkelman et al., 2012), only four (Burtin et al., 2009; Dantas et al., 2012; Denehy, Skinner, et al., 2013; Savci et al., 2011) reported that physical rehabilitation was available to the control group ≥ 5 days per week.

Meta-regression analysis examined the differences between the subgroups on the effect of the intervention. Post-hoc analysis of RCTs only was performed. Post-hoc sensitivity analyses were performed to ensure any decisions to exclude trials from the meta-analysis did not change the results of the primary pooled analysis.

Results

Flow of studies

Database searches totalled 7382 articles. After removing duplicates, screening by title, abstract and full-text, 62 reports (Table 5.2) of 60 trials were included in this review (Figure 5.1).

Characteristics of included studies

A total of 5352 participants were recruited across 60 trials, 2699 intervention, and 2653 control (Table 5.2). The cohort represented a mixture of medical and surgical patients across 21 countries, predominantly middle-aged, with a bias towards males. Most participants were recruited from Europe, America, and South America. Interventions and outcome measures for all included trials are summarised in supplemental results and listed in Table 5.2.

Risk of Bias

The risk of bias of included studies was considerable, with 31 of 57 RCTs classified as 'high' risk of bias (Figure 5.2 & 5.3), and four of five CCTs with a 'Serious or Critical' risk of bias (Figure 5.4). Major sources of bias for RCTs were due to domain two, deviations from intended interventions; and domain five, bias in selection of the reported result. Twenty-five RCTs rated "high" risk of bias for domain two, due to poor reporting of interventions and lack of an appropriate analysis to estimate the effect of intervention adherence. Forty-nine RCTs were rated "some concerns" for domain five by the two reviewers, due to lack of a pre-specified analysis plan before unblinded outcome data were available.

Pooled analysis of intervention effect

Duration of mechanical ventilation

Forty-six studies (Table 5.2) reported duration of MV. See supplemental results for details on these studies.

A meta-analysis of pooled data showed no difference in duration of MV between groups (mean difference, 95% CI) (-0.18, -0.37 to 0.02) (Figure 5.5). In studies where the control group received low-dose physical rehabilitation (n = 15), the intervention resulted in a reduction of MV duration by 1.6 days (mean difference, 95% CI) (-1.6, -2.49 to -0.71), but not in studies where the control group received high-dose physical rehabilitation (n= 18) (mean difference, 95% CI) (0.21, 0.03 to 0.40). Studies investigating functional experimental intervention (n = 16) demonstrated the intervention resulted in a reduction of MV duration (mean difference, 95% CI) (-1.15, -1.99 to -0.30), while non-functional experimental intervention (n = 18) increased duration of MV (mean difference, 95% CI) (0.14, 95% CI: 0.00 to 0.27). Meta-regression analysis of these study characteristics, sensitivity analysis and subgroup analysis of RCTs are included in supplemental results.

ICU length of stay

Forty-seven studies (Table 5.2) reported ICU LOS. See supplemental results for details on these studies.

Physical rehabilitation reduced ICU LOS by 0.8 days (mean difference, 95% CI) (-0.80, -1.37 to -0.23) (Figure 5.6). This effect was magnified in studies where the control group

received low-dose physical rehabilitation (n= 14), with a 1.87-days reduction in ICU LOS compared to control (mean difference, 95% CI) (-1.87, -3.16 to -0.58). In contrast, in studies where the control group received high-dose physical rehabilitation (n= 27), the intervention did not change the ICU LOS (mean difference, 95% CI) (0.23, -0.29 to 0.75). Subgroup analysis of studies with functional experimental intervention (n = 21) demonstrated the intervention resulted in a reduction of ICU LOS (mean difference, 95% CI) (-1.31, -2.46 to -0.16), while non-functional experimental intervention (n = 20) resulted in no difference between groups (mean difference, 95% CI) (-0.26, -0.98 to 0.45). Meta-regression analysis of these study characteristics, sensitivity analysis and subgroup analysis of RCTs are included in supplemental results.

Hospital length of stay

Thirty-three studies (Table 5.2) reported hospital LOS. See supplemental results for details on these studies.

Physical rehabilitation reduced hospital LOS by 1.75 days (mean difference, 95% CI) (-1.75, -3.03 to -0.48) (Figure 5.7). This effect was magnified in studies where the control group received low-dose physical rehabilitation (n= 11), with a 2.45-days reduction in hospital LOS compared to control (mean difference, 95% CI) (-2.45, -4.05 to -0.84), but not in studies where the control group received high-dose physical rehabilitation (n= 16) (mean difference, 95% CI) (0.16, -1.62 to 1.29). Subgroup analysis of studies with functional (n= 14) vs. non-functional experimental intervention (n= 13) demonstrated that

the functional experimental intervention resulted in a reduction of hospital LOS compared to control (mean difference, 95% CI) (-1.90, -3.74 to -0.06), while non-functional experimental intervention resulted in no difference between groups (mean difference, 95% CI) (-1.39, -3.43 to 0.66). Meta-regression analysis of these study characteristics, sensitivity analysis and subgroup analysis of RCTs are included in supplemental results.

Mortality

Thirty-one trials (Table 5.2) reported ICU mortality. Twenty-seven trials (Table 5.2) reported hospital mortality. Nine randomised controlled trials (Table 5.2) reported 6-months mortality. Pooled analysis demonstrated no difference between intervention and control groups at any of the time points (Figure 5.8). Subgroup analysis and sensitivity analysis are included in supplemental results.

Muscle strength

Six trials (Table 5.2) reported muscle strength on first awakening. Twenty-one trials (Table 5.2) reported at least one muscle strength outcome at ICU discharge. Eleven trials (Table 5.2) reported at least one muscle strength outcome at hospital discharge. See supplemental results for details on these studies.

Physical rehabilitation did not change the pooled standardised mean difference for muscle strength at any time point (Figure 5.9). Subgroup analysis and sensitivity analysis are included in supplemental results.

Physical function

Twenty-one (Table 5.2) studies reported at least one physical function outcome at ICU discharge. Fifteen trials (Table 5.2) reported at least one physical function outcome at hospital discharge. Eight randomised controlled trials (Table 5.2) reported at least one physical function outcome at 6 months. See supplemental results for details on these studies.

Physical rehabilitation resulted in a small improvement of the physical function at hospital discharge (standardised mean difference, 95% CI) (0.22, 0.00 to 0.44), but there was no difference between groups at ICU discharge and 6 months follow up (Figure 5.10). To aid interpretation, this magnitude of effect is similar to the trial by Wright et al. (Wright et al., 2018), who found the Functional Independence Measure was six points higher at ICU discharge compared with control, given their reported standard deviation of 26 (a standardised mean difference of 0.23). Subgroup and sensitivity analyses are included in supplemental results.

Mechanical ventilation free days at day 28

Six randomised controlled trials (Table 5.2) reported the number of MV free days at day 28. See supplemental results for details on these studies.

There was no difference between the number of MV free days comparing intervention and control groups at day 28 (Figure 5.11). Sensitivity analysis including a study with skewed data (Schweickert et al., 2009) did not change the pooled result. There were no differences between groups for any of the subgroup analyses.

Health-related quality of life

Ten randomised controlled trials (Table 5.2) reported at least one health-related quality of life outcome at 6 months. All were included in the pooled analysis. There was no difference in the health-related quality of life between intervention and control groups at 6 months (Figure 5.12). There were no differences between groups for any of the subgroup analyses.

Discussion

Key findings and clinical implications

This meta-analysis found that physical rehabilitation begun in the ICU improved physical function at hospital discharge and reduced ICU and hospital LOS compared to usual care.

It is highly plausible that physical rehabilitation would have beneficial effects on the ICU length of stay. Exercise has been shown to positively affect cognition and resolution of delirium (Needham et al., 2010; Schweickert et al., 2009). Sedation optimisation is a requirement for functional exercises, while sedation break alone has been shown to decrease MV duration and ICU length of stay (Jackson et al., 2010; Kress et al., 2000). Hospital LOS can be influenced by physical function, particularly if the discharge destination is directly home. We found the hospital LOS was shorter in the intervention group, with better physical function outcomes at hospital discharge.

In studies where the control group received low-dose physical rehabilitation, the intervention resulted in reductions in the duration of MV and ICU and hospital LOS. In contrast, the intervention did not improve any outcomes in studies where the control group received high-dose physical rehabilitation. Our results suggest the dose-response relationship of physical rehabilitation in the critically ill patient is not linear, with a diminishing benefit at higher doses. Diminishing returns is not a new concept in physical rehabilitation (Rose et al., 2017). Earlier, more intensive and higher dosage exercise does not always lead to better outcomes compared to standard practice, as demonstrated in stroke (Bernhardt et al., 2015), pulmonary rehabilitation (Greening et al., 2014), and thoracic surgery cohorts (Arbane et al., 2014). A higher dosage of therapy delivered to the control group makes it more difficult for the trial to achieve separation between the intervention and control groups. The muscle fatigue threshold required for a training

response may be lower in critical illness. The training response may also be limited by changes to nerves and muscles from critical illness.

Subgroup analysis of studies with functional experimental interventions resulted in reductions in the duration of MV and ICU and hospital LOS, but not in studies with non-functional experimental interventions. Functional exercises produce better physical function outcomes than non-functional exercises in non-ICU patients (de Vreede et al., 2005; Di Monaco et al., 2009; Lowe et al., 2009; Nadeau et al., 2013). Functional exercises also have benefits in other domains in the critically ill population, including cognition and resolution of delirium (Needham et al., 2010; Schweickert et al., 2009). Thus, it is highly plausible that functional exercises are superior to non-functional exercises in this population.

In summary, ICUs should have physical rehabilitation services available up to 5 days per week, as this frequency has led to improved physical function and health service outcomes. Wherever possible, functional exercises should be used. In ICUs that already provide physical rehabilitation services at least 5 days per week, a further increase in the dosage of rehabilitation is unlikely to improve outcomes further.

Relationship with existing literature

No reviews before this current review have considered the dose of physical rehabilitation available to control group participants as part of routine care, nor investigated the

effectiveness of task-specific training in the ICU. Therefore, our review had broad inclusion criteria and sought to examine whether the inconsistency in findings and conclusions in this field, along with the statistical heterogeneity identified in some previous reviews, could be explained by examining these factors as sources of heterogeneity.

Strength and limitations

This systematic review and meta-analysis address two major sources of heterogeneity not investigated in previous reviews, the type of exercise and intensity of control condition, which are essential in interpreting the body of evidence. Our review benefits from a novel data synthesis and analytic approach, and many included studies. Our results have excellent representation from across the globe, with the inclusion of 60 trials from 21 different countries. Numerous outcome measures and different time points of assessment were included in the pooled analysis.

There was considerable heterogeneity in the confidence intervals of the pooled results. Overall, the risk of bias in the included studies was also high. Therefore, caution should be exercised in the interpretation and application of the results.

Our review did not have the scope to investigate the effect of sedation practices on the effectiveness of physical rehabilitation. Sedation optimisations facilitate physical rehabilitation, particularly task-specific exercises. It may also decrease the time to initiation of physical rehabilitation, which is also an important factor in the effectiveness

of physical rehabilitation (Tipping et al., 2017). Sedation optimisation associated with trial interventions may have directly contributed to observed benefits; although in practice, it is highly recommended that sedation optimisation and physical rehabilitation are both included in a bundle of care to optimise the outcomes of critically ill patients (Barr & Pandharipande, 2013; Morandi et al., 2011; Vanhorebeek et al., 2020).

Included trials did not consistently report time-related outcomes such as MV duration, ICU, and hospital LOS, with some reporting outcomes only in survivors while others did not differentiate between survivors and non-survivors. While there were no mortality differences between groups, this was another source of heterogeneity and bias.

Future directions

We recommend better reporting of control and experimental interventions that would allow analysis based on the dosage of intervention delivered (i.e., using the TIDieR checklist (Hoffmann et al., 2014)). Future trials should use standardised outcome measures based on expert consensus, such as European quality of life-5 domains and 36-item Short Form Health Survey version 2 for the evaluation of HRQoL and pain; six-minute walk test for physical function, manual muscle test, and grip strength for muscle strength (Dale M. Needham et al., 2017). Reporting of time-related outcomes such as MV duration and LOS in a critically ill population should report survivors and non-survivors separately and follow-up for 60 days (Blackwood et al., 2019).

Conclusions

Physical rehabilitation that commences in the ICU improves physical function at hospital discharge and reduces ICU and hospital LOS. However, it does not appear to impact MV duration, muscle strength, HRQoL, and mortality. Wherever possible, task-specific exercises should be used, and the benefits of higher dose physical rehabilitation are unclear in patients already receiving regular exercise therapy.

Acknowledgements

We gratefully acknowledge Bernie Bissett for providing further information on the timing of interventions in Bisset et al. 2016; Claire Tipping et al. 2017, for the use of 6-month mortality data from Denehy et al. 2012, which was not published in the original report of the study.

References

References have been incorporated in the bibliography of the thesis.

Tables

Table 5.1 Inclusion and exclusion criteria of studies

Characteristics	Inclusion	Exclusion
Design	Randomised controlled trials and controlled clinical trials	Pre-post intervention trials, Case reports, reviews, editorials, descriptive commentary
Participants	Adults admitted to an ICU	Ages < 18; Participants with head injuries, cerebrovascular accidents, burns, and spinal injuries.
Intervention	Physical rehabilitation commenced in the intensive care unit, including but not limited to: Passive range of motions exercises; Active range of motion exercises; Resistance training; Positioning; Functional mobility and transfers; Respiratory muscle training; Neuromuscular electrical stimulation; Tilt tabling; Cycle ergometry or any combination of above.	Physical rehabilitation delivered only after discharge from ICU; Speech & Swallowing Rehabilitation; Cognitive rehabilitation
Control	Standard care	

Outcome measures	Muscle strength at awakening, ICU discharge, and hospital discharge. Physical function at ICU discharge, hospital discharge, and at 6 months. Mortality in ICU, in hospital, and at 6 months. Health-related quality of life at 6 months Duration of Mechanical ventilation Mechanical Ventilation-free days to day 28 ICU LOS Hospital LOS.	
Publication status	English only. Published after the year 2000.	Studies published before the year 2000.

Table 5.2 Characteristics of included studies

Study	Country and study design	Population	Participants Age, mean ± SD or median (IQR)	Intervention	Outcome measures
Abu-Khaber (Abu-Khaber et al., 2019)	Egypt RCT	Critically ill, on MV > 24 hours	n = 40 Age = 59.07 ± 5.32 60% male sex	Exp = NMES to bilateral quadriceps in addition to standard care, intense enough to cause visible and palpable contraction, 1 hour daily	Duration of MV Ventilator-free days at day 28* MRC-SS (on day 2, 3, 4, 5, 6, 7, 14, 21, 28 of ICU admission)
			n = 40 Age = 57.57 ± 6.80 67.5% male sex	Con = no NMES, no description of standard care	
Akar (Akar et al., 2017)	Turkey RCT	COPD patients MV > 24 hours	n = 10 Age = 70.00 ± 12.28	Exp 1 = NMES, active, active-assisted or passive ROM exercises to deltoid and quadriceps to deltoid and quadriceps, NMES intense enough to cause visible and	ICU LOS* Days where mobility milestones achieved

			40% male sex	palpable contraction, 5 days per week for a total of 20 sessions, session duration not reported	Deltoid and quadriceps strength before and after intervention
			n = 10 Age = 62.75 ± 6.80 60% male sex	Exp 2 = NMES to deltoid and quadriceps, NMES intense enough to cause visible and palpable contraction, 5 days per week for a total of 20 sessions, session duration not reported	
			n = 10 Age = 68.00 ± 17.77 50% male sex	Con = active, active-assisted, or passive ROM exercises to deltoid and quadriceps, 5 days per week for a total of 20 sessions, session duration not reported	
Amundadottir (Amundadottir et al., 2019)	Iceland RCT	Aged 18 – 80, mechanically ventilated for > 48 hours, able to cooperate with intervention and assessment,	n = 29 Age = 62 (50-70) 65.5% male sex	Exp = two sessions of progressive upright mobilisation daily, timed with sedation break, begun after 48 hours of MV, until ICU discharge, session duration not reported	MV duration* ICU LOS* Hospital LOS* Hospital mortality* Short Form 36 version 2 (pre-ICU, ICU discharge, hospital discharge, and at 3-, 6-* and 12-month)
			n = 21	Con = one session of passive to active exercises, functional exercises daily, not timed with sedation break, begun after	

		previously ambulant independently	Age = 64 (58-74) 66.7% male sex	96 hours of MV, until ICU discharge, session duration not reported	Six-Minute Walk Test (3-, 6- and 12-month) MRC-SS (ICU discharge*, hospital discharge*, 3-, 6- and 12-month after ICU discharge) Modified Barthel Index (pre-ICU, ICU discharge*, hospital discharge*, 3-, 6-* and 12-month)
Bianchi (Bianchi et al., 2018)	Brazil RCT	Adults who required MV for at least 48 hours, expected to stay in ICU for one week	n = 18 Age = 52.3 ± 22.7 27.8% male sex	Exp = Passive exercise on a cycle ergometer, 20 minutes daily for 7 days or until extubation; in addition to conventional physical therapy	MV duration* ICU LOS* Hospital LOS*
			n = 14 Age = 56.1 ± 23.0 42.9% male sex	Con = conventional physical therapy, which included respiratory therapy, upper and lower extremity proprioceptive neuromuscular facilitation exercises, 30 minutes twice daily	

Bissett (Bissett et al., 2016)	Australia RCT	Invasively mechanically ventilated for 7 days or more, successfully weaned from MV (> 48 hours)	n = 34 Age = 59 ± 16 71% male sex	Exp = inspiratory muscle training using threshold inspiratory trainer, 6 breaths per set, 5 sets daily on weekdays; in addition to standard care	MV duration ICU LOS* Hospital Mortality* Maximal inspiratory pressure (on enrolment and at the end of 2-week intervention) Short Form 36 version 2 (on enrolment and at the end of 2-week intervention) The EQ-5D three-level version (on enrolment and at the end of 2-week intervention) Acute care index of function (on enrolment and at the end of 2-week intervention)
			n = 36 Age = 59 ± 13 58% male sex	Con = standard care involves minimal sedation and proactive mobilisation, Including assisted mobilisation, secretion clearance treatments, upper and lower limb exercises, 1-2 sessions per day, session duration not reported	
Brummel (Brummel et al., 2014)	United States RCT	Adults with respiratory failure or shock	n = 22 Age = 62 (48-67) 59% male sex	Exp 1 = early physical therapy using an ICU mobility protocol, individually tailored to progress patients from passive ROM exercises to ambulation, once daily (median duration 15 minutes if delivered by nurses, 23 minutes if delivered by physical therapists)	ICU LOS* Hospital LOS* ICU mortality* Hospital mortality*

			n = 22 Age = 60 (51-69) 36% male sex	Con = standard care, physical therapy as ordered by physicians (typically 1-2 sessions per week), session duration not reported	Katz Index of Independence in Activities of Daily Living (on enrolment, hospital discharge, and 3-month) Timed up and Go test (hospital discharge and 3-month) EQ-5D (hospital discharge, 3-month) Ventilator-free days to day 30
			n = 43 Age = 62 (54-69) 65% male sex	Exp 2^ = once daily early physical therapy using an ICU mobility protocol, individually tailored to progress patients from passive ROM exercises to ambulation; Interdisciplinary cognitive therapy protocol delivered twice daily	
Burtin (Burtin et al., 2009)	Belgium RCT	Adults with expected prolonged stay in the ICU (≥ 7 more days)	n =31 Age = 56 ± 16 71% male sex	Exp = cycling exercise session, 5 days a week, 20 minutes per session, individually adjusted intensity; in addition to usual care	ICU LOS* Hospital LOS* Quadriceps force (ICU discharge, hospital discharge) Handgrip strength (ICU discharge*, hospital discharge*) Berg balance scale: sit to stand item (ICU discharge, hospital discharge)
			n = 36 Age = 57 ± 17	Con = standard care involves standardized mobilisation session of upper and lower extremities 5 days a week, plus respiratory physiotherapy adjusted to individual needs, session duration not reported	

			72% male sex		Short Form 36 version 2 (hospital discharge) 1-year mortality Six-Minute Walk Test (hospital discharge)*
Cader (Cader et al., 2010)	Brazil RCT	Older adults age ≥ 70, who required MV for at least 48 hours for type 1 respiratory failure, with some inspiratory muscle weakness	n = 21 Age = 83 ± 3 43% male sex	Exp = inspiratory muscle training using threshold inspiratory trainer, 5 minutes twice daily, 7 days per week; in addition to standard care	Maximal inspiratory pressure (once daily) ICU mortality*
			n = 20 Age = 82 ± 7 50% male sex	Con = regular physiotherapy including passive to active-assisted mobilisation of limbs, positioning, chest physiotherapy as indicated, frequency and session duration not reported	
Caruso (Caruso et al., 2005)	Brazil RCT	Adults with expected prolonged stay in the ICU (> 72 hours)	n = 12 Age = 67 ± 10 67% male sex	Exp = inspiratory muscle training using increasing trigger threshold, increments based on maximal inspiratory pressure, 30 minutes twice daily, until weaned from MV	MV duration* Maximal inspiratory pressure (baseline, after extubation)

			n = 13 Age = 66 ± 17 69% male sex	Con = no inspiratory muscle training, no description of standard care	
Chang (Chang et al., 2011)	Taiwan RCT	Adults who required MV for at leave 72 hours, and can be transferred from bed to chair by 2 nurses without a mechanical lifting machine	n = 18 Age = 65.3 ± 13.1 56% male sex	Exp = transfer from bed to an armchair for 30 – 120 minutes, based on patient tolerance, transfer performed by two ICU nurses, therapy performed at least once per day in 15 participants	Maximal inspiratory pressure (baseline, 30 minutes after intervention) MV duration* ICU LOS*
			n = 16 Age = 61.8 ± 22.6 69% male sex	Con = lying between supine and semi-recumbent, no physical therapy during the study period	
	Brazil RCT	Adults who required MV for at least 48 hours,	n = 45 Age = 64 ± 17	Exp = inspiratory muscle training using threshold inspiratory trainer, 5 sets of 10 breaths, twice daily, 7 days a week; in addition to standard care	Maximal inspiratory pressure (baseline, after extubation)

Condessa (Condessa et al., 2013)		haemodynamically stable and ready for weaning	51% male sex		Maximal expiratory pressure (baseline, after extubation) MV duration* ICU mortality*
			n = 47 Age = 65 ± 15 60% male sex	Con = standard physiotherapy intervention including passive and active ROM, chest physiotherapy, frequency, and session duration not reported	
Coutinho (Coutinho et al., 2016)	Brazil RCT	Adults mechanically ventilated for ≥ 24 hours and ≤ 48 hours	n = 14 Age = 61.8 ± 22.6 56% male sex	Exp = passive cycle ergometer exercises, 20 cycles per minute for 20 minutes, frequency not reported; in addition to conventional physiotherapy, 30 minutes per session, upper and lower extremity proprioceptive neuromuscular facilitation exercises, and respiratory physiotherapy, frequency not reported	MV duration* ICU LOS* Maximal inspiratory pressure (pre and post intervention) Hospital LOS* Hospital mortality*
			n = 11 Age = 55.2 ± 29.1 43% male sex	Con = conventional physiotherapy only, 30 minutes per session, upper and lower extremity proprioceptive neuromuscular facilitation exercises and respiratory physiotherapy, frequency not reported	

Dall'Acqua (Dall' Acqua et al., 2017)	Brazil RCT	Adults who have been hospitalised for ≤15 days and received > 24 h MV	n = 11 Age = 56 ± 13 64% male sex	Exp = NMES of the chest and abdominal muscles, intense enough to cause visible and palpable contraction, 30 minutes daily for 7 days or until extubation; in addition to conventional therapy, 30 minutes daily, tailored to the patient's ability	MV duration* ICU LOS* ICU mortality* Hospital LOS Hospital Mortality*
			n = 14 Age = 61 ± 15 64% male sex	Con = sham NMES of the chest and abdominal muscles, 30 minutes daily for 7 days or until extubation; in addition to conventional therapy, 30 minutes daily, tailored to the patient's ability	
Dantas (Dantas et al., 2012)	Brazil RCT	Adults on MV, with adequate cardiovascular reserve	n = 14 Age = 59.07 ± 15.22 50% male sex	Exp = systematic early mobilisation protocol, twice daily, 7 days per week, duration variable depending on the stage of the protocol	MV duration ICU LOS Hospital LOS ICU mortality* MRC-SS (enrolment, ICU discharge*) Maximal inspiratory pressure (enrolment, ICU discharge) Maximal expiratory pressure (enrolment, ICU discharge)
			n = 14 Age = 50.43 ± 20.45	Con = conventional physical therapy consists of passive mobilisation of four limbs 5 times per week, active-assisted exercises as able, session duration not reported	

			29% male sex		
Denehy (Denehy, Skinner, et al., 2013)	Australia RCT	Adults with ICU LOS > 5 days	n = 74 Age = 61.4 ± 15.9 58.1% male sex	Exp = active functional rehabilitation, intensity target modified Borg scale 3-5, 15 minutes daily for ventilated patients, 15 minutes twice daily for weaned patients	MV duration* ICU LOS* Hosp LOS* ICU mortality* Hospital mortality* Physical function in the ICU test (on enrolment and ICU discharge) Assessment of Quality of Life (on enrolment; 3-, 6-, and 12-month) Short Form 36 version 2 (on enrolment; 3-, 6-*, and 12-months after ICU discharge) Six-minute walk test (on ICU discharge*; discharge home*; 3-, 6-*, and 12-month) Timed up and Go test (on ICU discharge; discharge home; 3-, 6-, and 12-months)
			n = 76 Age = 60.1 ± 15.58 68.4% male sex	Con = standard care, physiotherapists provided both respiratory and mobility management based on individual patient assessment, available 7 days per week, session duration not reported	

					28-day mortality 6-month mortality* 12-month mortality
Dong (Dong et al., 2014)	China RCT	Adults mechanically ventilated > 48 hours and < 72 hours	n = 30 Age = 55.3 ± 16.1 70% male sex	Exp = twice daily rehabilitation, lifting heading up actively, sit on the edge of the bed, standing and walking, until return to the previous level of function or discharge, session duration not reported	MV duration* Days to first SOOB ICU LOS* ICU mortality* Hospital mortality*
			n = 30 Age = 55.5 ± 16.2 67% male sex	Con = no description of standard care	
Dong (Dong et al., 2016)	China RCT	Post CABG MV > 72 hours	n = 53 Age = 62.6 ± 12.8 38% male sex	Exp = progressive mobility protocol twice daily, lifting the head, sitting up, sit on the edge of the bed, sitting in a chair, standing and walking along the bed, session duration not reported	MV duration* ICU LOS* Hospital LOS* Hospital mortality*
			n = 53	Con = rehabilitation performed after ICU discharge by family	

			Age = 60.2 ± 15.1 42% male sex		
dos Santos (dos Santos et al., 2020)	Brazil RCT	Age ≥ 18, mechanically ventilated for less than 72 hours	n = 13 Age = 55.3 12.7 69.2% male sex	Exp 1 = Active exercise program applied by two physical therapists, initiated when awake, progressing from active-assisted to active and resisted exercises for upper and lower limbs, 3 sets of 10 repetitions, 55 minutes session duration until ICU discharge, an average total of 9.1 sessions per participant	MV duration ICU LOS* Mortality
			n = 11 Age = 50.2 12.8 66.7% male sex	Exp 2 = NMES of bilateral quadriceps, intense enough to cause visible or palpable contraction. 55 minutes twice daily until ICU discharge, an average total of 11.7 sessions per participant	
			n = 12 Age = 55.6 10.8	Exp 3 = NMES of bilateral quadriceps and active exercises in lower limbs were applied simultaneously in a synchronised manner, 55 minutes session duration twice	

			66.7% male sex	daily until ICU discharge, an average total of 10.3 sessions per participant	
			n = 15 Age = 51.8 73.3% male sex	Con = usual physical therapy consisting of in-bed exercises such as passive mobilisation, positioning and stretching, 55 minutes session duration twice daily until ICU discharge, the actual total number of sessions not reported	
Eggmann (Eggmann et al., 2018)	Switzerland RCT	Adults expected to stay on MV ≥ 72 hours, previously independent	n = 58 Age = 65 ± 15 62% male sex	Exp = endurance and resistance training program combined with early mobilisation, up to 3 sessions a day. Endurance training consisted of passive, machine-assisted, or active cycling in bed, 20 - 30 minutes per session. Resistance training included weights or resistance from the therapist, 8-12 repetitions with 2-5 sets. Early mobilisation progressed from in-bed exercises to ambulation.	MV duration* ICU LOS* Hospital LOS* ICU mortality* Hospital mortality* MRC-SS (ICU discharge)* Achieved ICU mobility (ICU discharge) FIM (ICU discharge, hospital discharge)* Handgrip strength (ICU discharge) Quadriceps force (ICU discharge) Limitations in ROM (ICU discharge) Six-minute walk test (hospital discharge)
			n = 57 Age = 63 ± 15 72% male sex	Con = standard physiotherapy included early mobilisation, respiratory therapy, and passive or active exercises. Initiated by the physiotherapist and individually tailored. Once-daily during the week, on the weekend if deemed necessary, session duration not reported	

					Timed up and go test (hospital discharge) Short Form 36 (6-month)* 6-month mortality*
Elbouhy (Elbouhy et al., 2014)	Egypt CCT	Adults with acute exacerbation of COPD, mechanically ventilated, and difficult weaning	n = 20 Age = 61.07 ± 12.4 80% male sex	Exp = inspiratory muscle training using increasing trigger threshold, increments based on maximal inspiratory pressure, 30 minutes twice daily, for 5 days or until weaned from MV	MV duration* ICU LOS* Hospital LOS*
			n = 20 Age = 64.33 ± 8.29 85% male sex	Con = standard medical care including physiotherapy (chest percussion), nil other intervention reported	
Fischer (Fischer et al., 2016)	Austria RCT	Adults post cardiac valve reconstruction and/or replacement,	n = 27 Age = 63.3 ± 15.5 67% male sex	Exp = NMES of bilateral quadriceps, intense enough to cause visible and palpable contraction. 30 minutes twice daily, up to 14 days postoperatively	MV duration* ICU LOS* Hospital LOS* ICU mortality*

		expected stay in ICU ≥ 48 hours	n = 27 Age = 69.7 ± 13.1 74% male sex	Con = Sham NMES, placement of electrodes without electricity, nil other intervention reported	Hospital mortality* MRC mean score (daily until ICU discharge) Quadriceps strength (daily until ICU discharge) Grip strength (daily until ICU discharge) Average mobility level (ICU discharge, Hospital discharge) Functional Independence Measure (hospital discharge) Timed Up and Go Test (hospital discharge) Short Form 12 (hospital discharge)
Fontes Cerqueira (Fontes	Brazil RCT	Adults post cardiothoracic surgery, age ≤ 75	n = 26 Age = 41.8 ± 13.7 69% male sex	Exp = NMES of bilateral quadriceps and gastrocnemius, intense enough to cause visible or palpable contraction. 60 minutes twice daily, every day up to 5 days postoperatively; in addition to usual physiotherapy	Six-Minute Walk Test (postoperative day 5) 10 metre Walking Speed Test (postoperative day 5)

Cerqueira et al., 2018)			n = 33 Age = 42.21 ± 14.36 70% male sex	Con = usual physiotherapy twice a day, session duration not reported	MRC-SS (preoperative, postoperative day 3 and 5) Functional Independence Measure (preoperative, postoperative day 3 and 5) Nottingham Health Profile (preoperative, postoperative day 3 and 5) ICU LOS*
Fossat (Fossat et al., 2018)	France RCT	Adults in ICU < 72 hours, expected to stay for at least further 48 hours, previously independent	n = 158 Age = 65 ± 13 65% male sex	Exp = leg cycling exercise 15 minutes each weekday; NMES to bilateral quadriceps 50 minutes each weekday	MV duration* Katz index of independence (enrolment, ICU discharge*) ICU mortality* Hospital mortality* ICU mobility scale (ICU discharge) MRC-SS (ICU discharge)* Barthel index (6-month)* Ventilator-free days at day 28* Short-Form 36 (6-month)* Mortality (28 days, 6 months*)
			n = 154 Age = 66 ± 15 64% male sex	Con = standardized early rehabilitation each weekday, tailored to the individual patient, progress from passive ROM to ambulation, session duration not reported	

Gama Lordello (Gama Lordello et al., 2020)	Brazil RCT	≥ 18 years of age admitted for cardiac surgery via median sternotomy with extracorporeal circulation	n = 111 Age = 57.2 13.2 59.5% male sex	Exp = upper and lower limb exercise using the cycle ergometer, duration 10 minutes, twice daily until ICU discharge	MV duration* ICU LOS* Hospital LOS*
			n = 117 Age = 58.2 12.9 57.3% male sex	Con = Active open kinetic chain exercises for upper and lower limbs, 10 repetitions per movement, duration 10 minutes, twice daily until ICU discharge	
Hanekom (Hanekom et al., 2012)	South Africa CCT	≥ 16 years of age and admitted to ICU	n = 96 Age = 52.07 ± 18.51 61% male sex	Exp = evidence-based protocol-care delivered by research therapists, who were available 12 hours per day during the week, 8 hours on the weekends plus an on-call service, average 1.38 sessions per participant per day, average session duration 22 minutes.	MV duration* Barthel Index (ICU discharge) ICU LOS* Hospital LOS* Hospital mortality
			n = 97 Age = 50.18 ± 17.86	Con = therapy delivered by a single physiotherapist, with limited time resources, average 0.57 sessions per participant per day, average session duration 23 minutes.	

			62% male sex		
Hickmann (Hickmann et al., 2018)	Belgium RCT	Adults admitted with septic shock admitted to ICU < 72 hours	n = 9 Age = 59 ± 19 56% male sex	Exp = passive/active cycling in 30 minutes, followed by passive/active limb mobilisation, twice daily, 7 days per week	ICU LOS* MV duration* ICU mortality* 28-day mortality
			n = 10 Age = 57 ± 20 60% male sex	Con = passive/active limb mobilisation, 5 days per week, session duration not reported	
Hodgson (Hodgson et al., 2016)	Australia RCT	Adults invasively ventilated and expected to be ventilated the day after tomorrow,	n = 29 Age = 64 ± 12 62% male sex	Exp = early goal-directed mobilisation driven by algorithm includes walking, standing, sitting, and active bed exercises. 15-60 minutes daily, session duration dependent on the functional level	MV duration* ICU mobility scale (Daily in ICU) ICU LOS* ICU mortality* Incidence of ICU-AW (ICU discharge)

		independent mobility before admission	n = 21 Age = 53 ± 15 59% male sex	Con = standard practice delivered by a dedicated physiotherapist includes daily assessment and treatment as appropriate, session duration not reported	Physical Function in the ICU Test Scored (ICU discharge)* Functional Status Score for the Intensive Care Unit (ICU discharge) MRC-SS (ICU discharge)* Hospital LOS* Hospital mortality* Ventilator-free days at day 28* ICU free days at day 28 Total inpatient stay Independent activities of daily living (6-month)* ED-5D (6-month)* 6-month mortality*
Hodgson (Hodgson et al., 2020)	Australia RCT	Adults in ICU, received extracorporeal membrane oxygenation	n = 10 Age = 49.3 ± 13.4 80% male sex	Exp = early goal-directed physiotherapy, a progression of exercises aimed at exercising at the highest functional level for the longest duration, intensity target of 3 to 5 on the modified Borg Scale of Perceived Exertion, up to 60 minutes per day for 7 days	MV duration ICU LOS Hospital LOS ICU mortality* Hospital mortality*

		(ECMO) for at least 24 hours, independent mobility before admission	n = 10 Age = 50.6 ± 17.1 80% male sex	Con = non-protocolised assessment of strength, ROM, and ability to participate in rehabilitation and early mobilisation, no specified dosage, treatment at the discretion of treating clinicians, duration and frequency not reported	MRC-SS (days 7, 10, 20) Katz Index of Independence in Activities of Daily Living (days 7, 10, 20 and at hospital discharge*) EQ5D-5L (90-day) Barthel Index (90-day) Lawton Instrumental Activities of Daily Living (90-day)
Karatzanos (Karatzanos et al., 2012)	Post hoc analysis of data from Routsi (Routsi et al., 2010)	Same as Routsi (Routsi et al., 2010)	Same as Routsi (Routsi et al., 2010)	Exp = Same as Routsi (Routsi et al., 2010)	Grip strength (first awakening) MRC-SS (first awakening)*
			Same as Routsi (Routsi et al., 2010)	Con = Same as Routsi (Routsi et al., 2010)	

Kayambu (Kayambu et al., 2015)	Australia RCT	Adults mechanically ventilated ≥ 48 hours and diagnosed with sepsis	n = 26 Age = 62.5 (30-83) 84% male sex	Exp = individualised early targeted physical rehabilitation program including NMES, ROM exercises, sitting out of bed, transfers, and ambulation. 30 minutes per session, 1-2 times daily until discharge from ICU	MV duration* ICU LOS* ICU mortality* Physical Function in the ICU Test Scored (ICU discharge)* MRC-SS (ICU discharge)* Hospital Anxiety and Depression Scale (ICU discharge) Hospital LOS* Ventilator-free days Acute care index of function (6-month)* Short Form 36 (6-month)* 90-day mortality 6-month mortality*
			n = 24 Age = 65.5 (37-85) 80% male sex	Con = standard ICU care including physiotherapy delivered by ICU physiotherapist, frequency and session duration reported in graph format only	
Kho (Kho et al., 2015)	United States Pilot RCT	Adults mechanically ventilated for at least 1 day and expected to	n = 16 Age = 54 ± 16 44% male sex	Exp = NMES to bilateral lower limb muscles (vastus medialis, vastus lateralis, tibialis anterior, and gastrocnemius), 1 hour daily, intense enough to cause visible and palpable contraction; in addition to standard	MV duration* MRC-SS (first awakening*, ICU discharge*, hospital discharge*) MRC score of quadriceps, tibialis anterior, and gastrocnemius (score of

		require at least 2 more days in ICU		rehabilitation by physical and occupational therapists, available daily, session duration not reported	30) (first awakening, ICU discharge, hospital discharge) Dynamometry quadriceps, tibialis anterior, and gastrocnemius (first awakening, ICU discharge, hospital discharge) Incidence of ICU-AW (first awakening, ICU discharge, hospital discharge) Maximal inspiratory pressure (first awakening, ICU discharge, hospital discharge) FSS-ICU (first awakening, ICU discharge, hospital discharge) Maximum walked distance (ICU discharge, hospital discharge)* Number of independent ADLs (first awakening, ICU discharge, hospital discharge) ICU LOS*
			n = 18 Age = 56 ± 18 50% male sex	Con = sham NMES to bilateral lower limb muscles, 1 hour daily, placement of electrodes without electricity; in addition to standard rehabilitation by physical and occupational therapists, available daily, session duration not reported	

					ICU mortality* Hospital LOS* Hospital mortality*
Kho (Kho et al., 2019)	Canada RCT	adults (≥18 years old) within the first 4 days of MV and first 7 days of ICU, and able to ambulate independently before hospital admission	n = 36 Age = 60.0 16.8 75% male sex	Exp = passive, active-assisted or active cycling 30 minutes daily until ICU discharge or 28 days, whichever occurred first, median duration per session 30 (30 – 31) minutes, over 3 (2 – 6) sessions; plus routine physical therapy interventions, median duration per session 20 (7 – 31) minutes, over 5 (3 – 9) sessions	MRC-SS (first awakening, ICU discharge, hospital discharge)* Physical Function in the ICU Test Scored (hospital discharge)* Hospital mortality MV duration* ICU LOS* Hospital LOS* ICU mortality* Hospital mortality* Katz Index of Independence in Activities of Daily Living (ICU discharge, hospital discharge)*
			n = 30 Age = 63.6 17.1 43.3% male sex	Con = routine physical therapy interventions available 5 days per week, including activities to maintain or increase limb range of motion and strength, in and out of bed mobility, and ambulation, median duration per session 23 (17 – 30), over 5 (3 – 9) sessions	
	Greece RCT	Adults mechanically ventilated for ≥ 96	n = 38 Age = 64 ± 12.4	Exp = NMES to bilateral quadriceps, intense enough to cause visible contraction, 1 hour daily for 10 days; in addition to conventional and respiratory physiotherapy 45	MRC-SS (4^{th} and 14^{th} day) MV duration ICU LOS*

Koutsioumpa (Koutsioumpa et al., 2018)		hours, ICU LOS ≥ 96 hours	68% male sex	minutes daily. Conventional physiotherapy include passive, active ROM, resisted exercises, and functional mobilisation	ICU mortality* 28-day mortality 1-year mortality
			n = 42 Age = 66 ± 13.1 81% male sex	Con = Conventional and respiratory physiotherapy 45 minutes daily. Conventional physiotherapy include passive, active ROM, resisted exercises, and functional mobilisation	
Kurtoglu (Kurtoğlu et al., 2015)	Turkey RCT	Adult patients with COPD requiring MV	n = 15 Age = 69.93 ± 11.0 93% male sex	Exp = NMES to auxiliary respiratory muscles (pectoral major, trapezius, and latissimus dorsi), 20 minutes daily for 10 days; in addition to upper limb passive ROM exercises, 10 minutes daily for 30 days	MV duration* Short Form 36 (1st day and 30th day) Functional Independence Measure (1st day and 30th day)
			n = 15 Age = 66.06 ± 13.86 93% male sex	Con = upper limb passive ROM exercises, 10 minutes daily for 30 days	
Leite (Leite et al., 2018)	Brazil CCT	Adults on mechanical	n = 17	Exp 1 = NMES of the diaphragm, intense enough to cause visible contraction, 45 minutes daily; in addition to	MRC-SS (first awakening*, ICU discharge*)

		ventilated ≥ 24 hours	Age = 41.3 ± 24.26 88.2% male sex	conventional physiotherapy once daily, session duration not reported	Maximal inspiratory pressure (on enrolment, ICU discharge) Barthel Index (ICU discharge)* Functional Status Score for the ICU (ICU discharge) MV duration* ICU LOS* Hospital LOS*
			n = 24 Age = 48.8 ± 19.69 75% male sex	Exp 2 = NMES of bilateral quadriceps, intense enough to cause visible contraction, 45 minutes daily; in addition to conventional physiotherapy once daily, session duration not reported	
			n = 26 Age = 42.4 ± 12.74 76.9% male sex	Con = conventional physiotherapy twice daily in ICU, gross motor and respiratory therapy, session duration not reported	
Machado (Machado et al., 2017)	Brazil RCT	Adults on MV, with Richmond Agitation Sedation Score of -2 and	n = 22 Age = 44.64 ± 19.23 72% male sex	Exp = Passive exercise on a cycle ergometer, 20 minutes daily 5 days per week, until discharge from ICU; in addition to conventional physiotherapy	MV duration* MRC-SS (first awakening*, ICU discharge*) ICU LOS* Hospital LOS*

		haemodynamically stable	n = 16 Age = 45.13 ± 18.91 43% male sex	Con = conventional physiotherapy, which included respiratory therapy, passive and active ROM exercises, 30 minutes twice daily, 7 days per week	ICU mortality*
Maffei (Maffei et al., 2017)	France RCT	Adults liver transplant recipients	n = 20 Age = 52 ± 9 80% male sex	Exp = rehabilitation protocol applied by physiotherapists, progressed patients from ROM exercises to ambulation, twice daily, 5 days per week, duration based on the functional level	MV duration* ICU LOS* Hospital LOS*
			n = 20 Age = 54 ± 9 75% male sex	Con = rehabilitation carried out under medical prescription for physiotherapist, 10-15 minutes daily, 5 days per week	
Martin (Martin et al., 2011)	United States RCT	Adults in ICU who have failed to wean from MV	n = 35 Age = 65.6 ± 11.7 46% male sex	Exp = inspiratory muscle training using threshold inspiratory trainer, 4 sets of 6-10 breaths daily on weekdays	Maximal inspiratory pressure (enrolment, every Monday, every spontaneous breathing trial) ICU mortality*

			n = 34 Age = 65.1 ± 10.7 44% male sex	Con = sham inspiratory muscle training with threshold modified threshold inspiratory training to provide minimal resistance, 4 sets of 6-10 breaths daily on weekdays	
McCaughey (McCaughey et al., 2019)	Australia RCT	Age ≥ 18, critically ill, mechanically ventilated	n = 10 Age = 56.5 ± 18.50 70% male sex	Exp = NMES of abdominal muscles during expiration, intense enough to cause a strong visible contraction, 30 minutes twice daily, 5 days per week until discharge from ICU, routine physiotherapy intervention not specified	MV duration ICU LOS
			n = 10 Age = 61.0 ± 17.25 50% male sex	Con = sham NMES of abdominal muscles with low current, with possible sensation but without muscle contraction, 30 minutes twice daily, 5 days per week until discharge from ICU, routine physiotherapy intervention not specified	
	United Kingdom RCT	Adults who have been invasively ventilated for at	n = 52 Age = 62 (46-68)	Exp = rehabilitation delivered by specialist critical care rehab team, included standardised comprehensive assessment, individually tailored program, weekly goal setting, and	MV duration* ICU LOS* ICU mortality*

McWilliams (McWilliams et al., 2018)		least 4 days and expected to continue for at least 24 hours	60% male sex	enhanced handover when discharged from ICU. Average session duration 38.3 minutes	MRC-SS (ICU discharge, hospital discharge)* Grip Strength (ICU discharge, hospital discharge) Hospital LOS* Hospital mortality* 3-month mortality Barthel index (ICU discharge*, hospital discharge*, 3- and 12-month) Short Form 36 (3- and 12-month)
			n = 50 Age = 61 (47-70) 62% male sex	Con = physiotherapy assessment within 24 hours of admission, daily physiotherapy sessions on weekdays. Average session duration of 35.4 minutes. Rehabilitation is based on the clinical reasoning of individual therapists.	
Morris (Morris et al., 2008)	United States CCT	Adults within 48 hours of intubation and 72 hours of admission to medical ICU	n = 165 Age = 54.0 ± 16.8 57% male sex	Exp = Four-level protocol, therapy based on patients' level of strength, progressed from passive ROM exercises to active transfer out of bed, 7 days per week, session duration not reported	MV duration* ICU LOS* Hospital LOS* Hospital mortality*
			n = 165 Age = 55.4 ± 16.8	Con = passive ROM exercises daily and position changes second hourly was delivered by the bedside nurse, physical therapy to ventilated patients was permitted, frequency and session duration not reported	

			54% male sex		
Morris (Morris et al., 2016)	United States RCT	Adults requiring invasive or non-invasive MV with a PaO2/FiO2 ratio < 300	n = 150 Age = 55 ± 17 44% male sex	Exp = standardised rehabilitation therapy progressing from bed mobility to ambulation, 3 times daily, 7 days per week until hospital discharge, session duration not reported	ICU LOS* Hospital mortality* Short Performance Physical Battery (ICU discharge*, hospital discharge*, 2-, 4-, and 6-month*) Handgrip strength (ICU discharge*, hospital discharge*, 2-, 4-, and 6-month) Composite value of muscle strength (ICU discharge, hospital discharge, 2-, 4-, and 6-month) Hospital LOS* Short Form 36 (hospital discharge, 2-, 4-, and 6-month*) Ventilator-free days at day 28* ICU free days to 28 days Hospital free days to 28 days 6-month mortality*
			n = 150 Age = 58 ± 14 45% male sex	Con = physical therapy could be ordered as part of routine care Monday to Friday	

Moss (Moss et al., 2016)	United States RCT	Adults requiring MV > 4 days	n = 59 Age = 56 ± 14 61% male sex	Exp = breathing exercises, ROM exercises, muscle strengthening, core strength, and functional mobility retraining guided by protocol. Average session duration 39.4 minutes, delivered daily up to 28 days, or until able to walk unassisted	MV duration* ICU LOS* Hosp LOS* ICU mortality* Hospital mortality* CS-PFP-10 (1, 3- and 6-month*) Short Form 36 (1-, 3-, and 6-month*) All-cause mortality at day 28 Five times sit to stand test (1-, 3- and 6-month) Timed Up and Go Test (1, 3- and 6-month) Berg balance test (1, 3- and 6-month) 6-month mortality*
			n = 61 Age = 49 ± 15 57% male sex	Con = breathing exercises, ROM exercises, muscle strengthening, core strength, and functional mobility retraining. Average session duration 21.8 minutes, 3 times per week up to 28 days or hospital discharge	
Nakamura (Nakamura et al., 2019)	Japan RCT	ICU patients aged ≥ 20 with expected ICU LOS of more than 3 days	n = 21 Age = 76.6 11.0 66.7% male sex	Exp = physical therapist applied belt-electrode EMS applied to the abdomen, quadriceps, and ankles, stimulation intense enough to trigger muscle contractions between the belts, 20 minutes per session once per day; in additional routine rehabilitation by nurses which including ROM exercises,	MV duration* ICU LOS* Barthel Index (hospital discharge)* Hospital LOS* 28-day mortality

				mobilisation, and ambulation, 5-20 minutes per session 3 times per day	
			n = 16 Age = 74.6 68.8 % male sex	Con = ROM exercise, kicking stability ball, standing and ambulation exercise by physical therapists, 20 minutes per session once per day; in addition to routine rehabilitation by nurses, 5-20 minutes per session 3 times per day	
Nickels (M. R. Nickels et al., 2020)	Australia RCT	Participants in a mixed medical and surgical ICU, MV > 48 hours, expected to stay in ICU for another 48 hours or more, recruited within 96 hours of ICU admission	n = 36 Age = 56 18 64% male sex	Exp = in bed leg cycling, progressed from passive to active-assisted and then resisted, 30 minutes once daily (up to 6 days per week), in addition to routine physiotherapy intervention	MV duration* ICU LOS* Hospital LOS* ICU morality* Hospital mortality* MRC-SS (ICU discharge*, 1-week post ICU discharge) Handgrip strength (ICU discharge, 1-week post ICU discharge) Functional Status Score for the ICU (ICU discharge*, 1-week post ICU discharge)
			n = 36 Age = 57 16 72% male sex	Con = routine physiotherapy interventions including daily assessment of physical and respiratory status and treatment, physical treatments were directed to functional goals including sitting, standing, and mobilising	

					Six-Minute Walk Test (1-week post ICU discharge) EQ-5D (6-month)*
Nydahl (Nydahl et al., 2019)	Germany Stepped-wedge, cluster RCT	Aged ≥ 18, order for mobilisation present	n = 120 Age = 74 (61 – 81) 54.1% male sex	Exp = during the intervention phase, training in study mobilisation protocol, inter-professional team assessing the feasibility of mobilisation using a standardised protocol, identification of mobility goals, mobilisation activities delivered by physiotherapists and nurses	ICU mortality* Hospital mortality* Ventilator-free days at day 28*
			n = 152 Age = 70 (58.0 – 79.7) 52.3% male sex	Con = during the control phase, no training in study mobilisation protocol, mobility practice based on clinicians' individual decision	
Pandey (Pandey et al., 2013)	India RCT	Adults admitted to ICU, previously independent with transfer to a chair	n = 59 Age = 56 ± 14 61% male sex	Exp = NMES to bilateral quadriceps and tibialis anterior, intense enough to cause visible contraction, 30 minutes to each muscle group, daily until ICU discharge; in addition to routine physiotherapy, which included passive and active-assisted movement, chest physiotherapy	Manual muscle test score for knee extensors and ankle dorsiflexors (ICU discharge)

			n = 59 Age = 56 ± 14 61% male sex	Con = routine physiotherapy included passive and active-assisted movement, chest physiotherapy, frequency, and session duration not reported	
Patman (Patman et al., 2001)	Australia RCT	Adults post elective or semi-urgent cardiac surgery	n = 101 Age = 62.8 ± 12.2 80% male sex	Exp = physiotherapy interventions as required, including positioning, manual hyperinflation, endotracheal suctioning, thoracic expansion exercises, and upper limb exercises while intubated, frequency and session duration not reported	MV duration* ICU LOS* Hospital LOS*
			n = 109 Age = 63.9 ± 14.4 71% male sex	Con = no physiotherapy whilst intubated	
Routsi (Routsi et al., 2010)	Greece RCT	Adults 24 to 48 hours after ICU admission, with an	n = 68 Age = 61 ± 19	Exp = NMES to bilateral lower limb muscles (vastus medialis, vastus lateralis, peroneus longus), intense enough to cause visible and palpable contraction, 55 minutes daily, until discharge from ICU	MV duration* MRC-SS (on awakening) ICU LOS* ICU mortality*

		APACHE II score of 13 or more	68% male sex		
			n = 72 Age = 58 ± 18 68% male sex	Con = no sham NMES, nil other intervention reported	
Sarfati (Sarfati et al., 2018)	France RCT	Adults within a cardiothoracic ICU, mechanically ventilated > 3 days	n = 72 Age = 62 (52-73) 64% male sex	Exp = tilted to 60 degrees on an electrical tilt-table for 1 hour daily; in addition to standardised rehabilitation therapy, which consisted of passive, active ROM exercises in bed, and sits out of bed at least 2 hours daily, ceased when patient able to stand up with help or discharged from ICU	MV duration* ICU LOS* ICU mortality* MRC-SS (ICU discharge*, hospital discharge*) Hospital LOS* Hospital mortality*
			n = 73 Age = 67 (54-75) 71% male sex	Con = standardised rehabilitation therapy consisted of passive, active exercises in bed and sit out of bed at least 2 hours daily, ceased when the patient can stand up with help or was discharged from ICU	

Savci (Savci et al., 2011)	Turkey RCT	Patients post coronary artery bypass grafting for coronary artery disease	n = 22 Age = 62.82 ± 8.69 86% male sex	Exp = inspiratory muscle training using threshold inspiratory trainer, 30 minutes twice daily, for 10 days; in addition to standard care	MV duration* ICU LOS* Hospital LOS* Maximal inspiratory pressure (baseline, after treatment) Maximal expiratory pressure (baseline, after treatment) Nottingham Health Profile (discharge) Six-Minute Walk Test (unknown timepoint)
			n = 21 Age = 57.48 ± 11.48 90% male sex	Con = standard care physiotherapy guided by pathway, SOOB and stand day one, walk 45 m day two, walk freely day three and four, climb a set of stairs day five, session duration not reported	
Schaller (Schaller et al., 2016)	International RCT	Adults in surgical ICU, mechanically ventilated < 48 hours, expected further ≥ 24 hours MV; previously independent	n = 104 Age = 66 (48-73) 62% male sex	Exp = daily mobilisation goal setting, goal implementation facilitated by inter-professional closed-loop communication, progression through five levels of activities based on ability to participate, strength and functional level, session duration not reported	Mean SOMS (SICU optimal mobilisation score) level achieved in ICU ICU LOS* Mini-modified Functional Independence Measure (ICU discharge, hospital discharge)* Hospital LOS* Hospital mortality* Short Form 36 (3-month)
			n = 96 Age = 64 (45-76)	Con = mobilisation was done in line with the individual centres' practice guidelines, frequency and session duration not reported	

			63% male sex		3-month mortality
Schweickert (Schweickert et al., 2009)	United States RCT	Adults on MV < 72 hours, expected further ≥ 24 hours MV; previously independent	n = 49 Age = 57.7 (36.3-69.1) 41% male sex	Exp = therapy delivered daily by physical and occupational therapist coordinated with sedation interruption. Therapy progressed patients from passive ROM, active ROM, bed mobility exercises, transfer and gait training. Median daily treatment time 0.32 hours on MV, 0.21 hours off MV, therapy continued until hospital discharge or returned to the premorbid functional level	MV duration* ICU LOS* Handgrip strength (hospital discharge)* Hospital LOS* Hospital mortality* Independent ADLs total at ICU discharge* Barthel index (hospital discharge)* Incidence of ICU-AW (hospital discharge) Greatest walking distance (hospital discharge) Ventilator-free days at day 28*
			n = 55 Age = 54.4 (46.5-66.4) 58% male sex	Con = standard care, no routine physiotherapy for patients who are on MV for less than 2 weeks, median daily treatment time 0 hours on MV, 0.19 hours off MV	
Seo (Seo & Shin, 2019)	Republic of Korea RCT	ICU LOS > 5 days, previously	n = 8 Age = 67.4 ± 10.8	Exp = exercise interventions such as strength, postural, balance, and training were performed by physical therapists, 30 minutes daily 5 times per week until ICU discharge	MV duration* ICU LOS* MRC-SS (baseline, ICU discharge*)

		independent with walking	75% male sex		Functional Status Scale for ICU (baseline, ICU discharge*) Short Form 36 (baseline, ICU discharge)
			n = 8 Age = 66.5 ± 8.7 37.5% male sex	Con = passive, active-assisted, or resisted exercises on a bedside cycle ergometer, 30 minutes daily 5 times per week until ICU discharge	
Shen (Shen et al., 2017)	Taiwan	Adults mechanically ventilated MV >72, fulfil criteria of sepsis	n = 18 Age = 77.5 (72-81) 67% male sex	Exp = NMES to bilateral quadriceps and biceps, intense enough to cause visible contraction, 32 minutes daily, 5 days per week	MV duration* Handgrip strength (every 3 days after enrolment) Hospital mortality*
			n = 7 Age = 78 (73-83) 29% male sex	Con = active or passive exercise of extremities, frequency, and session duration not reported	
	Brazil RCT	Age > 18 years old, mechanically	n = 11	Exp = electronic inspiratory muscle training, 3 sets of 10 repetitions, resistive load initially at 30% of maximal	MV duration*

Tonella (Tonella et al., 2017)		ventilated tracheostomised patients in the ICU, previously not requiring MV at home	median age = 58.0 73% male sex	inspiratory pressure, with a 10% increase each day, twice daily, duration of protocol not reported	Maximal inspiratory pressure (before and after training) Mortality
			n = 8 median age = 46.5 87.5% male sex	Con = intermittent nebulisation via T-piece, for progressively increasing duration, until participants have completed 48 hours of respiratory autonomy	
Winkelman (Winkelman et al., 2012)	United States CCT	Patients mechanically ventilated for ≥ 48 hours and expected to continue for ≥24 hours	n = 55 Age = 65 ± 13.27 53% male sex	Exp = in-bed and out-of-bed exercises assisted by research assistants, guided by protocol, average session duration 20 minutes, once daily until ICU discharge, 164 total sessions	MV duration* ICU LOS* ICU mortality* Muscle strength (ICU discharge) Katz Index of Independence in Activities of Daily Living (ICU discharge)
			n = 20 Age = 66 ± 11.03 40% male sex	Con = no routine physical therapy, nurse-initiated exercises, average session duration 17 minutes, 42 total sessions	

Winkelman (Winkelman et al., 2018)	United States RCT	Adults mechanically ventilated for 36 hours and expected further ≥ 24 hours MV	n = 25 Age = 52.68 ± 18.53 38% male sex	Exp = four-level protocol delivered by a trained nurse, therapy based on patients' level of strength, progressed from passive ROM exercises to active transfer out of bed, 20 minutes twice daily 7 days per week	MV duration* MRC-SS (day 1 and 3) Handgrip strength (day 1, day 3, ICU discharge) ICU LOS* ICU mortality*
			n = 29 Age = 59.48 ± 15.56 56% male sex	Con = same protocol as the experimental group but once daily	
Wolfe (Wolfe et al., 2013)	Secondary analysis of data from Schweickert (Schweickert et al., 2009)	Same as Schweickert [32]	Same as Schweickert [32]	Exp = Same as Schweickert [32]	6-month mortality*
			Same as Schweickert [32]	Con = Same as Schweickert [32]	
Wollersheim (Wollersheim et al., 2019)	Germany RCT	Aged ≥ 18 with sepsis-related multiorgan	n = 33 Age = 54 (45 – 68)	Exp = muscle activating measures such as NMES and/or whole-body vibration, 20 minutes daily in ICU up to 28 days,	ICU LOS* ICU mortality*

		dysfunction, Sequential Organ Failure Assessment (SOFA) Score ≥ 9, previously independent with ambulation	72.7% male sex	in addition to protocol-based physiotherapy, a median of 22.2 minutes per day	MRC-SS (awakening, ICU discharge, 12-month) Handgrip strength (awakening, ICU discharge, 12-month) Functional Independence Measure (ICU discharge)*
			n = 17 Age = 45 (39 – 61) 52.9% male sex	Con = protocol-based physiotherapy, starting on the day of ICU admission, consists of an individualised approach with daily predefined goals, closed-looped feedback system to achieve the highest possible level of physiotherapeutic care, a median of 22.3 minutes per day	
Wright (Wright et al., 2018)	United Kingdom RCT	Adults received invasive or non-invasive MV ≥48 hours	n = 150 Age = 60 ± 16 54% male sex	Exp = functional training and individually tailored exercise programme, target delivery of 90 minutes daily on weekdays, split between at least 2 sessions	MV duration* ICU LOS* ICU mortality* Functional Independence Measure (ICU discharge*, hospital discharge*, 3- and 6-month*) Modified Rivermead Mobility Index (ICU discharge) Handgrip strength (ICU discharge*, hospital discharge*, 3- and 6-month) Hospital LOS*
			n = 158 Age = 64 ± 16 63% male sex	Con = functional training and individually tailored exercise programmes, target delivery of 30 minutes daily on weekdays	

					Hospital mortality* Six-Minute Walk Test (hospital discharge) Short Form 36 (hospital discharge, 3- and 6-month) EQ-5D (hospital discharge, 3- and 6-month) 6-month mortality*
Yosef-Brauner (Yosef-Brauner et al., 2015)	Israel RCT	Adults mechanically ventilated for ≥ 48 hours and expected further ≥ 48 hours MV	n = 9 Age = 51.6 ± 18 33% male sex	Exp = physical therapy protocol, progressing from passive ROM, active ROM, bed mobility, sitting on the edge of the bed, transfer, and walking, twice daily, duration based on the functional level	MRC-SS (baseline, 48-72 hours after baseline, ICU discharge) Maximal Inspiratory Pressure (baseline, 48-72 hours after baseline, ICU discharge) Handgrip strength (baseline, 48-72 hours after baseline, ICU discharge) Sitting balance (baseline, 48-72 hours after baseline, ICU discharge) ICU mortality*
			n = 9 Age = 61.5 ± 12 44% male sex	Con = same protocol as the experimental group but once daily	

*Outcome measures that were included in the meta-analysis

^This group received treatment that met exclusion criteria and was not included in the meta-analysis

Abbreviations: SD: standard deviation; Con: Control group intervention; Exp: Experimental group intervention; EMS: Electrical muscle stimulation; NMES: Neuromuscular Electrical Stimulation; SOOB: Sit out of bed; ROM: range of motion; MV: Mechanical ventilation; LOS: Length of stay; ICU: Intensive care unit; MRC-SS: Medical research council sum score; ICU-AW: Intensive care unit acquired weakness

Figures

Figure 5.1 PRISMA flow diagram.

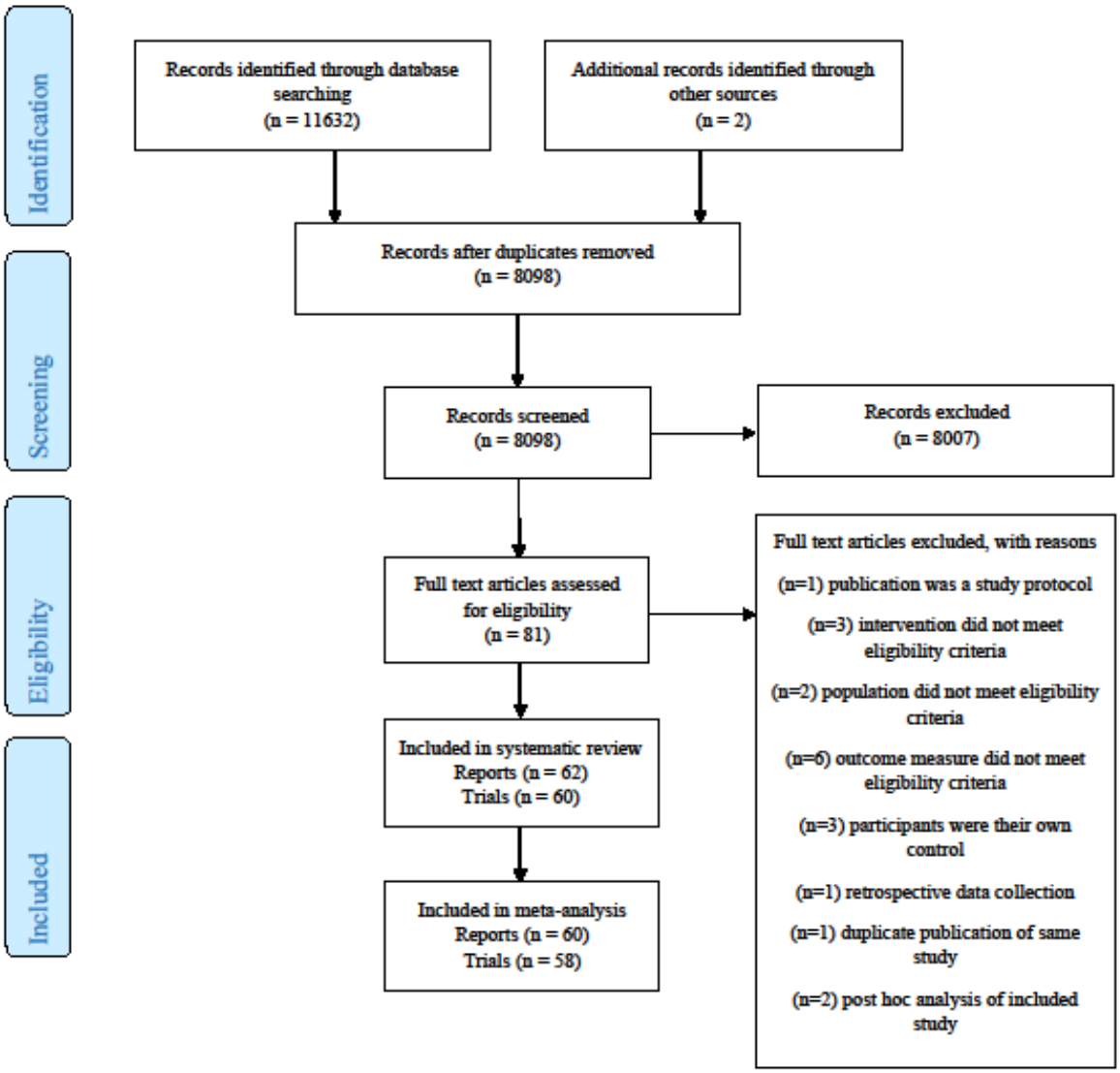


Figure 5.2 Risk of bias of RCTs assessed using RoB 2 tool.

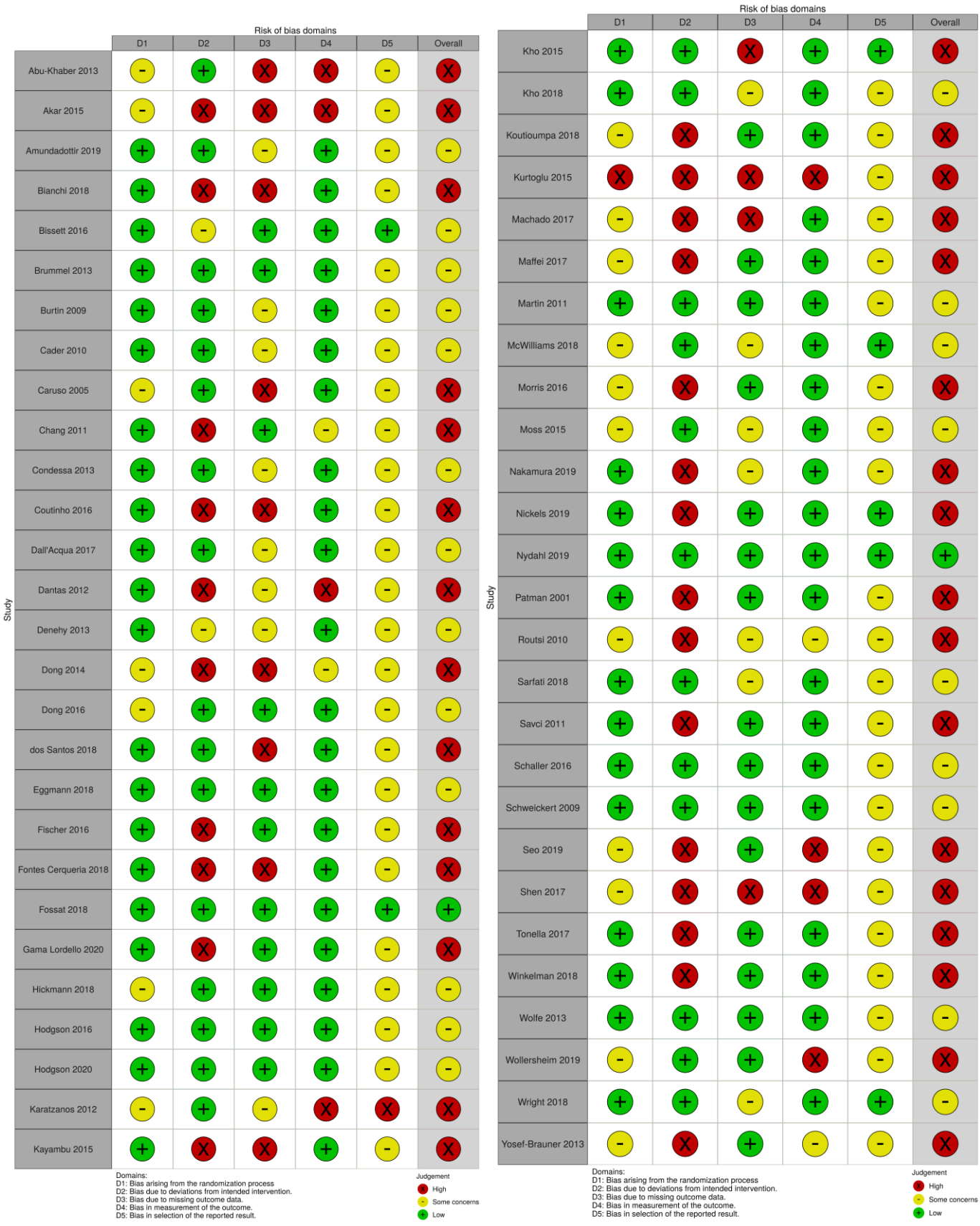


Figure 5.3 Summary of risk of bias of RCTs assessed using RoB 2 tool

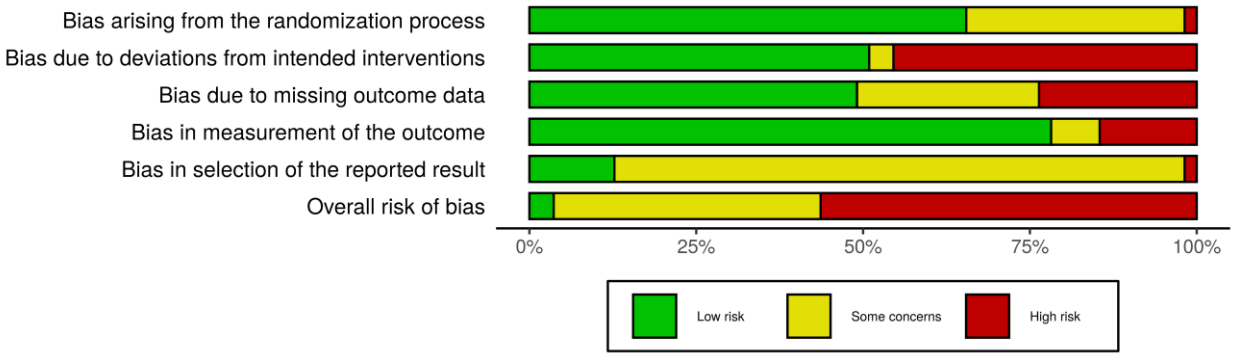


Figure 5.4 Risk of bias of controlled clinical trials assessed using ROBINS-I tool

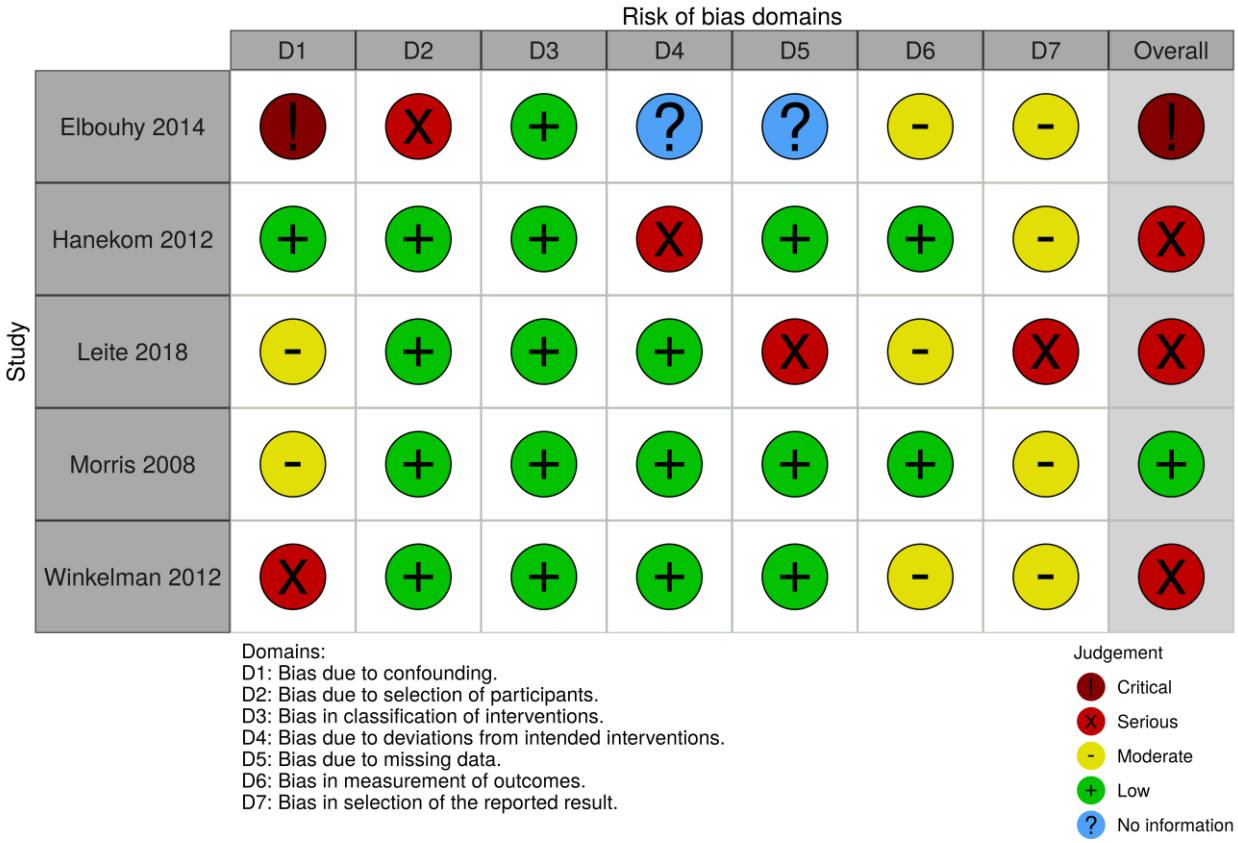


Figure 5.5 Meta-analysis and pooled effect sizes (raw mean difference in days) on the duration of mechanical ventilation for physical rehabilitation and standard care, with subgroup analysis according to the dosage of control therapy.

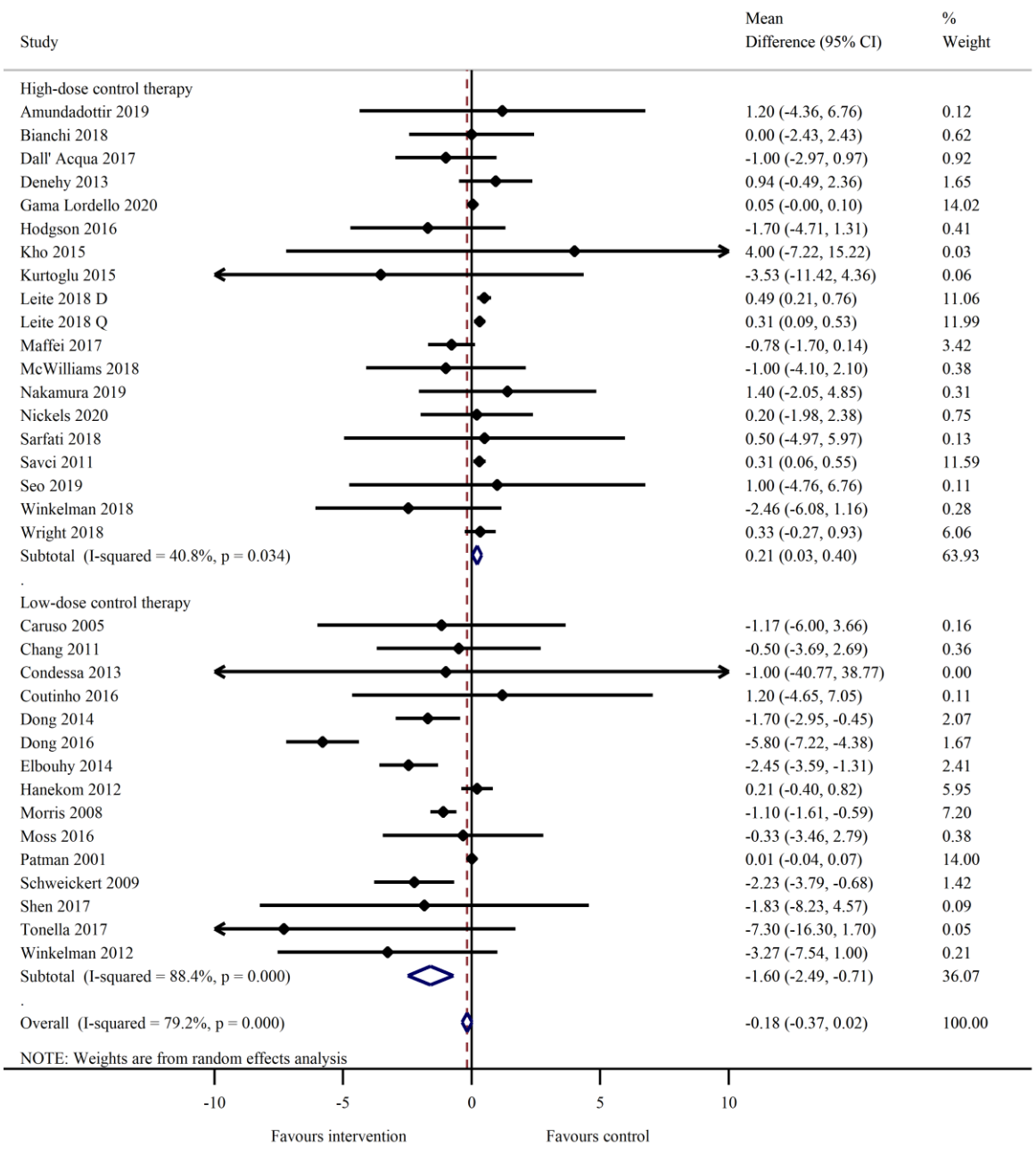


Figure 5.6 Meta-analysis and pooled effect sizes (raw mean difference in days) on the ICU LOS for physical rehabilitation and standard care, with subgroup analysis according to the type of exercise used in the intervention group.

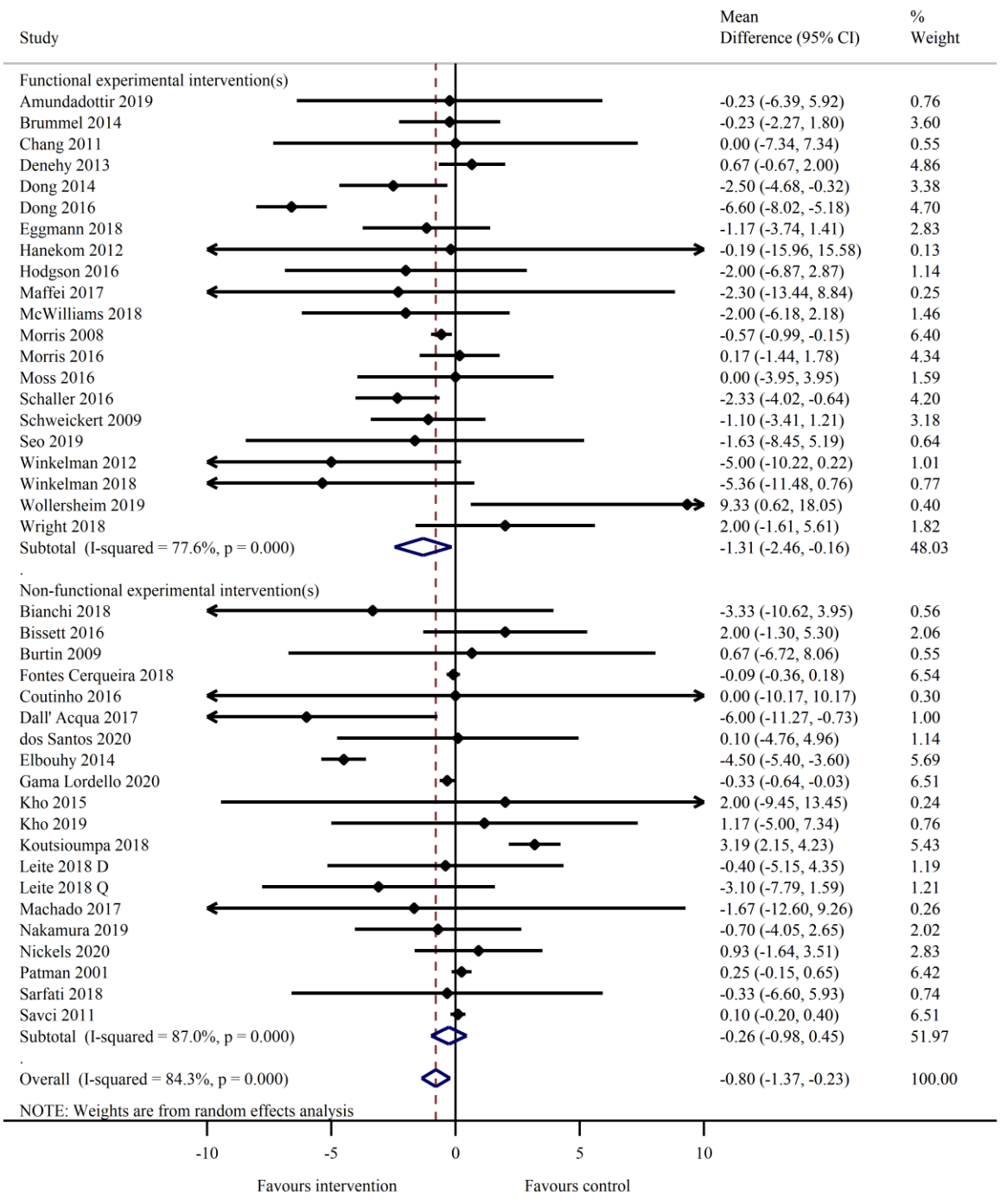


Figure 5.7 Meta-analysis and pooled effect sizes (raw mean difference in days) on the hospital LOS for physical rehabilitation and standard care, with subgroup analysis according to the dosage of control therapy.

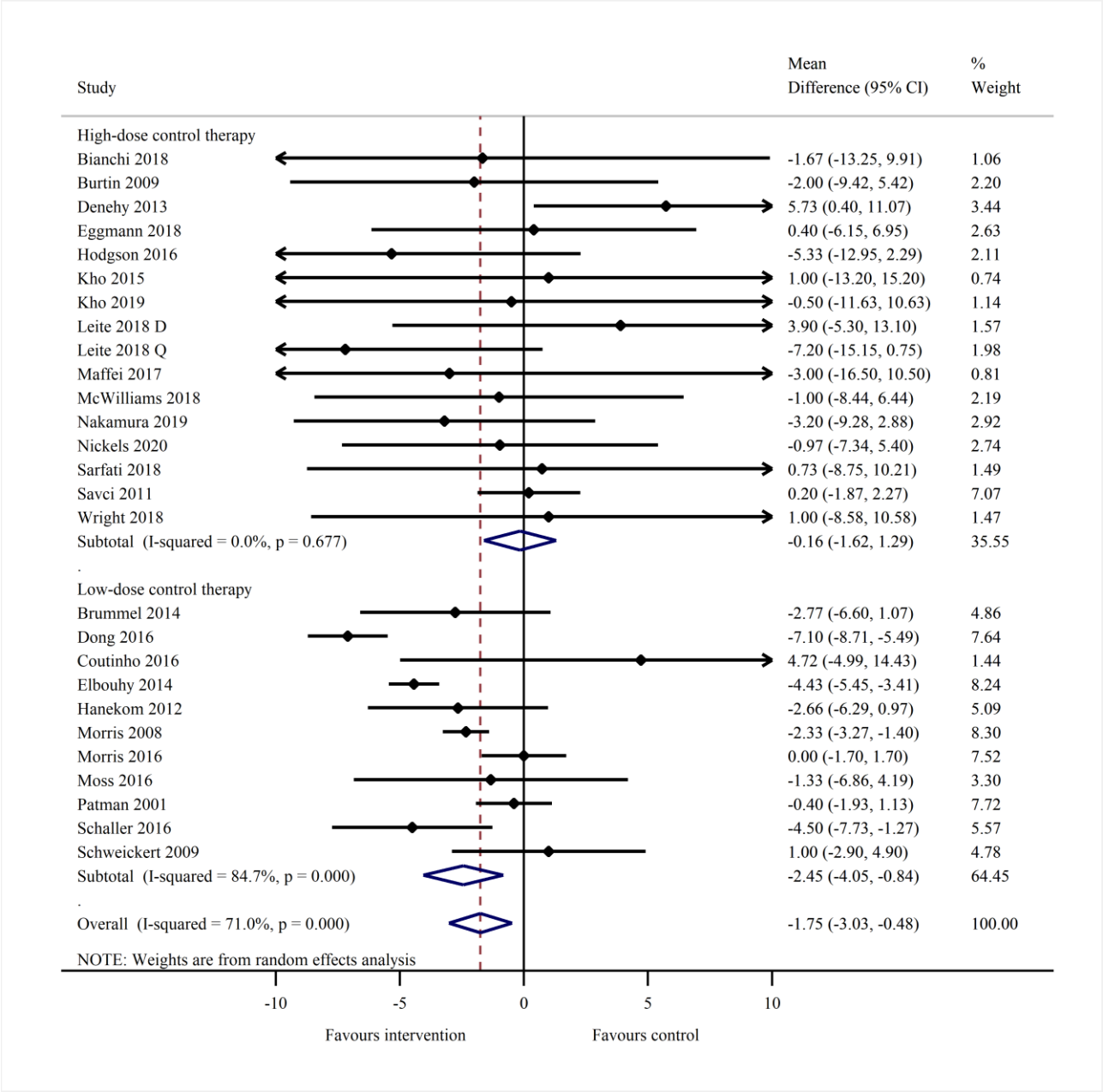


Figure 5.8 Meta-analysis and pooled effect sizes (risk difference) on the mortality outcomes for physical rehabilitation and standard care.

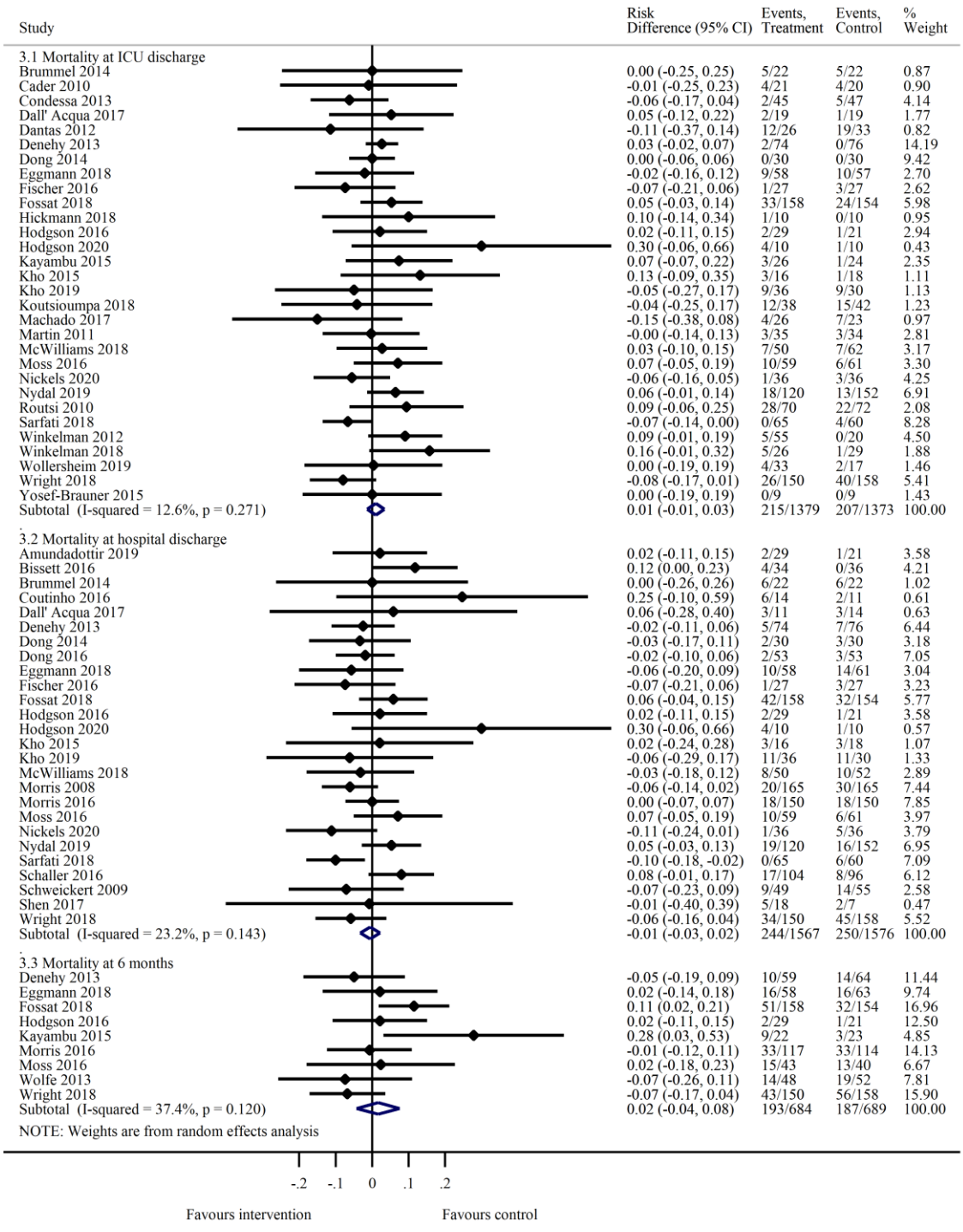


Figure 5.9 Meta-analysis and pooled effect sizes (standardised mean difference) on muscle strength outcomes for physical rehabilitation and standard care.

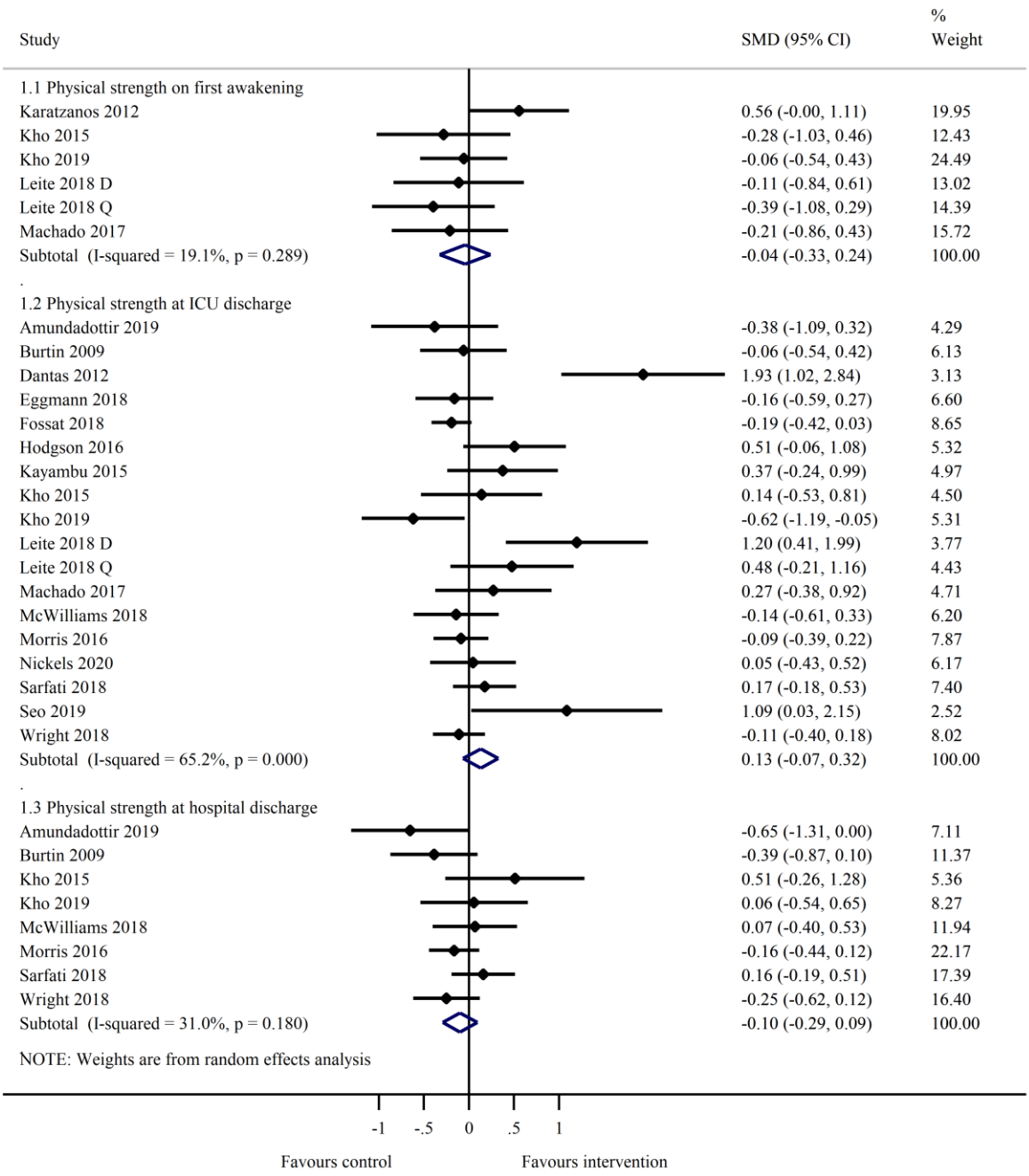


Figure 5.10 Meta-analysis and pooled effect sizes (standardised mean difference) on physical function outcomes for physical rehabilitation and standard care, at intensive care unit discharge, hospital discharge, and 6 months follow-up.

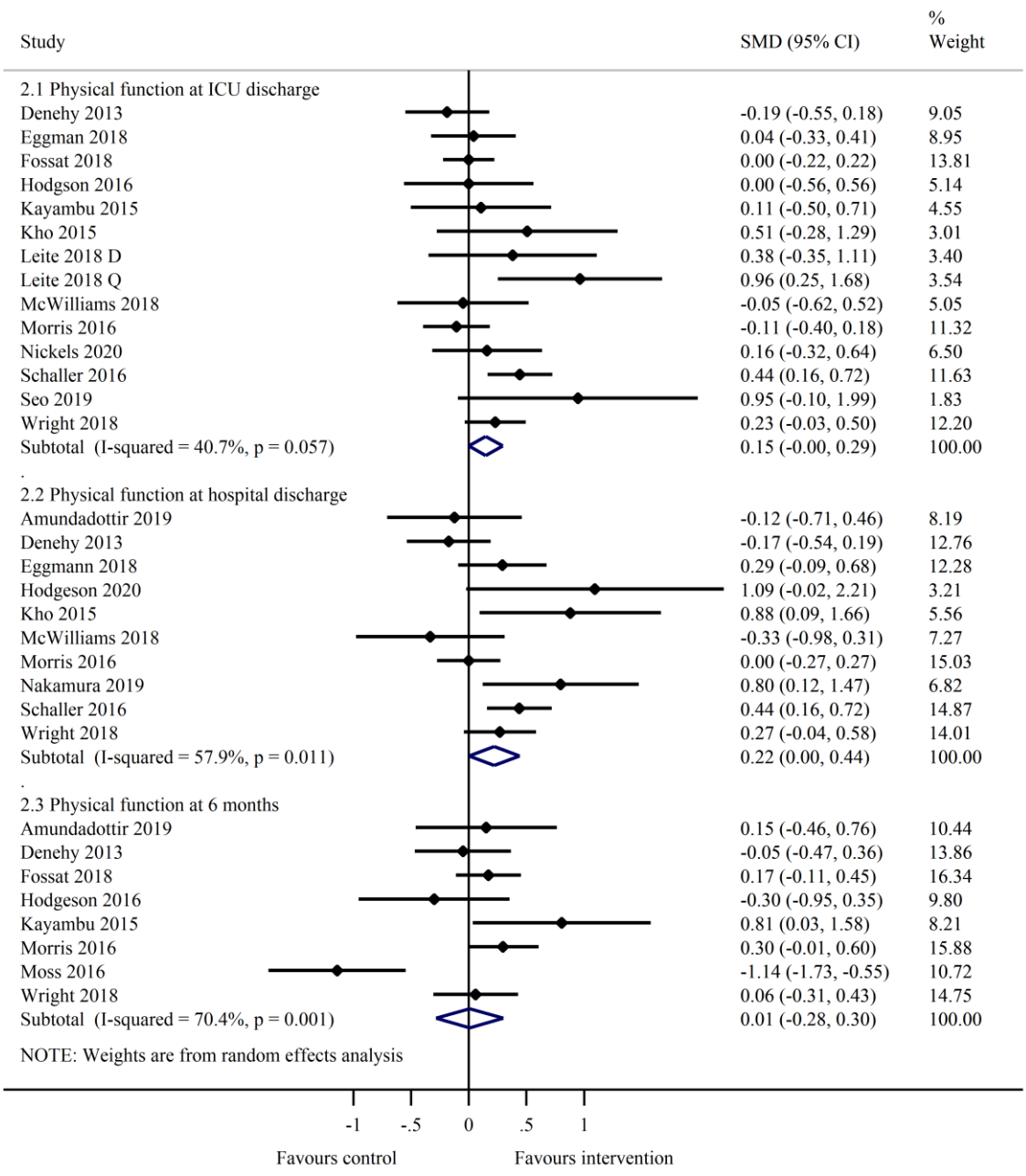


Figure 5.11 Meta-analysis and pooled effect sizes (raw mean difference in days) on MV free days to day-28 for physical rehabilitation and standard care.

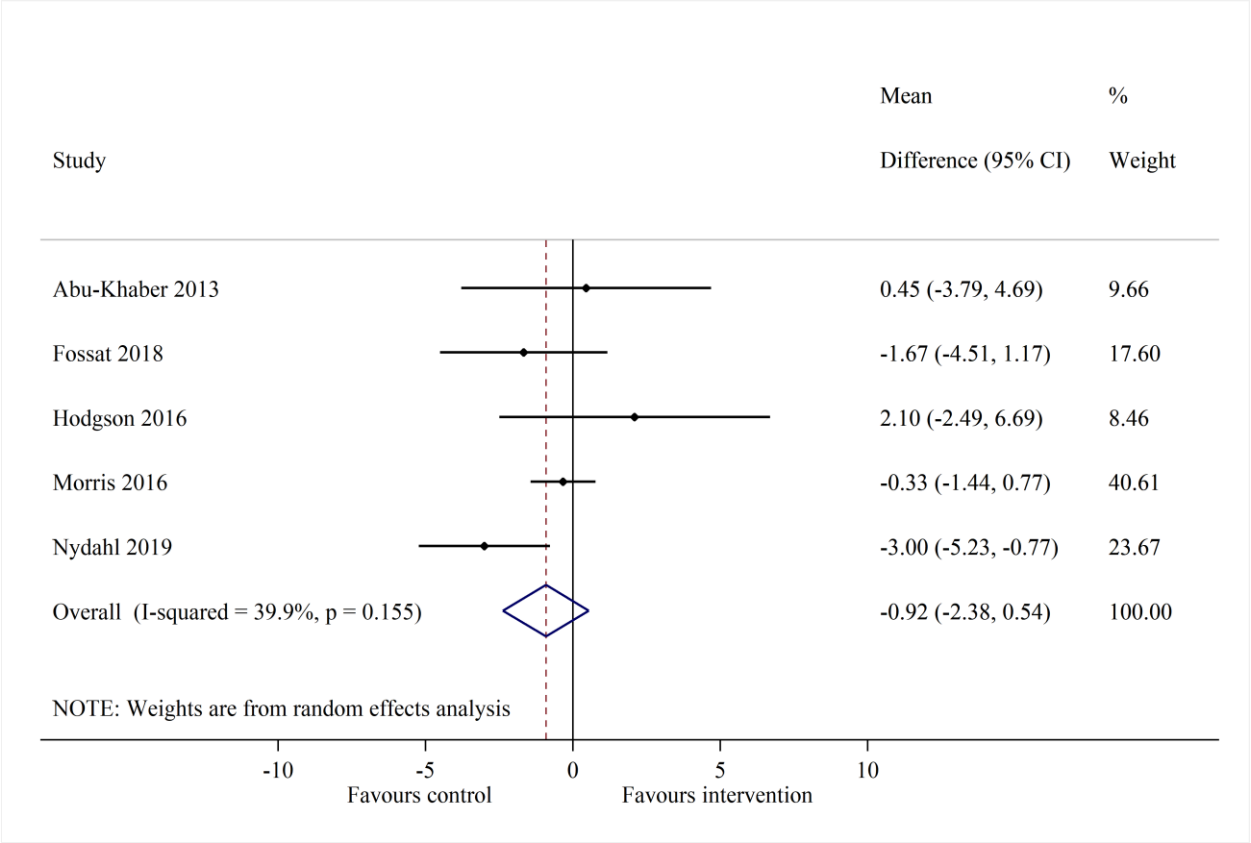
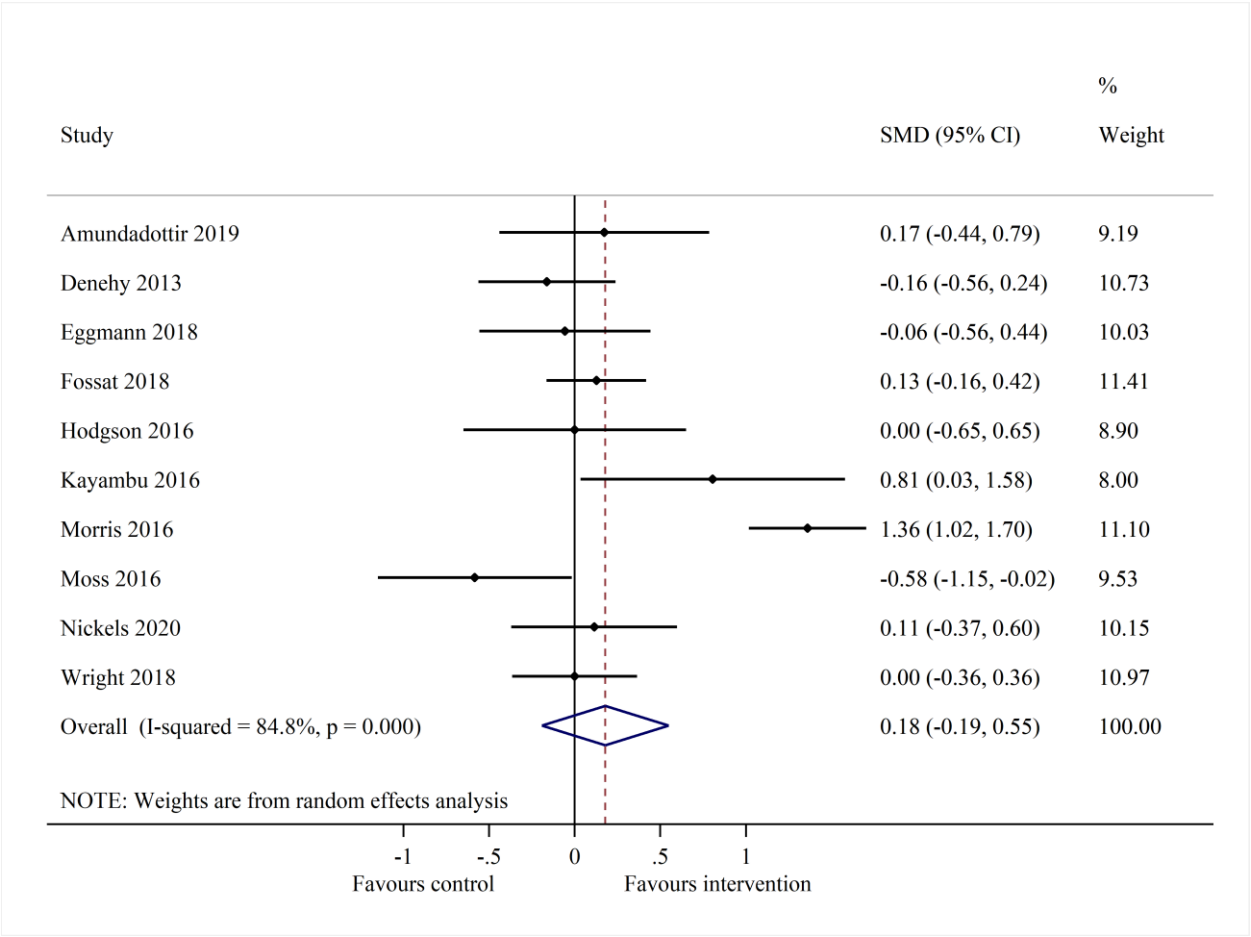


Figure 5.12 Meta-analysis and pooled effect sizes (standardised mean difference) on health-related quality of life at 6 months for physical rehabilitation and standard care.



Supplementary methods

Search strategies

CENTRAL, Cochrane Library search strategy

[mh "ICU"] OR [mh "Critical Illness"] OR [mh "Critical Care"] OR [mh "Critical Illness Polyneuropathy"] OR [mh “muscle weakness”] OR [mh “paresis”] OR [mh “MV”] OR [mh “Respiration, Artificial”] OR (critical* NEAR (ill* OR care*)):ti,ab OR "intensive NEXT care":ti,ab OR (ICU*):ti,ab OR ((critical* OR intensive) NEAR (paresis OR weakness OR *opathy)):ti,ab

AND

[mh “rehabilitation exercise”] OR [mh "Physiotherapy (Techniques)"] OR [mh "Exercise Therapy"] OR [mh "Physical Therapy Modalities"] OR [mh "Occupational Therapy"] OR mobili*:ti,ab OR exercis*:ti,ab OR (therap* NEAR (physical OR exercise OR occupation*)):ti,ab OR ((physical OR bed* OR "daily living") NEAR activit*):ti,ab OR (transfer OR training OR *gait OR walk* OR adl OR physiotherap* OR ambulat*):ti,ab OR ((cycle OR bicycle) NEAR ergomet*):ti,ab OR *musc* NEAR stimul*:ti,ab

Medline OVID search strategy

exp ICU/ OR exp critical illness/ OR exp intensive care/ OR exp critical illness polyneuropathy/ OR exp muscle weakness/ OR exp paresis/ OR exp MV/ OR critical* adj3 (ill* OR care*).tw. OR intensive adj3 care.tw. OR ICU*.tw. OR ((critical* or intensive) adj3 (paresis or weakness or myo* or neuro* or poly*)).tw.

AND

exp rehabilitation/ OR exp Physical Therapists/ or exp Physical Therapy Modalities/ OR exp exercise therapy/ OR exp occupational therapy/ OR mobili*.tw. OR exercis*.tw. OR therap* adj3 (physical OR exercise OR occupation*).tw. OR ((physical OR bed* OR "daily living") adj3 activit*).tw. OR (transfer OR training OR gait OR walk* OR adl OR physiotherap* OR ambulat*).tw. OR ((cycle OR bicycle) adj3 ergomet*).tw. OR (neuro* OR musc*) adj3 stimul*.tw. OR exp Electric Stimulation/ or exp Electric Stimulation Therapy/

AND

exp controlled clinical trial/ OR exp clinical trial/ OR exp randomized controlled trial/ OR exp multicenter study/

NOT

exp animal/

EMBASE search strategy

'ICU'/exp OR 'Critical Illness'/exp OR 'intensive care'/exp OR 'Critical Illness Polyneuropathy'/exp OR 'muscle weakness'/exp OR 'paresis'/exp OR 'artificial ventilation'/exp OR critical* NEAR/3 (ill* OR care*) OR intensive NEXT/3 care OR (ICU*):ti,ab OR (critical* OR intensive) NEAR/3 (paresis OR weakness OR myo* OR neuro* OR poly*)

AND

'rehabilitation'/exp OR 'physiotherapy'/exp OR 'exercise therapy'/exp OR 'occupational therapy'/exp OR mobili*:ti,ab OR exercis*:ti,ab OR therap* NEAR/3 (physical OR exercise OR occupation*) OR (physical OR bed* OR "daily living") NEAR/3 activit* OR (transfer OR training OR gait OR walk* OR adl OR physiotherap* OR ambulat*):ti,ab OR (cycle OR bicycle) NEAR/3 ergomet* OR (neuro* OR musc*) NEAR/3 stimul* OR 'electrostimulation'/exp OR 'electrotherapy'/exp

AND

'controlled study'/exp OR 'controlled clinical trial'/exp OR 'clinical trial'/exp OR 'randomized controlled trial'/exp OR 'multicenter study'/exp

NOT

'animal'/exp

CINAHL Plus (EBSCOhost) search strategy

TI (ICU*) OR TI intensive care OR TI critical* N3 (ill* or care*) OR TI (critical* OR intensive) N3 (paresis OR weakness OR myo* OR neuro* OR poly*)

AB (ICU*) OR AB intensive care OR AB critical* N3 (ill* or care*) OR AB (critical* OR intensive) N3 (paresis OR weakness OR myo* OR neuro* OR poly*)

OR (MH "ICUs+") OR (MH "Polyneuropathies+") OR (MH "Critical Care+") OR (MH "Muscle Weakness") OR (MH "Respiration, Artificial+") OR (MH "Critical Illness")

AND

(MH "Therapeutic Exercise+") OR (MH "Occupational Therapy") OR (MH "Physical Mobility") OR (MH "Electrical Stimulation, Neuromuscular") OR (MH "Electrical Stimulation, Functional") OR (MH "Ergometry") OR (MH "Physical Activity") OR (MH "Rehabilitation+") OR (MH "Physical Therapy+")

TI mobili* OR TI exercis* OR TI therap* N3 (physical OR exercise OR occupation*) OR TI (physical OR bed* OR "daily living") N3 activit* OR TI (transfer OR training OR gait OR walk* OR adl OR physiotherap* OR ambulat*) OR TI (cycle OR bicycle) N3 ergomet* OR TI (neuro* OR musc*) N3 stimul*

AB mobili* OR AB exercis* OR AB therap* N3 (physical OR exercise OR occupation*) OR AB (physical OR bed* OR "daily living") N3 activit* OR AB (transfer OR training OR gait

OR walk* OR adl OR physiotherap* OR ambulat*) OR AB (cycle OR bicycle) N3 ergomet* OR AB (neuro* OR musc*) N3 stimul*

AND

(MH “Clinical Trials+”) OR (MH “Randomized Controlled Trials+”) OR (MH “Multicenter Studies”)

NOT

(MH "Animal Studies") OR (MH "Animals, Laboratory") OR (MH "Animal Physical Therapy

Data extraction

Data items included:

a) Study design: author, publication year, the geographical location of the study, study design, patient group
b) Participant: demographics, eligibility criteria
c) Intervention and control: items 1 to 11 of the template for intervention description and replication (Hoffmann et al., 2014)
d) Outcome measures: muscle strength outcomes, physical function outcomes, mortality, health-related quality of life, duration of MV, MV-free days to day 28, and ICU and hospital LOS.

Data synthesis

Group means were presented as median with Interquartile range (IQR), mean and 95% confidence interval were included. Data presented in median and range were excluded. All data were converted to mean and standard deviations. Conversion from median and IQR to

mean and the standard deviation was done using the formula proposed by Wan et al. (Wan et al., 2014).

Studies with more than two groups

Trials with more than two groups were included in the meta-analysis as guided by the Cochrane Handbook (Higgins, 2019). Where feasible, we combined all relevant groups to create a single pair-wise comparison. In studies where two intervention groups received significantly different interventions, we split the 'shared' group into two or more groups with smaller sample sizes and included independent comparisons. All groups that satisfied the inclusion and exclusion criteria were included.

Supplementary results

Characteristics of included studies

Physical rehabilitation interventions

In twenty-nine trials (Abu-Khaber et al., 2019; Bianchi et al., 2018; Bissett et al., 2016; Burtin et al., 2009; Cader et al., 2010; Caruso et al., 2005; Chang et al., 2011; Condessa et al., 2013; Coutinho et al., 2016; Dall' Acqua et al., 2017; Elbouhy et al., 2014; Fischer et al., 2016; Fontes Cerqueira et al., 2018; Gama Lordello et al., 2020; Kho et al., 2019; Kho et al., 2015; Koutsioumpa et al., 2018; Kurtoğlu et al., 2015; Machado et al., 2017; Martin et al., 2011; McCaughey et al., 2019; Nakamura et al., 2019; M. R. Nickels et al., 2020; Pandey et al., 2013; Routsi et al., 2010; Sarfati et al., 2018; Savci et al., 2011; Shen et al., 2017; Tonella et al., 2017), the experimental therapy consisted of a single modality; in

thirteen trials (Amundadottir et al., 2019; Brummel et al., 2014; Dantas et al., 2012; Dong et al., 2016; Dong et al., 2014; Maffei et al., 2017; Morris et al., 2016; Morris et al., 2008; Moss et al., 2016; Schweickert et al., 2009; Winkelman et al., 2012; Winkelman et al., 2018; Yosef-Brauner et al., 2015) the experimental therapy was guided by a protocol; in eight trials (Denehy, Skinner, et al., 2013; Hanekom et al., 2012; Hodgson et al., 2016; Hodgson et al., 2020; McWilliams et al., 2018; Nydahl et al., 2019; Schaller et al., 2016; Wright et al., 2018) experimental therapy was individualised or goal directed, and in ten trials (Akar et al., 2017; dos Santos et al., 2020; Eggmann et al., 2018; Fossat et al., 2018; Hickmann et al., 2018; Kayambu et al., 2015; Leite et al., 2018; Patman et al., 2001; Seo & Shin, 2019; Wollersheim et al., 2019), a combination of more than one modality was used.

In twenty-six trials (Amundadottir et al., 2019; Brummel et al., 2014; Chang et al., 2011; Dantas et al., 2012; Denehy, Skinner, et al., 2013; Dong et al., 2016; Dong et al., 2014; Eggmann et al., 2018; Hanekom et al., 2012; Hodgson et al., 2016; Hodgson et al., 2020; Kayambu et al., 2015; Maffei et al., 2017; McWilliams et al., 2018; Morris et al., 2016; Morris et al., 2008; Moss et al., 2016; Nydahl et al., 2019; Sarfati et al., 2018; Schaller et al., 2016; Schweickert et al., 2009; Seo & Shin, 2019; Winkelman et al., 2012; Winkelman et al., 2018; Wright et al., 2018; Yosef-Brauner et al., 2015), the experimental intervention contained task-specific exercises, and thirty-four trials (Abu-Khaber et al., 2019; Akar et al., 2017; Bianchi et al., 2018; Bissett et al., 2016; Burtin et al., 2009; Cader et al., 2010; Caruso et al., 2005; Condessa et al., 2013; Coutinho et al., 2016; Dall' Acqua et al., 2017; dos Santos et al., 2020; Elbouhy et al., 2014; Fischer et al., 2016; Fontes Cerqueira et al., 2018; Fossat et al., 2018; Gama Lordello et al., 2020; Hickmann et al., 2018; Kho et al., 2019; Kho et al., 2015; Koutsioumpa et al., 2018; Kurtoğlu et al., 2015; Leite et al., 2018; Machado et al., 2017; Martin et al., 2011; McCaughey et al., 2019; Nakamura et al., 2019; M. R. Nickels et

al., 2020; Pandey et al., 2013; Patman et al., 2001; Routsi et al., 2010; Savci et al., 2011; Shen et al., 2017; Tonella et al., 2017; Wollersheim et al., 2019) did not.

In thirty-two trials (Akar et al., 2017; Amundadottir et al., 2019; Bianchi et al., 2018; Bissett et al., 2016; Burtin et al., 2009; Dall' Acqua et al., 2017; Dantas et al., 2012; Denehy, Skinner, et al., 2013; dos Santos et al., 2020; Eggmann et al., 2018; Fontes Cerqueira et al., 2018; Fossat et al., 2018; Gama Lordello et al., 2020; Hickmann et al., 2018; Hodgson et al., 2016; Kho et al., 2019; Kho et al., 2015; Koutsioumpa et al., 2018; Kurtoğlu et al., 2015; Leite et al., 2018; Machado et al., 2017; Maffei et al., 2017; McWilliams et al., 2018; Nakamura et al., 2019; M. R. Nickels et al., 2020; Sarfati et al., 2018; Savci et al., 2011; Seo & Shin, 2019; Winkelman et al., 2018; Wollersheim et al., 2019; Wright et al., 2018; Yosef-Brauner et al., 2015), the control group received physical rehabilitation at least 5 times per week, compared with twenty-eight trials (Abu-Khaber et al., 2019; Brummel et al., 2014; Cader et al., 2010; Caruso et al., 2005; Chang et al., 2011; Condessa et al., 2013; Coutinho et al., 2016; Dong et al., 2016; Dong et al., 2014; Elbouhy et al., 2014; Fischer et al., 2016; Hanekom et al., 2012; Hodgson et al., 2020; Kayambu et al., 2015; Martin et al., 2011; McCaughey et al., 2019; Morris et al., 2016; Morris et al., 2008; Moss et al., 2016; Nydahl et al., 2019; Pandey et al., 2013; Patman et al., 2001; Routsi et al., 2010; Schaller et al., 2016; Schweickert et al., 2009; Shen et al., 2017; Tonella et al., 2017; Winkelman et al., 2012) where they did not, or the dosage was not described in sufficient detail.

Outcomes measures

There was wide variation in the outcome measures used, as well as their timing. The most common outcome measures for muscle strength were handgrip dynamometry and Medical Research Council Sum Score (MRC-SS); the most used physical function outcome

measures were the Functional Independence Measure (FIM) and the Barthel index. The 36-Item Short Form Health Survey (SF-36) was the most used outcome measure for HRQoL.

Pooled analysis of intervention effect

Duration of mechanical ventilation

Inclusion of data into pooled analysis

Forty-six studies (Amundadottir et al., 2019; Bianchi et al., 2018; Bissett et al., 2016; Caruso et al., 2005; Chang et al., 2011; Condessa et al., 2013; Coutinho et al., 2016; Dall' Acqua et al., 2017; Dantas et al., 2012; Denehy, Skinner, et al., 2013; Dong et al., 2016; Dong et al., 2014; dos Santos et al., 2020; Eggmann et al., 2018; Elbouhy et al., 2014; Fischer et al., 2016; Fossat et al., 2018; Gama Lordello et al., 2020; Hanekom et al., 2012; Hickmann et al., 2018; Hodgson et al., 2016; Hodgson et al., 2020; Kayambu et al., 2015; Kho et al., 2019; Kho et al., 2015; Kurtoğlu et al., 2015; Leite et al., 2018; Machado et al., 2017; Maffei et al., 2017; McCaughey et al., 2019; McWilliams et al., 2018; Morris et al., 2008; Moss et al., 2016; Nakamura et al., 2019; M. R. Nickels et al., 2020; Patman et al., 2001; Routsi et al., 2010; Sarfati et al., 2018; Savci et al., 2011; Schweickert et al., 2009; Seo & Shin, 2019; Shen et al., 2017; Tonella et al., 2017; Winkelman et al., 2012; Winkelman et al., 2018; Wright et al., 2018) reported the duration of MV. Three studies (Dantas et al., 2012; dos Santos et al., 2020; McCaughey et al., 2019) were unable to be included due to incomplete reporting of results. Hodgson et al. (Hodgson et al., 2020) reported MV duration separately for survivors and non-survivors, in median and interquartile range, so the results of the survivors and non-survivors could not be combined.

A further nine studies (Bissett et al., 2016; Eggmann et al., 2018; Fischer et al., 2016; Fossat et al., 2018; Hickmann et al., 2018; Kayambu et al., 2015; Kho et al., 2019; Machado et al., 2017; Routsi et al., 2010) were excluded from the primary pooled analysis and were included in the sensitivity analysis only. The results of six studies (Eggmann et al., 2018; Fossat et al., 2018; Hickmann et al., 2018; Kayambu et al., 2015; Kho et al., 2019; Machado et al., 2017) were significantly skewed and presented as median with interquartile range. Two studies (Fischer et al., 2016; Routsi et al., 2010) reported MV duration using the median, minimum, and maximum. In one study (Bissett et al., 2016), the experimental intervention began after participants were weaned off MV.

The control group from Leite et al. (Leite et al., 2018) was divided into two groups to allow comparison with groups that received NMES of the diaphragm (Leite 2018 D) and NMES of bilateral quadriceps (Leite 2018 Q). Thirty-four pairwise comparisons from thirty-three studies (n=2831) (Amundadottir et al., 2019; Bianchi et al., 2018; Caruso et al., 2005; Chang et al., 2011; Condessa et al., 2013; Coutinho et al., 2016; Dall' Acqua et al., 2017; Denehy, Skinner, et al., 2013; Dong et al., 2016; Dong et al., 2014; Elbouhy et al., 2014; Gama Lordello et al., 2020; Hanekom et al., 2012; Hodgson et al., 2016; Kho et al., 2015; Kurtoğlu et al., 2015; Leite et al., 2018; Maffei et al., 2017; McWilliams et al., 2018; Morris et al., 2008; Moss et al., 2016; Nakamura et al., 2019; M. R. Nickels et al., 2020; Patman et al., 2001; Sarfati et al., 2018; Savci et al., 2011; Schweickert et al., 2009; Seo & Shin, 2019; Shen et al., 2017; Tonella et al., 2017; Winkelman et al., 2012; Winkelman et al., 2018; Wright et al., 2018) were included in the primary pooled analysis, with all units of measurement converted to days.

Sensitivity analysis

Sensitivity analysis including studies excluded from the primary pooled analysis showed a reduction of MV duration favouring the intervention group (mean difference, 95% confidence interval) (-1.03, 95% CI: -1.75 to -0.30). Five CCTs contributed to the primary pooled analysis, subgroup analysis involving the RCTs only showed that physical rehabilitation resulted in a decrease in the duration of MV (mean difference, 95% confidence interval) (-0.27, 95% CI: -0.50 to -0.04).

Subgroup analysis and meta-regression

Meta-regression analyses demonstrated a moderating effect of the intervention on this outcome by the presence of low-dose control group therapy. Physical rehabilitation was more effective in these studies, with a further 1.58-day reduction in duration of MV (meta-regression coefficient, 95% confidence interval, p-value) (-1.58, 95% CI: -2.70 to -0.48, p=0.006).

Meta-regression examining the moderating effect of functional experimental intervention did not reach statistical significance (meta-regression coefficient, 95% confidence interval, p-value) (-0.94, 95% CI: -2.15 to 0.27, p=0.123). However, the magnitude of the point estimate of this interaction effect was beyond the magnitude that would be considered a minimum clinically significant difference.

Further subgroup analysis combining exercise intervention type and the amount of physical rehabilitation available to control group participants demonstrated an interaction effect. The effect of the intervention on MV duration was magnified if the intervention group received functional exercises and the control group received low-dose physical rehabilitation, with a

reduction of 1.82 days. (mean difference, 95% confidence interval) (-1.82, 95% CI: -3.14 to -0.49). In contrast, in studies where the intervention group received non-functional exercises only, and if physical rehabilitation was available to the control group at least 5 times a week, the intervention resulted in a longer duration of MV (mean difference, 95% confidence interval) (0.25, 95% CI: 0.05 to 0.44). In meta-regression analysis, the control group receiving low-dose physical rehabilitation was a significant effect modifier after accounting for the effect of having functional experimental interventions, with a further 1.43-day reduction in duration of MV (meta-regression coefficient, 95% confidence interval, p-value) (-1.43, 95% CI: -2.6 to -0.26, p=0.018).

ICU length of stay

Inclusion of data into pooled analysis

Forty-seven studies (Akar et al., 2017; Amundadottir et al., 2019; Bianchi et al., 2018; Bissett et al., 2016; Brummel et al., 2014; Burtin et al., 2009; Chang et al., 2011; Coutinho et al., 2016; Dall' Acqua et al., 2017; Dantas et al., 2012; Denehy, Skinner, et al., 2013; Dong et al., 2016; Dong et al., 2014; dos Santos et al., 2020; Eggmann et al., 2018; Elbouhy et al., 2014; Fischer et al., 2016; Fontes Cerqueira et al., 2018; Gama Lordello et al., 2020; Hanekom et al., 2012; Hickmann et al., 2018; Hodgson et al., 2016; Hodgson et al., 2020; Kayambu et al., 2015; Kho et al., 2019; Kho et al., 2015; Koutsioumpa et al., 2018; Leite et al., 2018; Machado et al., 2017; Maffei et al., 2017; McWilliams et al., 2018; Morris et al., 2016; Morris et al., 2008; Moss et al., 2016; Nakamura et al., 2019; M. R. Nickels et al., 2020; Patman et al., 2001; Routsi et al., 2010; Sarfati et al., 2018; Savci et al., 2011; Schaller et al., 2016; Schweickert et al., 2009; Seo & Shin, 2019; Winkelman et al., 2012; Winkelman et al., 2018; Wollersheim et al., 2019; Wright et al., 2018) reported

the ICU LOS. One study (Dantas et al., 2012) was unable to be included due to incomplete reporting of results. Hodgson et al. (Hodgson et al., 2020) reported ICU LOS separately for survivors and non-survivors, in median and interquartile range, so the results of the survivors and non-survivors could not be combined.

Five further studies (Akar et al., 2017; Fischer et al., 2016; Hickmann et al., 2018; Kayambu et al., 2015; Routsi et al., 2010) were excluded from the primary pooled analysis and included in the sensitivity analysis only. Three studies (Akar et al., 2017; Fischer et al., 2016; Routsi et al., 2010) reported LOS using the median, minimum, and maximum. In two studies (Hickmann et al., 2018; Kayambu et al., 2015), the results were significantly skewed and presented as median with interquartile range. The control group from Leite et al. (Leite et al., 2018) was divided into two groups to allow comparison with groups that received NMES of the diaphragm (Leite 2018 D) and NMES of bilateral quadriceps (Leite 2018 Q). Dos Santos et al. (dos Santos et al., 2020) presented data from four groups: passive bed exercises, active bed exercises, NMES, and NMES plus active bed exercises. The groups were combined to form a single pairwise comparison to examine the main effect of NMES and NMES plus active bed exercises, comparing to passive and active exercises bed exercises without NMES.

Forty-one pairwise comparisons from forty studies (n=3804) (Amundadottir et al., 2019; Bianchi et al., 2018; Bissett et al., 2016; Brummel et al., 2014; Burtin et al., 2009; Chang et al., 2011; Coutinho et al., 2016; Dall' Acqua et al., 2017; Denehy, Skinner, et al., 2013; Dong et al., 2016; Dong et al., 2014; dos Santos et al., 2020; Eggmann et al., 2018; Elbouhy et al., 2014; Fontes Cerqueira et al., 2018; Gama Lordello et al., 2020; Hanekom et al., 2012; Hodgson et al., 2016; Kho et al., 2019; Kho et al., 2015; Koutsioumpa et al., 2018; Leite et al., 2018; Machado et al., 2017; Maffei et al., 2017; McWilliams et al., 2018;

Morris et al., 2016; Morris et al., 2008; Moss et al., 2016; Nakamura et al., 2019; M. R. Nickels et al., 2020; Patman et al., 2001; Sarfati et al., 2018; Savci et al., 2011; Schaller et al., 2016; Schweickert et al., 2009; Seo & Shin, 2019; Winkelman et al., 2012; Winkelman et al., 2018; Wollersheim et al., 2019; Wright et al., 2018) were included in the primary pooled analysis, with all units of measurement converted to days.

Sensitivity analysis

Sensitivity analysis including studies excluded from the primary pooled analysis showed a reduction of -0.86 days (mean difference, 95% confidence interval) (0.86, 95%CI: -1.45 to 0.26). Six pairwise comparisons from five CCTs contributed to the primary pooled analysis, in a subgroup analysis of the RCTs only, the intervention no longer had a significant effect on LOS in the ICU (mean difference, 95% confidence interval) (-0.45, 95% CI: -1.01 to 0.10).

Subgroup analysis and meta-regression

Meta-regression analyses demonstrated a moderating effect of the intervention on this outcome by the presence of low-dose control group therapy. Physical rehabilitation was more effective in these studies, with a further 1.82-day reduction in ICU LOS (meta-regression coefficient, 95% confidence interval, p-value) (-1.82, 95% CI: -3.41 to -0.24, p=0.026).

Meta-regression examining the moderating effect of function experimental intervention did not reach statistical significance (meta-regression coefficient, 95% confidence interval, p-value) (-0.96, 95% CI: -2.65 to 0.73, p=0.256). However, the magnitude of the point

estimate of this interaction effect was beyond the magnitude that would be considered a minimum clinically significant difference.

Further subgroup analysis combining exercise intervention type and control group therapy dosage was done to assess the interaction effect of the two study characteristics. The positive effect of the intervention on ICU LOS was magnified if the intervention group received functional exercises and if the control group received low-dose physical rehabilitation, with a reduction of 1.84 days (mean difference, 95% confidence interval) (-1.84, 95% CI: -3.44 to -0.25). Meanwhile, the effect of treatment was not significant in studies where the intervention group received non-functional exercises only or if physical rehabilitation was available to the control group at least 5 times a week. In meta-regression analysis, the control group receiving low-dose physical rehabilitation was not a significant effect modifier after accounting for the effect of having functional experimental interventions (meta-regression coefficient, 95% confidence interval, p-value) (-1.71, 95% CI: -3.5 to 0.09, p=0.062). However, the magnitude of the point estimate of this interaction effect was beyond the magnitude that would be considered a minimum clinically significant difference.

Hospital length of stay

Inclusion of data into pooled analysis

Thirty-three studies (Amundadottir et al., 2019; Bianchi et al., 2018; Brummel et al., 2014; Burtin et al., 2009; Coutinho et al., 2016; Dantas et al., 2012; Denehy, Skinner, et al., 2013; Dong et al., 2016; Eggmann et al., 2018; Elbouhy et al., 2014; Fischer et al., 2016; Gama Lordello et al., 2020; Hanekom et al., 2012; Hodgson et al., 2016; Hodgson et al., 2020; Kayambu et al., 2015; Kho et al., 2019; Kho et al., 2015; Leite et al., 2018; Machado et al.,

2017; Maffei et al., 2017; McWilliams et al., 2018; Morris et al., 2016; Morris et al., 2008; Moss et al., 2016; Nakamura et al., 2019; M. R. Nickels et al., 2020; Patman et al., 2001; Sarfati et al., 2018; Savci et al., 2011; Schaller et al., 2016; Schweickert et al., 2009; Wright et al., 2018) reported the hospital LOS. One study (Dantas et al., 2012) was unable to be included due to incomplete reporting of results. Hodgson et al. (Hodgson et al., 2020) reported Hospital LOS separately for survivors and non-survivors, in median and interquartile range, so the results of the survivors and non-survivors could not be combined. Five further studies were excluded from the primary pooled analysis and included in the sensitivity analysis only. In four studies (Amundadottir et al., 2019; Gama Lordello et al., 2020; Kayambu et al., 2015; Machado et al., 2017) the results were significantly skewed and presented as median with interquartile range. One study (Fischer et al., 2016) reported LOS using the median, minimum, and maximum.

The control group from Leite et al. (Leite et al., 2018) was divided into two groups to allow comparison with groups that received NMES of the diaphragm (Leite 2018 D) and NMES of bilateral quadriceps (Leite 2018 Q).

Twenty-seven pairwise comparisons from twenty-six studies (n=2845) (Bianchi et al., 2018; Brummel et al., 2014; Burtin et al., 2009; Coutinho et al., 2016; Denehy, Skinner, et al., 2013; Dong et al., 2016; Eggmann et al., 2018; Elbouhy et al., 2014; Hanekom et al., 2012; Hodgson et al., 2016; Kho et al., 2019; Kho et al., 2015; Leite et al., 2018; Maffei et al., 2017; McWilliams et al., 2018; Morris et al., 2016; Morris et al., 2008; Moss et al., 2016; Nakamura et al., 2019; M. R. Nickels et al., 2020; Patman et al., 2001; Sarfati et al., 2018; Savci et al., 2011; Schaller et al., 2016; Schweickert et al., 2009; Wright et al., 2018) were included in the primary pooled analysis, with all units of measurement converted to days.

Sensitivity analysis

Sensitivity analysis including studies excluded from the primary pooled analysis showed a reduction of 1.62 days (mean difference, 95% confidence interval) (1.62, 95% CI: 2.91 to 0.34). Five pairwise comparisons from four CCTs contributed to the primary pooled analysis, in a subgroup analysis of the RCTs only, the intervention no longer had a significant effect on hospital LOS (mean difference, 95% confidence interval) (-1.21, 95% CI: -2.91 to 0.49).

Subgroup analysis and meta-regression

Meta-regression analyses examining the moderating effect of the intervention on this outcome by the presence of low-dose control group therapy did not reach statistical significance (meta-regression coefficient, 95% confidence interval, p-value) (-2.00, 95% CI: -4.73 to 0.73, p=0.144). However, the magnitude of the point estimate of this interaction effect was beyond the magnitude that would be considered a minimum clinically significant difference.

Meta-regression analysis examining the moderating effect of functional experimental interventions did not reach statistical significance (meta-regression coefficient, 95% confidence interval, p-value) (-0.59, 95% CI: -3.43 to 2.26, p=0.675).

Further subgroup analysis combining exercise intervention type and control group therapy dosage was done to assess the interaction effect of the two study characteristics. The positive effect of the intervention on hospital LOS was magnified if the intervention group received functional exercises and if the control group received a low-dose physical rehabilitation, with a reduction of 2.63 days (mean difference, 95% confidence interval)

(-2.63, 95% CI: -4.69 to -0.57). Meanwhile, the effect of treatment was not significant in studies where the intervention group received non-functional exercises only, or if physical rehabilitation was available to the control group at least 5 times a week. In meta-regression analysis, the control group receiving low-dose physical rehabilitation was not a significant effect modifier after accounting for the effect of having functional experimental interventions (meta-regression coefficient, 95% confidence interval, p-value) (-1.99, 95% CI: -4.96 to 0.97, p=0.118). However, the magnitude of the point estimate of this interaction effect was beyond the magnitude that would be considered a minimum clinically significant difference.

Mortality

Sensitivity and subgroup analysis

Sensitivity analysis was not performed because all studies that reported mortality data were included in the primary pooled analysis. Two CCTs contributed to the pooled analysis, subgroup analysis involving the RCTs only did not alter the result.

At 6 months, mortality outcome in the subgroup with non-functional experimental interventions favoured the control group (risk difference, 95% confidence interval) (0.11, 95% CI: 0.02 to 0.21). However, this subgroup only had one study (Fossat et al., 2018) at this time point. There were no differences between groups for any of the other subgroup analyses.

Muscle strength

Inclusion of data into pooled analysis

Six trials (Karatzanos et al., 2012; Kho et al., 2019; Kho et al., 2015; Leite et al., 2018; Machado et al., 2017; Routsi et al., 2010) reported the muscle strength on first awakening. Karatzanos et al. (Karatzanos et al., 2012) and Routsi et al. (Routsi et al., 2010) reported data from the same trial. Routsi et al. reported strength on awakening in the median, minimum, and maximum. Therefore, data from Karatzanos et al. were included. The control group from Leite et al. [66] was divided into two groups to allow comparison with groups that received NMES of the diaphragm (Leite 2018 D) and NMES of bilateral quadriceps (Leite 2018 Q). Six pairwise comparisons from five trials (n=252) (Karatzanos et al., 2012; Kho et al., 2019; Kho et al., 2015; Leite et al., 2018; Machado et al., 2017) were included in the primary pooled analysis for muscle strength on first awakening.

Twenty trials (Amundadottir et al., 2019; Burtin et al., 2009; Dantas et al., 2012; Eggmann et al., 2018; Fischer et al., 2016; Fossat et al., 2018; Hodgson et al., 2016; Kayambu et al., 2015; Kho et al., 2019; Kho et al., 2015; Leite et al., 2018; Machado et al., 2017; McWilliams et al., 2018; Morris et al., 2016; Pandey et al., 2013; Sarfati et al., 2018; Seo & Shin, 2019; Winkelman et al., 2012; Wright et al., 2018; Yosef-Brauner et al., 2015) reported at least one muscle strength outcome at ICU discharge. Four trials (Fischer et al., 2016; Pandey et al., 2013; Winkelman et al., 2012; Yosef-Brauner et al., 2015) were unable to be included due to incomplete reporting of results. The control group from Leite et al. [66] was divided into two groups to allow comparison with groups that received NMES of the diaphragm (Leite 2018 D) and NMES of bilateral quadriceps (Leite 2018 Q). Seventeen pairwise comparisons from sixteen trials (n=1366) (Amundadottir et al., 2019; Burtin et al., 2009; Dantas et al., 2012; Eggmann et al., 2018; Fossat et al., 2018; Hodgson et al., 2016; Kayambu et al., 2015; Kho et al., 2019; Kho et al., 2015; Leite et al., 2018; Machado et al., 2017; McWilliams

et al., 2018; Morris et al., 2016; Sarfati et al., 2018; Seo & Shin, 2019; Wright et al., 2018) were included in the primary pooled analysis for muscle strength at ICU discharge.

Twelve trials (Amundadottir et al., 2019; Burtin et al., 2009; Fischer et al., 2016; Kho et al., 2019; Kho et al., 2015; McWilliams et al., 2018; Morris et al., 2016; M. R. Nickels et al., 2020; Sarfati et al., 2018; Schweickert et al., 2009; Wright et al., 2018; Yosef-Brauner et al., 2015) reported at least one muscle strength outcome at hospital discharge. Two trials (Fischer et al., 2016; Yosef-Brauner et al., 2015) were unable to be included due to incomplete reporting of results. One trial (Schweickert et al., 2009) was excluded from the primary pooled analysis and included in the sensitivity analysis only, as the results were significantly skewed and presented as median with interquartile range. Nine pairwise comparisons from nine randomised controlled trials (n=751) (Amundadottir et al., 2019; Burtin et al., 2009; Kho et al., 2019; Kho et al., 2015; McWilliams et al., 2018; Morris et al., 2016; M. R. Nickels et al., 2020; Sarfati et al., 2018; Wright et al., 2018) were included in the primary pooled analysis for muscle strength at hospital discharge.

Sensitivity and subgroup analysis

Sensitivity analysis including the study (Schweickert et al., 2009) with the skewed data did not change the pooled result at hospital discharge (standardised mean difference, 95% confidence interval) (-0.02, 95% CI: -0.21 to 0.18). Sensitivity analysis excluding CCTs did not change the outcome at any of the time points. There were no differences between groups for any of the subgroup analyses.

Physical function

Inclusion of data into pooled analysis

Twenty-one (Amundadottir et al., 2019; Burtin et al., 2009; Denehy, Skinner, et al., 2013; Eggmann et al., 2018; Fischer et al., 2016; Fossat et al., 2018; Hodgson et al., 2016; Kayambu et al., 2015; Kho et al., 2019; Kho et al., 2015; Leite et al., 2018; McWilliams et al., 2018; Morris et al., 2016; M. R. Nickels et al., 2020; Schaller et al., 2016; Schweickert et al., 2009; Seo & Shin, 2019; Winkelman et al., 2012; Wollersheim et al., 2019; Wright et al., 2018; Yosef-Brauner et al., 2015) studies reported at least one physical function outcome at ICU discharge. Four studies (Burtin et al., 2009; Fischer et al., 2016; Winkelman et al., 2012; Yosef-Brauner et al., 2015) were unable to be included due to incomplete reporting of results. A further four studies (Amundadottir et al., 2019; Kho et al., 2019; Schweickert et al., 2009; Wollersheim et al., 2019) were excluded from the primary pooled analysis and were included in the sensitivity analysis only, as their results were significantly skewed and presented as median with interquartile range. The control group from Leite et al. [66] was divided into two groups to allow comparison with groups that received NMES of the diaphragm (Leite 2018 D) and NMES of bilateral quadriceps (Leite 2018 Q). Fourteen pairwise comparisons from thirteen studies (n=1465) (Denehy, Skinner, et al., 2013; Eggmann et al., 2018; Fossat et al., 2018; Hodgson et al., 2016; Kayambu et al., 2015; Kho et al., 2015; Leite et al., 2018; McWilliams et al., 2018; Morris et al., 2016; M. R. Nickels et al., 2020; Schaller et al., 2016; Seo & Shin, 2019; Wright et al., 2018) were included in the primary pooled analysis.

Fifteen trials (Amundadottir et al., 2019; Brummel et al., 2014; Burtin et al., 2009; Denehy, Skinner, et al., 2013; Eggmann et al., 2018; Fischer et al., 2016; Hodgson et al., 2020; Kho et al., 2019; Kho et al., 2015; McWilliams et al., 2018; Morris et al., 2016; Nakamura et al., 2019; Schaller et al., 2016; Schweickert et al., 2009; Wright et al., 2018) reported at least

one physical function outcome at hospital discharge. Two trials (Brummel et al., 2014; Fischer et al., 2016) were unable to be included due to incomplete reporting of results. Three trials (Burtin et al., 2009; Kho et al., 2019; Schweickert et al., 2009) were excluded from the primary pooled analysis and included in the sensitivity analysis only, as their results were significantly skewed and presented as median with interquartile range. Ten pairwise comparisons from ten randomised controlled trials (n=949) (Amundadottir et al., 2019; Denehy, Skinner, et al., 2013; Eggmann et al., 2018; Hodgson et al., 2020; Kho et al., 2015; McWilliams et al., 2018; Morris et al., 2016; Nakamura et al., 2019; Schaller et al., 2016; Wright et al., 2018) were included in the primary pooled analysis.

Sensitivity analysis

Sensitivity analysis including studies excluded from the primary pooled analysis showed a small difference between groups at ICU discharge, favouring the intervention group (standardised mean difference, 95% confidence interval) (0.13, 95% CI: 0.01 to 0.25), while there were no differences between groups at hospital discharge and 6 months. Pooled analysis of RCTs only did not change the results from the primary pooled analysis.

Subgroup analysis

Subgroup analysis of studies with functional (n= 8) vs. non-functional experimental interventions (n= 2) demonstrated that in the non-functional experimental interventions (Kho et al., 2015; Nakamura et al., 2019), resulted in an improvement of physical function compared to control (standardised mean difference, 95% confidence interval) (0.83, 95% CI 0.32 to 1.34), while the functional intervention resulted in no difference between groups (standardized mean difference, 95% confidence interval) (0.14, 95% CI: -0.08 to 0.35).

Subgroup analysis by the dose of control group therapy showed that physical rehabilitation did not change physical function in either subgroup.

MV free days

Inclusion of data into pooled analysis

Six randomised controlled trials (Abu-Khaber et al., 2019; Fossat et al., 2018; Hodgson et al., 2016; Morris et al., 2016; Nydahl et al., 2019; Schweickert et al., 2009) reported ventilatory free days at day 28. One trial [18] was excluded from the primary pooled analysis and included only in the sensitivity analysis, as their results were significantly skewed and presented as median with interquartile range. Five pairwise comparisons from five RCTs (n=1014) were included in the primary pooled analysis.

References

References have been incorporated into the thesis bibliography.

5.3. Chapter summary

This systematic review and meta-analysis found that physical rehabilitation in the ICU improves physical function at hospital discharge and reduces ICU and hospital LOS. However, it does not appear to impact MV duration, muscle strength, HRQoL, and mortality.

The results of this systematic review and meta-analysis suggest the dose-response relationship of physical rehabilitation in critically ill patients is not linear, with a diminishing benefit at higher doses. Task-specific exercises produced better outcomes than non-functional exercises and should be the focus of care delivery in the clinical setting.

Chapter 6. Conclusions

6.1. Summary of research findings

The aims of this body of research presented in this thesis were to explore the mechanism of muscle wasting in the critically ill; investigate the safety and feasibility of a physical activity program in ICU patients requiring CRRT, and investigate the effectiveness of physical rehabilitation in the ICU.

The first aim of the thesis was to investigate the relationship between serum activin A levels, muscle strength, and physical function. Serum activin A concentration was elevated in a cohort of critically ill patients. Higher peak activin A concentrations were associated with worse muscle strength and physical function. High activin A concentrations were also associated with increased ICU and hospital mortality. Activin A is a potential therapeutic target to prevent and treat muscle wasting in critically ill patients.

The second aim was to test the safety and feasibility of mobilisation in ICU patients with femoral vascular catheter placement during CRRT. This study demonstrated an extremely low incidence of adverse events in critically ill patients requiring CRRT participating in functional and bed-based physical rehabilitation. Patient mobilisation was associated with extended filter life.

The systematic review and meta-analysis aimed to investigate the effectiveness of physical rehabilitation that begins in the ICU, focusing on task-specific interventions and the dosage of control group therapy. Physical rehabilitation in the ICU improves physical function at hospital discharge and reduces ICU and hospital LOS. However, it does not appear to impact MV duration, muscle strength, HRQoL, and mortality.

The experimental intervention reduced the duration of MV, ICU and hospital LOS in the subgroup of studies where control therapy was available for 5 days per week or less. However, in the subgroup of studies where control therapy was available for at least 5 days per week, the experimental intervention did not result in benefits.

Subgroup analysis of studies with functional experimental interventions resulted in reductions in the duration of MV, ICU and hospital LOS, but not in studies with non-functional experimental interventions.

6.2. Clinical significance of the research

In the first observational study, I have explored and identified a relationship between activin A concentration, muscle strength, and physical function in the critically ill. Elevated peak activin A concentration was associated with worse muscle strength and physical function at different time points in the patient's ICU and hospital stay. This is of particular significance because inhibition of ActRIIB has been shown to increase muscle mass in healthy volunteers (Attie et al., 2013) and patients with chronic obstructive pulmonary disease (Polkey et al., 2019). The data suggest activin A is an influential factor in the muscle catabolism observed in critical illness survivors and a potential therapeutic target.

In the second clinical study, I have demonstrated that mobilisation of patients with femoral vascular catheters receiving CRRT in the ICU was safe and feasible. The intervention did not result in vascular catheter dislodgement, haematoma, or bleeding, and there were no detectable clinical sequelae, including suspected thrombosis or filter circuit disruption. The results of this study have directly influenced clinical practice guidelines for active

mobilisation of mechanically ventilated critically ill adults (Hodgson et al., 2014). Patients undergoing CRRT are no longer precluded from early mobilisation on the basis that a vascular catheter or CRRT is in situ. The results of this study have contributed to and are supported by a recent systematic review and meta-analysis of fifteen studies (K. P. Mayer et al., 2020).

My findings also suggest that stasis of blood influences filter life, which may be a significant contributor to ICU morbidity and mortality in this population. However, this concept remains unexplored in the ICU literature. Further research is necessary to optimise the delivery of CRRT in the ICU, which is a critical component of the care of patients with acute kidney injury.

The systematic review and meta-analysis found that physical rehabilitation commenced in an intensive care unit improves physical function at hospital discharge and reduces ICU and hospital LOS compared to usual care.

Physical rehabilitation was associated with a shorter LOS in the hospital, with improved physical function at hospital discharge. The rate of recovery in physical function was faster in participants who received the intervention. However, this more rapid rate of recovery has not led to improved outcomes at 6-month follow-up. In comparison to in-hospital data, only a small number of included studies have reported physical function and health-related quality of life beyond discharge from the acute hospital. Further high-quality studies are required to investigate the long-term effect of physical rehabilitation in the ICU.

The present data suggest that additional rehabilitation intervention, when compared to control therapy that is infrequent (< 5 days per week), provided benefits, but not when

compared to control therapy that is available frequently (≥ 5 days per week). This result suggests that the dose-response relationship of physical rehabilitation in the critically ill patient is not linear, with benefits diminishing at higher doses (Figure 6.1). Diminishing returns with increasing dosage is not a new concept in physical rehabilitation (Rose et al., 2017). This is the first study to demonstrate a diminishing benefit of increased dosage of physical rehabilitation in the critically ill.

Studies with task-specific experimental intervention resulted in improved outcomes, but studies with non-functional experimental interventions did not. Functional exercises produce better physical function outcomes than non-functional exercises in non-ICU patients (de Vreede et al., 2005; Di Monaco et al., 2009; Lowe et al., 2009; Nadeau et al., 2013). Functional exercises also have benefits in other domains in the critically ill population, including cognition and resolution of delirium (Needham et al., 2010; Schweickert et al., 2009).

In summary, intensive care units should have physical rehabilitation services available up to 5 days per week, leading to decreased healthcare utilisation and improved physical function. When interpreting trials investigating rehabilitation in the ICU, it is crucial to consider the intervention provided to the control group. Wherever possible, progressive functional exercises should be used for the physical rehabilitation of patients in the ICU. In ICUs that already offer physical rehabilitation services at least five days per week, the evidence does not support a further increase in the dosage of rehabilitation to improve outcomes.

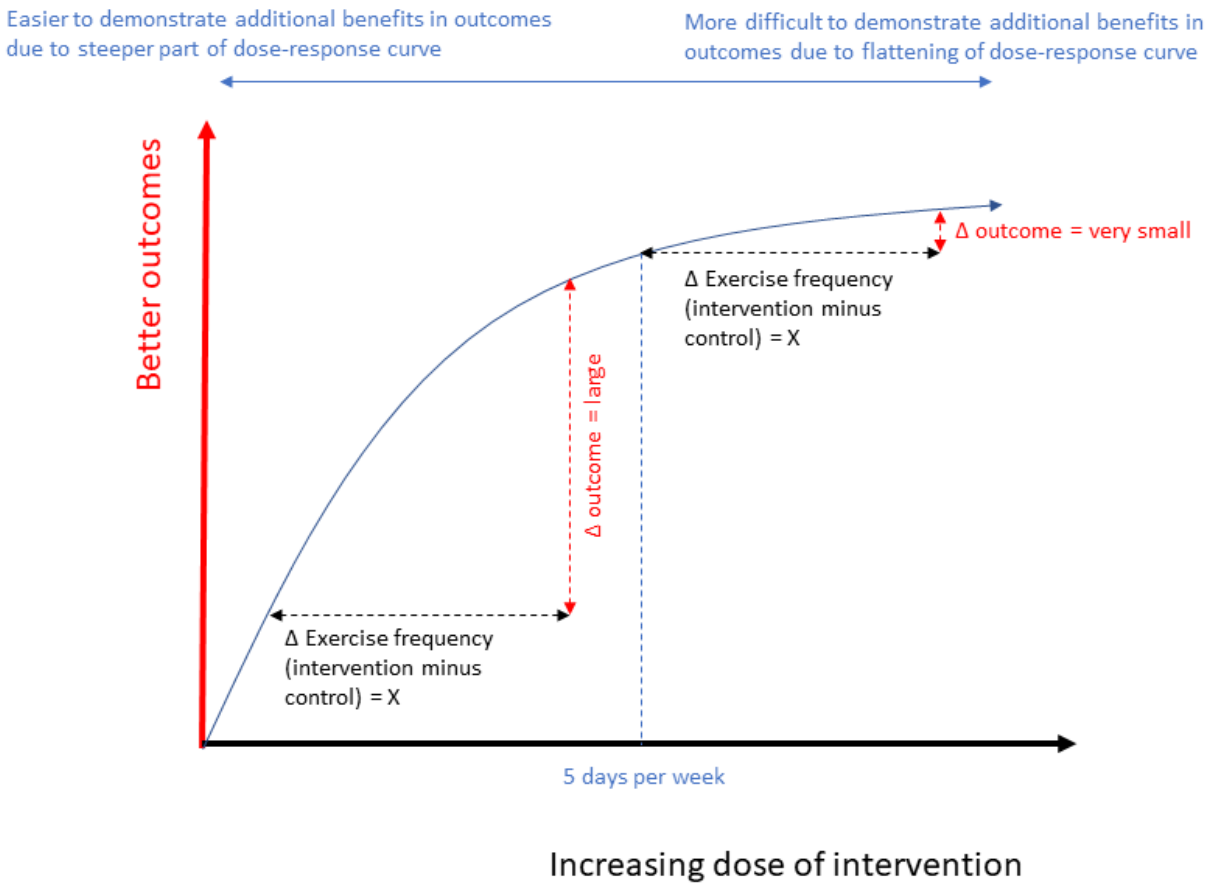


Figure 6.1 A conceptual dose-response relationship of physical rehabilitation in the ICU.

6.3. Strengths and limitations of the research

The observational study investigating the relationship of activin A and patient outcomes was a novel proof-of-concept study, with daily measurements of activin A concentrations during the intensive care unit stay. However, this study was underpowered with a small consecutive sample to thoroughly investigate the relationship between activin A and patient outcomes. Several outcome measures did not have significant associations with activin measures. While the directions of coefficients were consistent with our hypothesis, the confidence intervals were wide. I therefore cannot be sure that a clinically meaningful association with these variables does not exist due to our small sample size. A consecutive sample also

meant there was heterogeneity in the participant cohort, with a mixture of medical and surgical patients, and different admission diagnoses. The effect of activin A could have been variable across this cohort.

At the time of the study, there was no feasible and accurate method to measure total skeletal muscle mass. Therefore I did not include muscle mass as an outcome. Consequently, I need to consider the possibility that activin A impacts muscle strength and physical function through mechanisms other than muscle mass. I also did not have the opportunity to investigate the expression of key genes involved in the UPS and ALS, which would have provided further insight into the role of activin A in muscle catabolism in the critically ill.

Since the design and conduct of this study, the importance of pre-ICU physical function and frailty has been highlighted in the literature. Unfortunately, it was not considered in the design of this present study. Therefore I do not have data on the pre-ICU physical function of the participants and how that may have affected the results.

Activin A concentrations had to be treated as an ordinal dependent variable because low-level measurements of activin A taken using the assay approach return a result of “<24 pg/ml”. While this was the most appropriate way to analyse the data, it was impossible to investigate the accuracy of activin as a predictor variable while adjusting for other confounders with patient outcomes.

The safety and feasibility study in the cohort of patients undergoing renal replacement therapy utilised comprehensive outcome measures for both safety and feasibility, including

careful measurement of adverse events such as dislodgement, bleeding, bruising, and neurovascular observations.

This study was limited by its single-health-service design, and the sample size was small (albeit one of the largest to date in this field reported in the literature). Large multicentre studies are warranted to confirm our findings and further strengthen our conclusions, particularly those pertaining to filter life. Delivery of CRRT was not standardized, and the filter failure criteria were not specified *a priori*.

The systematic review and meta-analysis address two major sources of heterogeneity not investigated in previous reviews, the type of exercise and intensity of control condition, which are essential in interpreting the body of evidence. This review benefits from a novel data synthesis and analytic approach, and many included studies.

The main limitation of this review was the existing heterogeneity and lack of adequate reporting of interventions. I aimed to investigate the dose-responsiveness of physical rehabilitation and compare the efficacy of different exercise modalities; however, these were limited by insufficient reporting of frequency, intensity, and duration of therapy. Reid and colleagues (Reid et al., 2018) found similar results in a scoping review of 117 studies, wherein the interventions provided in most studies were poorly described, particularly the amount of physical rehabilitation available to the control group participants.

As an ICU physiotherapist working clinically, I have been exposed to ongoing trials and systematic reviews investigating physical rehabilitation in the ICU before undertaking this review. Therefore, I acknowledge that my perception of what should be defined as functional exercise and what represents standard practice may have been influenced by this.

This systematic review did not have the scope to investigate the effect of sedation practices on the delivery and effectiveness of physical rehabilitation. Sedation breaks or lighter sedation targets allow volitional participation in physical rehabilitation, particularly task-specific exercises. Sedation practices may also influence the time to initiation of physical rehabilitation, which is also an important factor in the effectiveness of physical rehabilitation (Tipping et al., 2017). The positive benefits of MV duration, ICU length of stay and hospital length of stay may be confounded by sedation practices. Although in practice, it is highly recommended that sedation management and physical rehabilitation are both included in a bundle of care to optimise the outcomes of critically ill patients (Barr & Pandharipande, 2013; Morandi et al., 2011; Vanhorebeek et al., 2020).

It also must be noted that overall, the risk of bias in the included studies was high. Therefore, caution should be exercised in interpreting and applying the results based on the risk of bias of the included trials. This is an important consideration, for the interpretation of this evidence and the planning of future trials, given that a generally positive view of early rehabilitation can create a cognitive bias leading to other positive beliefs about early rehabilitation (Goddard et al., 2018).

There was no scope within our research program to follow up on findings from the individual studies. Activin was identified as a potential explanatory variable of ICU-AW; physical rehabilitation was safe, feasible, and effective. Investigating the response of activin A concentrations to physical rehabilitation would have provided further insight into the prevention and management of ICU-AW.

6.4. Recommendations

Most recommendations from this body of work primarily relate to suggestions for future research.

A single physical function outcome measure that is responsive to change across the continuum of care needs to be developed to support future observational and interventional studies in this population. In addition, an accurate and practical method to measure total skeletal mass in critically ill patients is needed. Recent work by Cawthon and colleagues (Cawthon et al., 2019) using D3-creatine dilution to measure muscle mass shows promise and should be validated in this population.

Activin A concentrations should be described in populations at risk of ICU-AW, such as patients undergoing continuous renal replacement therapy or patients with acute respiratory failure. The associations between initial activin A concentration should be investigated in an adequately powered study. Activities of signalling pathways upstream to activin A should also be investigated. The pre-ICU frailty of the participants should be considered.

It is recommended that future research take serial measurements of activin A so the peak value can be identified. This will allow activin A to be investigated as an independent continuous variable, alongside other predictors of physical function and mortality. In addition, a larger study in a more homogenous patient cohort such as sepsis or acute respiratory failure is warranted to explore further the relationship between activin receptor agonists and patient outcomes, including measurements of muscle mass and gene expression.

The activities of the activin A receptor pathway in response to treatments proposed to prevent or treat ICU-AW should be investigated. The reaction of activin A concentrations to physical rehabilitation would have provided further insight into the prevention and

management of ICU-AW. Phase I clinical trials involving activin receptor antagonists, such as bimagrumab (Lach-Trifilieff et al., 2014; Polkey et al., 2019) and ACE-031 (Attie et al., 2013), should be planned in the critically ill populations susceptible to muscle catabolism.

Patients undergoing CRRT should no longer be precluded from early mobilisation on the basis that CRRT is in situ via a femoral dialysis catheter. Given the established benefit of early mobilisation in the critical care population, early mobilisation should be considered as part of the management of patients undergoing CRRT. Early mobilisation protocols aimed to ensure safety and feasibility should be developed by multidisciplinary teams within individual institutions, considering patient, equipment, and staffing profiles. Stasis secondary to immobility may contribute to the life of the haemodiafiltration circuit. Large multicentre studies are warranted to confirm our research findings and further strengthen our conclusions, particularly those pertaining to filter life. In future studies, researchers could investigate a possible dose-response relationship between mobilisation and filter life.

From the systematic review and meta-analysis of physical rehabilitation, it is recommended that future trials report control and experimental interventions in a fashion that would allow analysis based on type and dosage of intervention delivered (i.e., using the TIDieR checklist (Hoffmann et al., 2014)). Future trials should use standardised outcome measures and time points that are meaningful to ICU survivors and healthcare providers, such as European quality of life-5 domains and 36-item Short-Form Health Survey version 2 for the evaluation of HRQoL and pain; six-minute walk test for physical function, manual muscle test, and grip strength for muscle strength (D. M. Needham et al., 2017). Studies reporting time-related outcomes such as MV duration and LOS in a critically ill population should report survivors and non-survivors separately and follow-up for 60 days (Blackwood et al., 2019). Embedding biochemical outcomes measures such as activin A concentration in future trials investigating

physical rehabilitation in the ICU would help to bridge the knowledge gap between pathophysiologic mechanisms and patient outcomes. Specific dose-response trials are needed, where the type of intervention is held constant, and different dosages of physical rehabilitation are investigated. As standard practice evolves to include routine physical activity in the ICU and with diminishing benefits of physical rehabilitation at higher doses, larger sample sizes may be needed for future trials.

6.5. Conclusions

In conclusion, Activin A appears to be a promising pharmacological target for physical disability in critical illness. Mobilisation during CRRT via a vascular catheter in patients who are critically ill is safe and feasible. Physical rehabilitation in the ICU improves physical function at hospital discharge and reduces ICU and hospital LOS. However, it has no impact on MV duration, muscle strength, HRQoL, and mortality. Wherever possible, task-specific exercises should be used for patients in the ICU, and the benefits of higher dose physical rehabilitation are unclear in patients already receiving regular exercise therapy.

Bibliography

1. Abu-Khaber, H. A., Abouelela, A. M. Z., & Abdelkarim, E. M. (2019). Effect of electrical muscle stimulation on prevention of ICU acquired muscle weakness and facilitating weaning from mechanical ventilation. *Alexandria journal of medicine, 49*(4), 309-315. doi:10.1016/j.ajme.2013.03.011

2. ACCCN. (2003). ACCCN ICU staffing position statement on intensive care nursing staffing.

3. Adler, J., & Malone, D. (2012). Early mobilization in the intensive care unit: a systematic review. *Cardiopulm Phys Ther J, 23*(1), 5-13.

4. Akar, O., Gunay, E., Sarinc Ulasli, S., Ulasli, A. M., Kacar, E., Sariaydin, M., . . . Unlu, M. (2017). Efficacy of neuromuscular electrical stimulation in patients with COPD followed in intensive care unit. *Clin Respir J, 11*(6), 743-750. doi:10.1111/crj.12411

5. Al-Wakeel, J., Milwalli, A., Malik, G., Huraib, S., Al-Mohaya, S., Abu-Aisha, H., & Memon, N. (1998). Dual-lumen femoral vein catheterization as vascular access for haemodialysis. *Angiology, 49*(7), 557-562.

6. Ali, N. A., O'Brien, J. M., Jr., Hoffmann, S. P., Phillips, G., Garland, A., Finley, J. C., . . . Midwest Critical Care, C. (2008). Acquired weakness, handgrip strength, and mortality in critically ill patients. *Am J Respir Crit Care Med, 178*(3), 261-268. doi:10.1164/rccm.200712-1829OC

7. Allen, D. C., Arunachalam, R., & Mills, K. R. (2008). Critical illness myopathy: further evidence from muscle-fiber excitability studies of an acquired channelopathy. *Muscle Nerve, 37*(1), 14-22. doi:10.1002/mus.20884

8. Amundadottir, O., Jonasdottir, R., Sigvaldason, K., Gunnsteinsdottir, E., Haraldsdottir, B., Sveinsson, T., . . . Dean, E. (2019). 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*. Retrieved from doi:10.1080/21679169.2019.1645880

9. Anekwe, D. E., Biswas, S., Bussières, A., & Spahija, J. (2020). Early rehabilitation reduces the likelihood of developing intensive care unit-acquired weakness: a systematic review and meta-analysis. *Physiotherapy, 107*, 1-10. doi:10.1016/j.physio.2019.12.004

10. Anekwe, D. E., Milner, S. C., Bussières, A., de Marchie, M., & Spahija, J. (2020). Intensive care unit clinicians identify many barriers to, and facilitators of, early mobilisation: a qualitative study using the Theoretical Domains Framework. *Journal of physiotherapy, 66*(2), 120-127. doi:https://doi.org/10.1016/j.jphys.2020.03.001

11. Annane, D., Bellissant, E., Bollaert, P. E., Briegel, J., Keh, D., & Kupfer, Y. (2015). Corticosteroids for treating sepsis. *Cochrane Database Syst Rev, 2015*(12), Cd002243. doi:10.1002/14651858.CD002243.pub3

12. Appleton, R. T., MacKinnon, M., Booth, M. G., Wells, J., & Quasim, T. (2011). Rehabilitation within Scottish intensive care units: a national survey. *Journal of the intensive care society, 12*(3), 221-227.

13. Arabi, Y., Venkatesh, S., Haddad, S., Al-Shimemeri, A., & Al-Malik, S. (2002). A prospective study of prolonged stay in the intensive care unit: predictors and impact on resource utilization. *International Journal for Quality in Health Care, 14*(5), 403-410.

14. Arbane, G., Douiri, A., Hart, N., Hopkinson, N. S., Singh, S., Speed, C., . . . Garrod, R. (2014). Effect of postoperative physical training on activity after curative surgery for non-small cell lung cancer: a multicentre randomised controlled trial. *Physiotherapy, 100*(2), 100-107. doi:10.1016/j.physio.2013.12.002

15. ATS. (2002). ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med, 166*(1), 111-117. doi:10.1164/ajrccm.166.1.at1102

16. ATS/ERS. (2002). ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med, 166*(4), 518-624. doi:10.1164/rccm.166.4.518

17. Attie, K. M., Borgstein, N. G., Yang, Y., Condon, C. H., Wilson, D. M., Pearsall, A. E., . . . Sherman, M. L. (2013). A single ascending‐dose study of muscle regulator ACE‐031 in healthy volunteers. *Muscle & nerve, 47*(3), 416-423.

18. Australian and New Zealand Intensive Care Society. (2020). ANZICS Adult Patient Database 2020, Data Dictionary. Retrieved from https://www.anzics.com.au/wp-content/uploads/2018/08/ANZICS-APD-Data-Dictionary.pdf

19. Bakhru, R. N., McWilliams, D. J., Wiebe, D. J., Spuhler, V. J., & Schweickert, W. D. (2016). Intensive Care Unit Structure Variation and Implications for Early Mobilization Practices. An International Survey. *Ann Am Thorac Soc, 13*(9), 1527-1537. doi:10.1513/AnnalsATS.201601-078OC

20. Bakhru, R. N., Wiebe, D. J., McWilliams, D. J., Spuhler, V. J., & Schweickert, W. D. (2015). An Environmental Scan for Early Mobilization Practices in U.S. ICUs. *Crit Care Med, 43*(11), 2360-2369. doi:10.1097/ccm.0000000000001262

21. Balas, M. C., Burke, W. J., Gannon, D., Cohen, M. Z., Colburn, L., Bevil, C., . . . Vasilevskis, E. E. (2013). Implementing the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle into everyday

care: opportunities, challenges, and lessons learned for implementing the ICU Pain, Agitation, and Delirium Guidelines. *Critical Care Medicine, 41*(9), S116-S127.

22. Baldwin, C. E., Paratz, J. D., & Bersten, A. D. (2013). Muscle strength assessment in critically ill patients with handheld dynamometry: an investigation of reliability, minimal detectable change, and time to peak force generation. *J Crit Care, 28*(1), 77-86. doi:10.1016/j.jcrc.2012.03.001

23. Baracos, V., Rodemann, H. P., Dinarello, C. A., & Goldberg, A. L. (1983). Stimulation of muscle protein degradation and prostaglandin E2 release by leukocytic pyrogen (interleukin-1). A mechanism for the increased degradation of muscle proteins during fever. *N Engl J Med, 308*(10), 553-558. doi:10.1056/nejm198303103081002

24. Barber, E. A., Everard, T., Holland, A. E., Tipping, C., Bradley, S. J., & Hodgson, C. L. (2015). Barriers and facilitators to early mobilisation in intensive care: a qualitative study. *Australian Critical Care, 28*(4), 177-182.

25. Barnato, A. E., Albert, S. M., Angus, D. C., Lave, J. R., & Degenholtz, H. B. (2011). Disability among elderly survivors of mechanical ventilation. *Am J Respir Crit Care Med, 183*(8), 1037-1042. doi:10.1164/rccm.201002-0301OC

26. Barohn, R. J., Jackson, C. E., Rogers, S. J., Ridings, L. W., & McVey, A. L. (1994). Prolonged paralysis due to nondepolarizing neuromuscular blocking agents and corticosteroids. *Muscle Nerve, 17*(6), 647-654. doi:10.1002/mus.880170613

27. Barr, J., & Pandharipande, P. P. (2013). The pain, agitation, and delirium care bundle: synergistic benefits of implementing the 2013 Pain, Agitation, and Delirium Guidelines in an integrated and interdisciplinary fashion. *Crit Care Med, 41*(9 Suppl 1), S99-115. doi:10.1097/CCM.0b013e3182a16ff0

28. Bashar, F. R., Vahedian-Azimi, A., Hajiesmaeili, M., Salesi, M., Farzanegan, B., Shojaei, S., . . . Miller, A. C. (2018). Post-ICU psychological morbidity in very long ICU stay patients with ARDS and delirium. *Journal of Critical Care, 43*, 88-94. doi:https://doi.org/10.1016/j.jcrc.2017.08.034

29. Bassett, R., Adams, K. M., Danesh, V., Groat, P. M., Haugen, A., Kiewel, A., . . . Ely, E. W. (2015). Rethinking critical care: decreasing sedation, increasing delirium monitoring, and increasing patient mobility. *The Joint Commission Journal on Quality and Patient Safety, 41*(2), 62-74.

30. Bassett, R. D., Vollman, K. M., Brandwene, L., & Murray, T. (2012). Integrating a multidisciplinary mobility programme into intensive care practice (IMMPTP): a multicentre collaborative. *Intensive and Critical Care Nursing, 28*(2), 88-97.

31. Batt, J., dos Santos, C. C., Cameron, J. I., & Herridge, M. S. (2013). Intensive care unit-acquired weakness: clinical phenotypes and molecular mechanisms. *Am J Respir Crit Care Med, 187*(3), 238-246. doi:10.1164/rccm.201205-0954SO

32. Bednarík, J., Vondracek, P., Dusek, L., Moravcova, E., & Cundrle, I. (2005). Risk factors for critical illness polyneuromyopathy. *J Neurol, 252*(3), 343-351. doi:10.1007/s00415-005-0654-x

33. Bercker, S., Weber-Carstens, S., Deja, M., Grimm, C., Wolf, S., Behse, F., . . . Kaisers, U. (2005). Critical illness polyneuropathy and myopathy in patients with acute respiratory distress syndrome. *Crit Care Med, 33*(4), 711-715.

34. Berney, S., Haines, K., Skinner, E. H., & Denehy, L. (2012). Safety and feasibility of an exercise prescription approach to rehabilitation across the continuum of care for survivors of critical illness. *Physical Therapy, 92*, 1524-1535.

35. Berney, S. C., Harrold, M., Webb, S. A., Seppelt, I., Patman, S., Thomas, P. J., & Denehy, L. (2013). Intensive care unit mobility practices in Australia and New Zealand: a point prevalence study. *Crit Care Resusc, 15*(4), 260-265.

36. Berney, S. C., Rose, J. W., Bernhardt, J., & Denehy, L. (2015). Prospective observation of physical activity in critically ill patients who were intubated for more than 48 hours. *Journal of Critical Care, 30*(4), 658-663.

37. Bernhardt, J., Langhorne, P., Lindley, R. I., Thrift, A. G., Ellery, F., Collier, J., . . . Donnan, G. (2015). Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. *Lancet, 386*(9988), 46-55.

38. Bersten, A. a. H., J. (2019). *Oh's Intensive Care Manual. 8th ed.*: Elsevier.

39. Bianchi, T., dos Santos, L., Aguiar Lemos, F., Sachetti, A., & Dall'Acqua, A. (2018). The Effect of Passive Cycle Ergometry Exercise on Dia-Phragmatic Motion of Invasive Mechanically Ventilated Critically Ill Patients in Intensive Care Unit: A Randomized Clinical Trial. *Int J Phys Med Rehabil, 6*(499), 2.

40. Bierbrauer, J., Koch, S., Olbricht, C., Hamati, J., Lodka, D., Schneider, J., . . . Weber-Carstens, S. (2012). Early type II fiber atrophy in intensive care unit patients with nonexcitable muscle membrane. *Crit Care Med, 40*(2), 647-650. doi:10.1097/CCM.0b013e31823295e6

41. Bissett, B. M., Leditschke, I. A., Neeman, T., Boots, R., & Paratz, J. (2016). Inspiratory muscle training to enhance recovery from mechanical ventilation: a randomised trial. *Thorax, 71*(9), 812 - 819. doi:10.1136/thoraxjnl-2016-208279

42. Bittner, E. A., Martyn, J. A., George, E., Frontera, W. R., & Eikermann, M. (2009). Measurement of muscle strength in the intensive care unit. *Crit Care Med, 37*(10 Suppl), S321-330. doi:10.1097/CCM.0b013e3181b6f727

43. Blackwood, B., Ringrow, S., Clarke, M., Marshall, J. C., Connolly, B., Rose, L., & McAuley, D. F. (2019). A Core Outcome Set for Critical Care Ventilation Trials. *Crit Care Med, 47*(10), 1324-1331. doi:10.1097/CCM.0000000000003904

44. Bloch, S., Polkey, M. I., Griffiths, M., & Kemp, P. (2012). Molecular mechanisms of intensive care unit-acquired weakness. *Eur Respir J, 39*(4), 1000-1011. doi:10.1183/09031936.00090011

45. Bodine, S. C., Latres, E., Baumhueter, S., Lai, V. K., Nunez, L., Clarke, B. A., . . . Glass, D. J. (2001). Identification of ubiquitin ligases required for skeletal muscle atrophy. *Science, 294*(5547), 1704-1708. doi:10.1126/science.1065874

46. Boehm, L. M., Lauderdale, J., Garrett, A. N., & Piras, S. E. (2020). A multisite study of multidisciplinary ICU team member beliefs toward early mobility. *Heart & Lung: The Journal of Cardiopulmonary and Acute Care*.

47. Bolton, C. F. (2005). Neuromuscular manifestations of critical illness. *Muscle Nerve, 32*(2), 140-163. doi:10.1002/mus.20304

48. Bolton, C. F., Gilbert, J. J., Hahn, A. F., & Sibbald, W. J. (1984). Polyneuropathy in critically ill patients. *J Neurol Neurosurg Psychiatry, 47*(11), 1223-1231.

49. Boucher, P.-A., Joós, B., & Morris, C. E. (2012). Coupled left-shift of Nav channels: modeling the Na+-loading and dysfunctional excitability of damaged axons. *Journal of computational neuroscience, 33*(2), 301-319.

50. Brealey, D., Brand, M., Hargreaves, I., Heales, S., Land, J., Smolenski, R., . . . Singer, M. (2002). Association between mitochondrial dysfunction and severity and outcome of septic shock. *Lancet, 360*(9328), 219-223. doi:10.1016/s0140-6736(02)09459-x

51. Brummel, N. E., Girard, T. D., Ely, E. W., Pandharipande, P. P., Morandi, A., Hughes, C. G., . . . Jackson, J. C. (2014). Feasibility and safety of early combined cognitive and physical therapy for critically ill medical and surgical patients: the Activity and Cognitive Therapy in ICU (ACT-ICU) trial. *Intensive Care Med, 40*(3), 370-379. doi:10.1007/s00134-013-3136-0

52. Brunello, A.-G., Haenggi, M., Wigger, O., Porta, F., Takala, J., & Jakob, S. M. (2010). Usefulness of a clinical diagnosis of ICU-acquired paresis to predict outcome in patients with SIRS and acute respiratory failure. *Intensive Care Medicine, 36*(1), 66-74. doi:10.1007/s00134-009-1645-7

53. Burford, E. (2012). *The analysis of the strain level and the predicted human error probability for critical hospital tasks.* (Master of Science), Rhodes University, Grahamstown.

54. Burtin, C., Clerckx, B., Robbeets, C., Ferdinande, P., Langer, D., Troosters, T., . . . Gosselink, R. (2009). Early exercise in critically ill patients enhances short-term functional recovery. *Crit Care Med, 37*(9), 2499-2505. doi:10.1097/CCM.0b013e3181a38937

55. Cader, S. A., Vale, R. G., Castro, J. C., Bacelar, S. C., Biehl, C., Gomes, M. C. V., . . . Dantas, E. H. (2010). Inspiratory muscle training improves maximal inspiratory pressure and may assist weaning in older intubated patients: a randomised trial. *Journal of Physiotherapy (Australian Physiotherapy Association), 56*(3), 171-177.

56. Callahan, L. A., & Supinski, G. S. (2009). Sepsis-induced myopathy. *Critical Care Medicine, 37*(10 (Suppl.)), S354-S367.

57. Campellone, J. V., Lacomis, D., Kramer, D. J., Van Cott, A. C., & Giuliani, M. J. (1998). Acute myopathy after liver transplantation. *Neurology, 50*(1), 46-53.

58. Capell, E. L., Tipping, C. J., & Hodgson, C. L. (2019). Barriers to implementing expert safety recommendations for early mobilisation in intensive care unit during mechanical ventilation: A prospective observational study. *Australian Critical Care, 32*(3), 185-190. doi:https://doi.org/10.1016/j.aucc.2018.05.005

59. Carrothers, K. M., Barr, J., Spurlock, B., Ridgely, M. S., Damberg, C. L., & Ely, E. W. (2013). Contextual issues influencing implementation and outcomes associated with an integrated approach to managing pain, agitation, and delirium in adult ICUs. *Critical Care Medicine, 41*(9), S128-S135.

60. Carson, S. S., & Bach, P. B. (2002). The epidemiology and costs of chronic critical illness. *Critical Care Clinics, 18*(3), 461-476.

61. Caruso, P., Denari, S. D., Ruiz, S. A., Bernal, K. G., Manfrin, G. M., Friedrich, C., & Deheinzelin, D. (2005). Inspiratory muscle training is ineffective in mechanically ventilated critically ill patients. *Clinics (sao paulo, brazil), 60*(6), 479 - 484.

62. Castro-Avila, A. C., Seron, P., Fan, E., Gaete, M., & Mickan, S. (2015). Effect of Early Rehabilitation during Intensive Care Unit Stay on Functional Status: Systematic Review and Meta-Analysis. *PLoS One, 10*(7), e0130722. doi:10.1371/journal.pone.0130722

63. Castro, E., Turcinovic, M., Platz, J., & Law, I. (2015). Early Mobilization: Changing the Mindset. *Crit Care Nurse, 35*(4), e1-5; quiz e6. doi:10.4037/ccn2015512

64. Cawthon, P. M., Orwoll, E. S., Peters, K. E., Ensrud, K. E., Cauley, J. A., Kado, D. M., . . . Glynn, N. W. (2019). Strong relation between muscle mass determined by D3-creatine dilution, physical performance, and incidence of falls and mobility limitations in a prospective cohort of older men. *The Journals of Gerontology: Series A, 74*(6), 844-852.

65. Chambers, M. A., Moylan, J. S., & Reid, M. B. (2009). Physical inactivity and muscle weakness in the critically ill. *Critical Care Medicine, 37*(10 (Suppl.)), S337-S346.

66. Chan, K. S., Mourtzakis, M., Friedman, L. A., Dinglas, V. D., Hough, C. L., Ely, E. W., . . . Needham, D. M. (2018). Evaluating muscle mass in survivors of ARDS: a 1-year multi-center longitudinal study. *Critical Care Medicine, 46*(8), 1238.

67. Chang, M. Y., Chang, L. Y., Huang, Y. C., Lin, K. M., & Cheng, C. H. (2011). Chair-sitting exercise intervention does not improve respiratory muscle function in mechanically ventilated intensive care unit patients. *Respir Care, 56*(10), 1533-1538. doi:10.4187/respcare.00938

68. Chen, J. L., Walton, K. L., Winbanks, C. E., Murphy, K. T., Thomson, R. E., Makanji, Y., . . . Gregorevic, P. (2014). Elevated expression of activins promotes muscle wasting and cachexia. *The FASEB Journal, 28*(4), 1711-1723.

69. CICM. (2016). Minimum standards for intensive care units.

70. Clarke, B. A., Drujan, D., Willis, M. S., Murphy, L. O., Corpina, R. A., Burova, E., . . . Latres, E. (2007). The E3 Ligase MuRF1 degrades myosin heavy chain protein in dexamethasone-treated skeletal muscle. *Cell metabolism, 6*(5), 376-385.

71. Cohen, J. (2013). *Statistical power analysis for the behavioral sciences*: Academic press.

72. Cohen, S., Brault, J. J., Gygi, S. P., Glass, D. J., Valenzuela, D. M., Gartner, C., . . . Goldberg, A. L. (2009). During muscle atrophy, thick, but not thin, filament components are degraded by MuRF1-dependent ubiquitylation. *Journal of Cell Biology, 185*(6), 1083-1095.

73. Cohen, S., Nathan, J. A., & Goldberg, A. L. (2015). Muscle wasting in disease: molecular mechanisms and promising therapies. *Nat Rev Drug Discov, 14*(1), 58-74. doi:10.1038/nrd4467

74. Cohen, S., Zhai, B., Gygi, S. P., & Goldberg, A. L. (2012). Ubiquitylation by Trim32 causes coupled loss of desmin, Z-bands, and thin filaments in muscle atrophy. *J Cell Biol, 198*(4), 575-589. doi:10.1083/jcb.201110067

75. Condessa, R. L., Brauner, J. S., Saul, A. L., Baptista, M., Silva, A. C., & Vieira, S. R. (2013). Inspiratory muscle training did not accelerate weaning from mechanical

ventilation but did improve tidal volume and maximal respiratory pressures: a randomised trial. *J Physiother, 59*(2), 101-107. doi:10.1016/S1836-9553(13)70162-0

76. Connolly, B., MacBean, V., Crowley, C., Lunt, A., Moxham, J., Rafferty, G. F., & Hart, N. (2015). Ultrasound for the assessment of peripheral skeletal muscle architecture in critical illness: a systematic review. *Critical care medicine, 43*(4), 897-905.

77. Constantin, D., McCullough, J., Mahajan, R. P., & Greenhaff, P. L. (2011). Novel events in the molecular regulation of muscle mass in critically ill patients. *J Physiol, 589*(Pt 15), 3883-3895. doi:10.1113/jphysiol.2011.206193

78. Cooney, R. N., Maish, G. O., 3rd, Gilpin, T., Shumate, M. L., Lang, C. H., & Vary, T. C. (1999). Mechanism of IL-1 induced inhibition of protein synthesis in skeletal muscle. *Shock, 11*(4), 235-241. doi:10.1097/00024382-199904000-00002

79. Cottereau, G., Dres, M., Avenel, A., Fichet, J., Jacobs, F. M., Prat, D., . . . Sztrymf, B. (2015). Handgrip Strength Predicts Difficult Weaning But Not Extubation Failure in Mechanically Ventilated Subjects. *Respir Care, 60*(8), 1097-1104. doi:10.4187/respcare.03604

80. Coutinho, W. M., Santos, L. J. d., Fernandes, J., Vieira, S. R. R., Forgiarini Junior, L. A., & Dias, A. S. (2016). Efeito agudo da utilização do cicloergômetro durante atendimento fisioterapêutico em pacientes críticos ventilados mecanicamente. *Fisioterapia e Pesquisa, 23*(3), 278-283. doi:10.1590/1809-2950/15549123032016

81. Cunningham, J. N., Jr., Carter, N. W., Rector, F. C., Jr., & Seldin, D. W. (1971). Resting transmembrane potential difference of skeletal muscle in normal subjects and severely ill patients. *J Clin Invest, 50*(1), 49-59. doi:10.1172/jci106483

82. Dafoe, S., Chapman, M. J., Edwards, S., & Stiller, K. (2015). Overcoming barriers to the mobilisation of patients in an intensive care unit. *Anaesth Intensive Care, 43*(6), 719-727. doi:10.1177/0310057x1504300609

83. Dall' Acqua, A. M., Sachetti, A., Santos, L. J., Lemos, F. A., Bianchi, T., Naue, W. S., . . . MoVe, I. C. U. G. (2017). Use of neuromuscular electrical stimulation to preserve the thickness of abdominal and chest muscles of critically ill patients: A randomized clinical trial. *J Rehabil Med, 49*(1), 40-48. doi:10.2340/16501977-2168

84. Damas, P., Ledoux, D., Nys, M., Vrindts, Y., De Groote, D., Franchimont, P., & Lamy, M. (1992). Cytokine serum level during severe sepsis in human IL-6 as a marker of severity. *Ann Surg, 215*(4), 356-362. doi:10.1097/00000658-199204000-00009

85. Damluji, A., Zanni, J. M., Mantheiy, E., Colantuoni, E., Kho, M. E., & Needham, D. M. (2013). Safety and feasibility of femoral catheters during physical rehabilitation in the intensive care unit. *Journal of Critical Care, in press*.

86. Dammeyer, J. A., Baldwin, N., Packard, D., Harrington, S., Christofferson, B., Christopher, J., . . . Iwashyna, J. (2013). Mobilizing outcomes: implementation of a nurse-led multidisciplinary mobility program. *Crit Care Nurs Q, 36*(1), 109-119. doi:10.1097/CNQ.0b013e31827535db

87. Dantas, C. M., Silva, P. F., Siqueira, F. H., Pinto, R. M., Matias, S., Maciel, C., . . . Franca, E. E. (2012). Influence of early mobilization on respiratory and peripheral muscle strength in critically ill patients. *Rev Bras Ter Intensiva, 24*(2), 173-178.

88. Davidson, J. E., Harvey, M. A., Bemis-Dougherty, A., Smith, J. M., & Hopkins, R. O. (2013). Implementation of the Pain, Agitation, and Delirium Clinical Practice Guidelines and promoting patient mobility to prevent post-intensive care syndrome. *Crit Care Med, 41*(9 Suppl 1), S136-145. doi:10.1097/CCM.0b013e3182a24105

89. De Jonghe, B., Bastuji-Garin, S., Durand, M. C., Malissin, I., Rodrigues, P., Cerf, C., . . . Groupe de Reflexion et d'Etude des Neuromyopathies en, R. (2007). Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. *Crit Care Med, 35*(9), 2007-2015.

90. De Jonghe, B., Bastuji-Garin, S., Sharshar, T., Outin, H., & Brochard, L. (2004). Does ICU-acquired paresis lengthen weaning from mechanical ventilation? *Intensive Care Med, 30*(6), 1117-1121. doi:10.1007/s00134-004-2174-z

91. De Jonghe, B., Sharshar, T., Hopkinson, N., & Outin, H. (2004). Paresis following mechanical ventilation. *Curr Opin Crit Care, 10*(1), 47-52. doi:00075198-200402000-00008 [pii]

92. De Jonghe, B., Sharshar, T., Lefaucheur, J. P., Authier, F. J., Durand-Zaleski, I., Boussarsar, M., . . . Groupe de Reflexion et d'Etude des Neuromyopathies en, R. (2002). Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA, 288*(22), 2859-2867. doi:10.1001/jama.288.22.2859

93. de Kretser, D. M., Bensley, J. G., Pettila, V., Linko, R., Hedger, M. P., Hayward, S., . . . Phillips, D. J. (2013). Serum activin A and B levels predict outcome in patients with acute respiratory failure: a prospective cohort study. *Crit Care, 17*(5), R263. doi:10.1186/cc13093

94. de Letter, M. A., Schmitz, P. I., Visser, L. H., Verheul, F. A., Schellens, R. L., Op de Coul, D. A., & van der Meche, F. G. (2001). Risk factors for the development of polyneuropathy and myopathy in critically ill patients. *Crit Care Med, 29*(12), 2281-2286.

95. de Vreede, P. L., Samson, M. M., van Meeteren, N. L., Duursma, S. A., & Verhaar, H. J. (2005). Functional-task exercise versus resistance strength exercise to improve daily function in older women: a randomized, controlled trial. *J Am Geriatr Soc, 53*(1), 2-10. doi:10.1111/j.1532-5415.2005.53003.x

96. Dellinger, R. P., Levy, M. M., Rhodes, A., Annane, D., Gerlach, H., Opal, S. M., . . . Subgroup, a. t. S. S. C. G. C. i. t. P. (2013). Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012. *Critical Care Medicine, 41*(2), 580-637. doi:10.1097/CCM.0b013e31827e83af

97. Denehy, L., de Morton, N. A., Skinner, E. H., Edbrooke, L., Haines, K., Warrillow, S., & Berney, S. (2013). A physical function test for use in the intensive care unit: validity, responsiveness, and predictive utility of the physical function ICU test (scored). *Phys Ther, 93*(12), 1636-1645. doi:10.2522/ptj.20120310

98. Denehy, L., Skinner, E. H., Edbrooke, L., Haines, K., Warrillow, S., Hawthorne, G., . . . Berney, S. (2013). Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up. *Crit Care, 17*(4), R156. doi:10.1186/cc12835

99. Derde, S., Hermans, G., Derese, I., Guiza, F., Hedstrom, Y., Wouters, P. J., . . . Vanhorebeek, I. (2012). Muscle atrophy and preferential loss of myosin in prolonged critically ill patients. *Crit Care Med, 40*(1), 79-89. doi:10.1097/CCM.0b013e31822d7c18

100. Dettling-Ihnenfeldt, D. S., Wieske, L., Horn, J., Nollet, F., & van der Schaaf, M. (2017). Functional Recovery in Patients With and Without Intensive Care Unit-Acquired Weakness. *Am J Phys Med Rehabil, 96*(4), 236-242. doi:10.1097/PHM.0000000000000586

101. Di Giovanni, S., Mirabella, M., D'Amico, A., Tonali, P., & Servidei, S. (2000). Apoptotic features accompany acute quadriplegic myopathy. *Neurology, 55*(6), 854. doi:10.1212/WNL.55.6.854

102. Di Monaco, M., Vallero, F., Tappero, R., & Cavanna, A. (2009). Rehabilitation after total hip arthroplasty: a systematic review of controlled trials on physical exercise programs. *Eur J Phys Rehabil Med, 45*(3), 303-317.

103. Diaz, N., Finol, H. J., Torres, S., Zambrano, C., & Adjounian, H. (1998). Histochemical and ultrastructural study of skeletal muscle in patients with sepsis and multiple organ failure syndrome (MOFS).

104. Diaz, N. L., Finol, H. J., Torres, S. H., Zambrano, C. I., & Adjounian, H. (1998). Histochemical and ultrastructural study of skeletal muscle in patients with sepsis and multiple organ failure syndrome (MOFS). *Histol Histopathol, 13*(1), 121-128. doi:10.14670/HH-13.121

105. Ding, N., Zhang, Z., Zhang, C., Yao, L., Yang, L., Jiang, B., . . . Tian, J. (2019). What is the optimum time for initiation of early mobilization in mechanically ventilated patients? A network meta-analysis. *Plos one, 14*(10), e0223151. doi:10.1371/journal.pone.0223151

106. Dinglas, V. D., Aronson Friedman, L., Colantuoni, E., Mendez-Tellez, P. A., Shanholtz, C. B., Ciesla, N. D., . . . Needham, D. M. (2017). Muscle Weakness and 5-Year Survival in Acute Respiratory Distress Syndrome Survivors. *Crit Care Med, 45*(3), 446-453. doi:10.1097/CCM.0000000000002208

107. Dinglas, V. D., Colantuoni, E., Ciesla, N., Mendez-Tellez, P. A., Shanholtz, C., & Needham, D. M. (2013). Occupational therapy for patients with acute lung injury: factors associated with time to first intervention in the intensive care unit. *American Journal of Occupational Therapy, 67*(3), 355-362.

108. Doig, G. S., Simpson, F., Sweetman, E. A., Finfer, S. R., Cooper, D. J., Heighes, P. T., . . . Peake, S. (2013). Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. *JAMA, 309*(20), 2130-2138. doi:10.1001/jama.2013.5124

109. Dong, Z., Yu, B., Zhang, Q., Pei, H., Xing, J., Fang, W., . . . Song, Z. (2016). Early Rehabilitation Therapy Is Beneficial for Patients With Prolonged Mechanical Ventilation After Coronary Artery Bypass Surgery. *Int Heart J, 57*(2), 241-246. doi:10.1536/ihj.15-316

110. Dong, Z. H., Yu, B. X., Sun, Y. B., Fang, W., & Li, L. (2014). Effects of early rehabilitation therapy on patients with mechanical ventilation. *World J Emerg Med, 5*(1), 48-52. doi:10.5847/wjem.j.issn.1920-8642.2014.01.008

111. Dos Santos, C., Hussain, S. N., Mathur, S., Picard, M., Herridge, M., Correa, J., . . . Canadian Critical Care Translational Biology, G. (2016). Mechanisms of Chronic Muscle Wasting and Dysfunction after an Intensive Care Unit Stay. A Pilot Study. *Am J Respir Crit Care Med, 194*(7), 821-830. doi:10.1164/rccm.201512-2344OC

112. dos Santos, F. V., Cipriano Jr, G., Vieira, L., Güntzel Chiappa, A. M., Cipriano, G. B. F., Vieira, P., . . . Chiappa, G. R. (2020). Neuromuscular electrical stimulation combined with exercise decreases duration of mechanical ventilation in ICU patients: a randomized controlled trial. *Physiotherapy theory and practice, 36*(5), 580-588. Retrieved from doi:10.1080/09593985.2018.1490363

113. Dowdy, D. W., Eid, M. P., Sedrakyan, A., Mendez-Tellez, P. A., Pronovost, P. J., Herridge, M. S., & Needham, D. M. (2005). Quality of life in adult survivors of critical illness: a systematic review of the literature. *Intensive Care Med, 31*(5), 611-620. doi:10.1007/s00134-005-2592-6

114. Dres, M., Dubé, B. P., Mayaux, J., Delemazure, J., Reuter, D., Brochard, L., . . . Demoule, A. (2017). Coexistence and Impact of Limb Muscle and Diaphragm

Weakness at Time of Liberation from Mechanical Ventilation in Medical Intensive Care Unit Patients. *Am J Respir Crit Care Med, 195*(1), 57-66. doi:10.1164/rccm.201602-0367OC

115. Eggmann, S., Verra, M. L., Luder, G., Takala, J., & Jakob, S. M. (2018). Effects of early, combined endurance and resistance training in mechanically ventilated, critically ill patients: A randomised controlled trial. *Plos one, 13*(11), e0207428. doi:10.1371/journal.pone.0207428

116. Eikermann, M., Koch, G., Gerwig, M., Ochterbeck, C., Beiderlinden, M., Koeppen, S., . . . Peters, J. (2006). Muscle force and fatigue in patients with sepsis and multiorgan failure. *Intensive Care Medicine, 32*(2), 251-259.

117. Elbouhy, M. S., AbdelHalim, H. A., & Hashem, A. M. A. (2014). Effect of respiratory muscles training in weaning of mechanically ventilated COPD patients. *Egyptian journal of chest diseases and tuberculosis, 63*(3), 679-687. doi:10.1016/j.ejcdt.2014.03.008

118. Elkins, M., & Dentice, R. (2015). Inspiratory muscle training facilitates weaning from mechanical ventilation among patients in the intensive care unit: a systematic review. *Journal of physiotherapy, 61*(3), 125-134. doi:https://doi.org/10.1016/j.jphys.2015.05.016

119. Ely, E. W., Inouye, S. K., Bernard, G. R., Gordon, S., Francis, J., May, L., . . . Dittus, R. (2001). Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA, 286*(21), 2703-2710. doi:10.1001/jama.286.21.2703

120. Engel, H. J., Tatebe, S., Alonzo, P. B., Mustille, R. L., & Rivera, M. J. (2013). Physical therapist–established intensive care unit early mobilization program: quality improvement project for critical care at the University of California San Francisco Medical Center. *Physical Therapy, 93*(7), 975-985.

121. Erie, R., & Kandel, J. H. (2000). Principles of neural science 4th edition. In: McGraw-Hill Companies, Inc.

122. Evans, W. J., Hellerstein, M., Orwoll, E., Cummings, S., & Cawthon, P. M. (2019). D3‐Creatine dilution and the importance of accuracy in the assessment of skeletal muscle mass. *Journal of cachexia, sarcopenia and muscle, 10*(1), 14-21.

123. Fan, E., Cheek, F., Chlan, L., Gosselink, R., Hart, N., Herridge, M. S., . . . American Thoracic, S. (2014). An official American Thoracic Society Clinical Practice guideline: the diagnosis of intensive care unit-acquired weakness in adults. *Am J Respir Crit Care Med, 190*(12), 1437-1446. doi:10.1164/rccm.201411-2011ST

124. Fan, E., Dowdy, D. W., Colantuoni, E., Mendez-Tellez, P. A., Sevransky, J. E., Shanholtz, C., . . . Needham, D. M. (2014). Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. *Crit Care Med, 42*(4), 849-859. doi:10.1097/CCM.0000000000000040

125. Fenzi, F., Latronico, N., Refatti, N., & Rizzuto, N. (2003). Enhanced expression of E-selectin on the vascular endothelium of peripheral nerve in critically ill patients with neuromuscular disorders. *Acta Neuropathol, 106*(1), 75-82. doi:10.1007/s00401-003-0704-3

126. Ferrando, A. A., Stuart, C. A., Sheffield-Moore, M., & Wolfe, R. R. (1999). Inactivity amplifies the catabolic response of skeletal muscle to cortisol. *Journal of Clinical Endocrinology and Metabolism, 84*(10), 3515-3521.

127. Ferrante, L. E., Pisani, M. A., Murphy, T. E., Gahbauer, E. A., Leo-Summers, L. S., & Gill, T. M. (2015). Functional trajectories among older persons before and after critical illness. *JAMA Intern Med, 175*(4), 523-529. doi:10.1001/jamainternmed.2014.7889

128. Fielitz, J., Kim, M.-S., Shelton, J. M., Latif, S., Spencer, J. A., Glass, D. J., . . . Olson, E. N. (2007). Myosin accumulation and striated muscle myopathy result from the loss of muscle RING finger 1 and 3. *The Journal of clinical investigation, 117*(9), 2486-2495.

129. Filatov, G. N., Pinter, M. J., & Rich, M. M. (2009). Role of Ca2+ in injury-induced changes in sodium current in rat skeletal muscle. *American Journal of Physiology-Cell Physiology, 297*(2), C352-C359.

130. Finfer, S., Chittock, D. R., Su, S. Y., Blair, D., Foster, D., Dhingra, V., . . . Ronco, J. J. (2009). Intensive versus conventional glucose control in critically ill patients. *N Engl J Med, 360*(13), 1283-1297. doi:10.1056/NEJMoa0810625

131. Fink, H., Helming, M., Unterbuchner, C., Lenz, A., Neff, F., Martyn, J. A., & Blobner, M. (2008). Systemic inflammatory response syndrome increases immobility-induced neuromuscular weakness. *Critical Care Medicine, 36*(3), 910-916.

132. Finn, P. J., Plank, L. D., Clark, M. A., Connolly, A. B., & Hill, G. L. (1996). Assessment of involuntary muscle function in patients after critical injury or severe sepsis. *JPEN. Journal of Parenteral and Enteral Nutrition, 20*(5), 332-337.

133. Finn, P. J., Plank, L. D., Clark, M. A., Connolly, A. B., & Hill, G. L. (1996). Progressive cellular dehydration and proteolysis in critically ill patients. *Lancet, 347*(9002), 654-656.

134. Fischer, A., Spiegl, M., Altmann, K., Winkler, A., Salamon, A., Themessl-Huber, M., . . . Hiesmayr, M. (2016). Muscle mass, strength and functional outcomes in critically ill patients after cardiothoracic surgery: does neuromuscular electrical stimulation help? The Catastim 2 randomized controlled trial. *Crit Care, 20*, 30. doi:10.1186/s13054-016-1199-3

135. Fivez, T., Kerklaan, D., Mesotten, D., Verbruggen, S., Wouters, P. J., Vanhorebeek, I., . . . Casaer, M. P. (2016). Early versus late parenteral nutrition in critically ill children. *New England journal of medicine, 374*(12), 1111-1122.

136. Flakoll, P. J., Hill, J. O., & Abumrad, N. N. (1993). Acute hyperglycemia enhances proteolysis in normal man. *Am J Physiol, 265*(5 Pt 1), E715-721. doi:10.1152/ajpendo.1993.265.5.E715

137. Fletcher, S. N., Kennedy, D. D., Ghosh, I. R., Misra, V. P., Kiff, K., Coakley, J. H., & Hinds, C. J. (2003). Persistent neuromuscular and neurophysiologic abnormalities in long-term survivors of prolonged critical illness. *Critical Care Medicine, 31*(4), 1012-1016.

138. Fontes Cerqueira, T. C., Cerqueira Neto, M. L., Cacau, L. A. P., Oliveira, G. U., Silva Junior, W. M. D., Carvalho, V. O., . . . Santana Filho, V. J. (2018). Ambulation capacity and functional outcome in patients undergoing neuromuscular electrical stimulation after cardiac valve surgery: A randomised clinical trial. *Medicine (Baltimore), 97*(46), e13012. doi:10.1097/MD.0000000000013012

139. Fossat, G., Baudin, F., Courtes, L., Bobet, S., Dupont, A., Bretagnol, A., . . . Boulain, T. (2018). Effect of In-Bed Leg Cycling and Electrical Stimulation of the Quadriceps on Global Muscle Strength in Critically Ill Adults: A Randomized Clinical Trial. *JAMA, 320*(4), 368-378. doi:10.1001/jama.2018.9592

140. Fram, R. Y., Cree, M. G., Wolfe, R. R., Mlcak, R. P., Qian, T., Chinkes, D. L., & Herndon, D. N. (2010). Intensive insulin therapy improves insulin sensitivity and mitochondrial function in severely burned children. *Critical Care Medicine, 38*(6), 1475-1483. doi:10.1097/CCM.0b013e3181de8b9e

141. Fredriksson, K., Hammarqvist, F., Strigård, K., Hultenby, K., Ljungqvist, O., Wernerman, J., & Rooyackers, O. (2006). Derangements in mitochondrial metabolism in intercostal and leg muscle of critically ill patients with sepsis-induced multiple organ failure. *Am J Physiol Endocrinol Metab, 291*(5), E1044-1050. doi:10.1152/ajpendo.00218.2006

142. Fredriksson, K., & Rooyackers, O. (2007). Mitochondrial function in sepsis: respiratory versus leg muscle. *Crit Care Med, 35*(9 Suppl), S449-453. doi:10.1097/01.Ccm.0000278048.00896.4b

143. Friedrich, O., Reid, M. B., Van den Berghe, G., Vanhorebeek, I., Hermans, G., Rich, M. M., & Larsson, L. (2015). The Sick and the Weak:

Neuropathies/Myopathies in the Critically Ill. *Physiol Rev, 95*(3), 1025-1109. doi:10.1152/physrev.00028.2014

144. Fuke, R., Hifumi, T., Kondo, Y., Hatakeyama, J., Takei, T., Yamakawa, K., . . . Nishida, O. (2018). Early rehabilitation to prevent postintensive care syndrome in patients with critical illness: a systematic review and meta-analysis. *BMJ open, 8*(5), e019998. doi:10.1136/bmjopen-2017-019998

145. Fumis, R., Martins, P., & Schettino, G. (2012). Incidence of post-traumatic stress, anxiety and depression symptoms in patients and relatives during the ICU stay and after discharge. *Critical Care, 16*(1), P497. doi:10.1186/cc11104

146. Gama Lordello, G. G., Goncalves Gama, G. G., Lago Rosier, G., Viana, P., Correia, L. C., & Fonteles Ritt, L. E. (2020). Effects of cycle ergometer use in early mobilization following cardiac surgery: a randomized controlled trial. *Clin Rehabil, 34*(4), 450-459. doi:10.1177/0269215520901763

147. García-Martínez, C., Llovera, M., Agell, N., López-Soriano, F. J., & Argilés, J. M. (1994). Ubiquitin gene expression in skeletal muscle is increased by tumour necrosis factor-alpha. *Biochem Biophys Res Commun, 201*(2), 682-686. doi:10.1006/bbrc.1994.1754

148. García-Martínez, M. Á., González, J. C. M., García-de-Lorenzo, A., & Teijeira, S. (2019). Muscle weakness: Understanding the principles of myopathy and neuropathy in the critically ill patient and the management options. *Clinical Nutrition*.

149. Garnacho-Montero, J., Amaya-Villar, R., Garcia-Garmendia, J. L., Madrazo-Osuna, J., & Ortiz-Leyba, C. (2005). Effect of critical illness polyneuropathy on the withdrawal from mechanical ventilation and the length of stay in septic patients. *Critical Care Medicine, 33*(2), 349-354.

150. Garnacho-Montero, J., Madrazo-Osuna, J., García-Garmendia, J. L., Ortiz-Leyba, C., Jiménez-Jiménez, F. J., Barrero-Almodóvar, A., . . . Moyano-Del-Estad, M. R. (2001). Critical illness polyneuropathy: risk factors and clinical consequences. A cohort study in septic patients. *Intensive Care Med, 27*(8), 1288-1296. doi:10.1007/s001340101009

151. Garzon-Serrano, J., Ryan, C., Waak, K., Hirschberg, R., Tully, S., Bittner, E. A., . . . Benjamin, J. (2011). Early mobilization in critically ill patients: patients' mobilization level depends on health care provider's profession. *Pm&r, 3*(4), 307-313.

152. Goddard, S. L., Lorencatto, F., Koo, E., Rose, L., Fan, E., Kho, M. E., . . . Cuthbertson, B. H. (2018). Barriers and facilitators to early rehabilitation in mechanically ventilated patients—a theory-driven interview study. *Journal of intensive care, 6*(1), 4. doi:10.1186/s40560-018-0273-0

153. Goossens, C., Marques, M. B., Derde, S., Vander Perre, S., Dufour, T., Thiessen, S. E., . . . Langouche, L. (2017). Premorbid obesity, but not nutrition, prevents critical illness-induced muscle wasting and weakness. *Journal of cachexia, sarcopenia and muscle, 8*(1), 89-101. doi:10.1002/jcsm.12131

154. Greening, N. J., Williams, J. E., Hussain, S. F., Harvey-Dunstan, T. C., Bankart, M. J., Chaplin, E. J., . . . Steiner, M. C. (2014). An early rehabilitation intervention to enhance recovery during hospital admission for an exacerbation of chronic respiratory disease: randomised controlled trial. *BMJ, 349*, g4315. doi:10.1136/bmj.g4315

155. Grill, M. F., & Maganti, R. K. (2011). Neurotoxic effects associated with antibiotic use: management considerations. *Br J Clin Pharmacol, 72*(3), 381-393. doi:10.1111/j.1365-2125.2011.03991.x

156. Guarneri, B., Bertolini, G., & Latronico, N. (2008). Long-term outcome in patients with critical illness myopathy or neuropathy: the Italian multicentre CRIMYNE study. *J Neurol Neurosurg Psychiatry, 79*(7), 838-841. doi:10.1136/jnnp.2007.142430

157. Gumucio, J. P., Sugg, K. B., & Mendias, C. L. (2015). TGF-β superfamily signaling in muscle and tendon adaptation to resistance exercise. *Exercise and sport sciences reviews, 43*(2), 93-99. doi:10.1249/jes.0000000000000041

158. Hamnegåard, C. H., Wragg, S., Kyroussis, D., Mills, G., Bake, B., Green, M., & Moxham, J. (1995). Mouth pressure in response to magnetic stimulation of the phrenic nerves. *Thorax, 50*(6), 620-624. doi:10.1136/thx.50.6.620

159. Han, H., Zhou, X., Mitch, W. E., & Goldberg, A. L. (2013). Myostatin/activin pathway antagonism: molecular basis and therapeutic potential. *The international journal of biochemistry & cell biology, 45*(10), 2333-2347.

160. Hanekom, S. D., Louw, Q., & Coetzee, A. (2012). The way in which a physiotherapy service is structured can improve patient outcome from a surgical intensive care: a controlled clinical trial. *Crit Care, 16*(6), R230. doi:10.1186/cc11894

161. Harris, C. L., & Shahid, S. (2014). *Physical therapy–driven quality improvement to promote early mobility in the intensive care unit.* Paper presented at the Baylor University Medical Center Proceedings.

162. Harrold, M. E., Salisbury, L. G., Webb, S. A., Allison, G. T., Australia, & Scotland, I. C. U. P. C. (2015). Early mobilisation in intensive care units in Australia and Scotland: a prospective, observational cohort study examining mobilisation practises and barriers. *Crit Care, 19*(1), 336. doi:10.1186/s13054-015-1033-3

163. Hart, S. G., & Staveland, L. E. (1988). Development of NASA-TLX (Task Load Index): Results of empirical and theoretical research. In P. A. Hancock & N. Meshkati (Eds.), *Human Mental Workload*. Amsterdam: North Holland Press.

164. Hasselgren, P.-O., James, J. H., Benson, D. W., Hall-Angerås, M., Angerås, U., Hiyama, D. T., . . . Fischer, J. E. (1989). Total and myofibrillar protein breakdown in different types of rat skeletal muscle: effects of sepsis and regulation by insulin. *Metabolism, 38*(7), 634-640.

165. Hasselgren, P., James, J. H., & Fischer, J. E. (1986). Inhibited muscle amino acid uptake in sepsis. *Annals of surgery, 203*(4), 360.

166. Hauerslev, S., Sveen, M.-L., Duno, M., Angelini, C., Vissing, J., & Krag, T. O. (2012). Calpain 3 is important for muscle regeneration: Evidence from patients with limb girdle muscular dystrophies. *BMC musculoskeletal disorders, 13*(1), 43. doi:10.1186/1471-2474-13-43

167. Hayes, K., Holland, A. E., Pellegrino, V. A., Mathur, S., & Hodgson, C. L. (2018). Acute skeletal muscle wasting and relation to physical function in patients requiring extracorporeal membrane oxygenation (ECMO). *J Crit Care, 48*, 1-8. doi:10.1016/j.jcrc.2018.08.002

168. Heckman, C. J., & Enoka, R. M. (2004). Physiology of the motor neuron and the motor unit. In A. Eisen (Ed.), *Handbook of Clinical Neurophysiology* (Vol. 4, pp. 119-147): Elsevier.

169. Hedger, M. P., Winnall, W. R., Phillips, D. J., & de Kretser, D. M. (2011). The regulation and functions of activin and follistatin in inflammation and immunity. In *Vitamins & Hormones* (Vol. 85, pp. 255-297): Elsevier.

170. Heidegger, C. P., Berger, M. M., Graf, S., Zingg, W., Darmon, P., Costanza, M. C., . . . Pichard, C. (2013). Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. *Lancet, 381*(9864), 385-393. doi:10.1016/s0140-6736(12)61351-8

171. Helliwell, T. R., Wilkinson, A., Griffiths, R. D., McClelland, P., Palmer, T. E., & Bone, J. M. (1998). Muscle fibre atrophy in critically ill patients is associated with the loss of myosin filaments and the presence of lysosomal enzymes and ubiquitin. *Neuropathology and Applied Neurobiology, 24*(6), 507-517.

172. Hermans, G., Casaer, M. P., Clerckx, B., Guiza, F., Vanhullebusch, T., Derde, S., . . . Vanhorebeek, I. (2013). Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. *Lancet Respir Med, 1*(8), 621-629. doi:10.1016/S2213-2600(13)70183-8

173. Hermans, G., Clerckx, B., Vanhullebusch, T., Segers, J., Vanpee, G., Robbeets, C., . . . Van Den Berghe, G. (2012). Interobserver agreement of Medical Research Council sum-score and handgrip strength in the intensive care unit. *Muscle Nerve, 45*(1), 18-25. doi:10.1002/mus.22219

174. Hermans, G., & Van den Berghe, G. (2015). Clinical review: intensive care unit acquired weakness. *Crit Care, 19*, 274. doi:10.1186/s13054-015-0993-7

175. Hermans, G., Van Mechelen, H., Clerckx, B., Vanhullebusch, T., Mesotten, D., Wilmer, A., . . . Van den Berghe, G. (2014). Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. *Am J Respir Crit Care Med, 190*(4), 410-420. doi:10.1164/rccm.201312-2257OC

176. Hermans, G., Wilmer, A., Meersseman, W., Milants, I., Wouters, P. J., Bobbaers, H., . . . Van den Berghe, G. (2007). Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. *Am J Respir Crit Care Med, 175*(5), 480-489. doi:10.1164/rccm.200605-665OC

177. Herridge, M. S., Cheung, A. M., Tansey, C. M., Matte-Martyn, A., Diaz-Granados, N., Al-Saidi, F., . . . Slutsky, A. S. (2003). One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med, 348*(8), 683-693. doi:10.1056/NEJMoa022450

178. Herridge, M. S., Tansey, C. M., Matte, A., Tomlinson, G., Diaz-Granados, N., Cooper, A., . . . Cheung, A. M. (2011). Functional Disability 5 Years After Acute Respiratory Distress Syndrome. *The New England Journal of Medicine, 364*(14), 1293-1304.

179. Hickmann, C. E., Castanares-Zapatero, D., Deldicque, L., Van den Bergh, P., Caty, G., Robert, A., . . . Laterre, P. F. (2018). Impact of Very Early Physical Therapy During Septic Shock on Skeletal Muscle: A Randomized Controlled Trial. *Crit Care Med, 46*(9), 1436-1443. doi:10.1097/CCM.0000000000003263

180. Hicks, P., Huckson, S., Fenney, E., Leggett, I., Pilcher, D., & Litton, E. (2019). The financial cost of intensive care in Australia: a multicentre registry study. *Medical Journal of Australia, 211*(7), 324-325.

181. Higgins, J. T., J; Chandler, J; Cumpston, M; Li, T; Page, MJ; Welch, VA. (2019). *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)*. In.

182. Hodgson, C., Bellomo, R., Berney, S., Bailey, M., Buhr, H., Denehy, L., . . . Webb, S. (2015). Early mobilization and recovery in mechanically ventilated patients in the ICU: a bi-national, multi-centre, prospective cohort study. *Critical care (london, england), 19*, 81.

183. Hodgson, C., Webb, S., Berney, S., Denehy, L., Harrold, M., Higgins, A., . . . Bellomo, R. (2013). TEAM: A Prospective Multi-Centre Cohort Study Of Early Activity And Mobilisation In ICU. *Am J Respir Crit Care Med, 187*, A3625.

184. Hodgson, C. L., Bailey, M., Bellomo, R., Berney, S., Buhr, H., Denehy, L., . . . Mobilization Study, I. (2016). A Binational Multicenter Pilot Feasibility Randomized Controlled Trial of Early Goal-Directed Mobilization in the ICU. *Crit Care Med, 44*(6), 1145-1152. doi:10.1097/CCM.0000000000001643

185. Hodgson, C. L., Capell, E., & Tipping, C. J. (2018). Early Mobilization of Patients in Intensive Care: Organization, Communication and Safety Factors that Influence Translation into Clinical Practice. *Critical care (london, england), 22*(1), 77-77. doi:10.1186/s13054-018-1998-9

186. Hodgson, C. L., Hayes, K., Linnane, M., Tronstad, O., Reddy, N., Young, M., . . . International, E. N. (2020). Early mobilisation during extracorporeal membrane oxygenation was safe and feasible: a pilot randomised controlled trial. *Intensive Care Med, 46*(5), 1057-1059. doi:10.1007/s00134-020-05994-8

187. Hodgson, C. L., Stiller, K., Needham, D. M., Tipping, C. J., Harrold, M., Baldwin, C. E., . . . Webb, S. A. (2014). Expert consensus and recommendations on safety criteria for active mobilization of mechanically ventilated critically ill adults. *Critical Care, 18*(6), 658. doi:10.1186/s13054-014-0658-y

188. Hoffmann, T. C., Glasziou, P. P., Boutron, I., Milne, R., Perera, R., Moher, D., . . . Michie, S. (2014). Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ, 348*, g1687. doi:10.1136/bmj.g1687

189. Holdsworth, C., Haines, K. J., Francis, J. J., Marshall, A., O'Connor, D., & Skinner, E. H. (2015). Mobilization of ventilated patients in the intensive care unit: an elicitation study using the theory of planned behavior. *Journal of Critical Care, 30*(6), 1243-1250.

190. Hooijman, P. E., Beishuizen, A., Witt, C. C., de Waard, M. C., Girbes, A. R. J., Spoelstra-de Man, A. M. E., . . . Ottenheijm, C. A. C. (2015). Diaphragm muscle fiber weakness and ubiquitin-proteasome activation in critically ill patients. *American journal of respiratory and critical care medicine, 191*(10), 1126-1138. doi:10.1164/rccm.201412-2214OC

191. Hoonakker, P., Carayon, P., Gurses, A., Brown, R., McGuire, K., Khunlertkit, A., & Walker, J. M. (2011). Measuring Workload of Icu Nurses with a Questionnaire Survey: The Nasa Task Load Index (Tlx). *IIE Trans Healthc Syst Eng, 1*(2), 131-143. doi:10.1080/19488300.2011.609524

192. Howard, R. S., Tan, S. V., & Z'Graggen, W. J. (2008). Weakness on the intensive care unit. *Pract Neurol, 8*(5), 280-295. doi:10.1136/jnnp.2008.157263

193. Hussain, S. N. A., Mofarrahi, M., Sigala, I., Kim, H. C., Vassilakopoulos, T., Maltais, F., . . . Goldberg, P. (2010). Mechanical Ventilation–induced Diaphragm Disuse in Humans Triggers Autophagy. *American journal of respiratory and critical care medicine, 182*(11), 1377-1386. doi:10.1164/rccm.201002-0234OC

194. Intiso, D., Amoruso, L., Zarrelli, M., Pazienza, L., Basciani, M., Grimaldi, G., . . . Di Rienzo, F. (2011). Long-term functional outcome and health status of patients with critical illness polyneuromyopathy. *Acta Neurol Scand, 123*(3), 211-219. doi:10.1111/j.1600-0404.2010.01414.x

195. Iwashyna, T. J., Netzer, G., Langa, K. M., & Cigolle, C. (2012). Spurious inferences about long-term outcomes: the case of severe sepsis and geriatric conditions. *American journal of respiratory and critical care medicine, 185*(8), 835-841. doi:10.1164/rccm.201109-1660OC

196. Jaber, S., Petrof, B. J., Jung, B., Chanques, G., Berthet, J. P., Rabuel, C., . . . Matecki, S. (2011). Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. *Am J Respir Crit Care Med, 183*(3), 364-371. doi:10.1164/rccm.201004-0670OC

197. Jackson, D. L., Proudfoot, C. W., Cann, K. F., & Walsh, T. (2010). A systematic review of the impact of sedation practice in the ICU on resource use, costs and patient safety. *Critical Care, 14*(2), R59.

198. Jacob, P., Surendran, P. J., E M, M. A., Papasavvas, T., Praveen, R., Swaminathan, N., & Milligan, F. (2021). Early Mobilization of Patients Receiving Vasoactive Drugs in Critical Care Units: A Systematic Review. *Journal of Acute Care Physical Therapy, 12*(1), 37-48. doi:10.1097/jat.0000000000000140

199. Jagoe, R. T., & Goldberg, A. L. (2001). What do we really know about the ubiquitin-proteasome pathway in muscle atrophy? *Current Opinion in Clinical Nutrition & Metabolic Care, 4*(3), 183-190.

200. Joannidis, M., & Oudemans-van Straaten, H. M. (2007). Clinical review: patency of the circuit in continuous renal replacement therapy. *Critical Care, 11*, 218.

201. Jolley, S. E., Dale, C. R., & Hough, C. L. (2015). Hospital-level factors associated with report of physical activity in patients on mechanical ventilation across Washington State. *Annals of the american thoracic society, 12*(2), 209-215.

202. Jolley, S. E., Moss, M., Needham, D. M., Caldwell, E., Morris, P. E., Miller, R. R., . . . Acute Respiratory Distress Syndrome Network, I. (2017). Point Prevalence Study

of Mobilization Practices for Acute Respiratory Failure Patients in the United States. *Critical Care Medicine, 45*(2), 205-215. doi:10.1097/CCM.0000000000002058

203. Jolley, S. E., Regan-Baggs, J., Dickson, R. P., & Hough, C. L. (2014). Medical intensive care unit clinician attitudes and perceived barriers towards early mobilization of critically ill patients: a cross-sectional survey study. *BMC anesthesiology, 14*(1), 84.

204. Jones, K. L., De Kretser, D. M., Patella, S., & Phillips, D. J. (2004). Activin A and follistatin in systemic inflammation. *Molecular and cellular endocrinology, 225*(1-2), 119-125.

205. Jones, K. L., Mansell, A., Patella, S., Scott, B. J., Hedger, M. P., de Kretser, D. M., & Phillips, D. J. (2007). Activin A is a critical component of the inflammatory response, and its binding protein, follistatin, reduces mortality in endotoxemia. *Proceedings of the National Academy of Sciences, 104*(41), 16239-16244.

206. Kamei, Y., Miura, S., Suzuki, M., Kai, Y., Mizukami, J., Taniguchi, T., . . . Ezaki, O. (2004). Skeletal muscle FOXO1 (FKHR) transgenic mice have less skeletal muscle mass, down-regulated Type I (slow twitch/red muscle) fiber genes, and impaired glycemic control. *J Biol Chem, 279*(39), 41114-41123. doi:10.1074/jbc.M400674200

207. Kara, A., Akin, S., & Ince, C. (2016). Monitoring microcirculation in critical illness. *Current opinion in critical care, 22*(5).

208. Karatzanos, E., Gerovasili, V., Zervakis, D., Tripodaki, E. S., Apostolou, K., Vasileiadis, I., . . . Nanas, S. (2012). Electrical muscle stimulation: an effective form of exercise and early mobilization to preserve muscle strength in critically ill patients. *Crit Care Res Pract, 2012*, 432752. doi:10.1155/2012/432752

209. Kayambu, G., Boots, R., & Paratz, J. (2013). Physical therapy for the critically ill in the ICU: a systematic review and meta-analysis. *Crit Care Med, 41*(6), 1543-1554. doi:10.1097/CCM.0b013e31827ca637

210. Kayambu, G., Boots, R., & Paratz, J. (2015). Early physical rehabilitation in intensive care patients with sepsis syndromes: a pilot randomised controlled trial. *Intensive Care Med, 41*(5), 865-874. doi:10.1007/s00134-015-3763-8

211. Kho, M. E., Molloy, A. J., Clarke, F. J., Reid, J. C., Herridge, M. S., Karachi, T., . . . Cook, D. J. (2019). Multicentre pilot randomised clinical trial of early in-bed cycle ergometry with ventilated patients. *BMJ Open Respir Res, 6*(1), e000383. doi:10.1136/bmjresp-2018-000383

212. Kho, M. E., Truong, A. D., Zanni, J. M., Ciesla, N. D., Brower, R. G., Palmer, J. B., & Needham, D. M. (2015). Neuromuscular electrical stimulation in mechanically

ventilated patients: a randomized, sham-controlled pilot trial with blinded outcome assessment. *J Crit Care, 30*(1), 32-39. doi:10.1016/j.jcrc.2014.09.014

213. Kim, J.-m., Lee, J.-K., Choi, S. M., Lee, J., Park, Y. S., Lee, C.-H., . . . Lee, S.-M. (2019). Diagnostic and prognostic values of serum activin-a levels in patients with acute respiratory distress syndrome. *BMC Pulmonary Medicine, 19*(1), 115. doi:10.1186/s12890-019-0879-6

214. Kim, W. Y., Suh, H. J., Hong, S.-B., Koh, Y., & Lim, C.-M. (2011). Diaphragm dysfunction assessed by ultrasonography: influence on weaning from mechanical ventilation. *Critical Care Medicine, 39*(12), 2627-2630.

215. King, J., & Crowe, J. (1998). Mobilization practices in Canadian critical care units. *Physiotherapy Canada, 50*(3), 206-211.

216. Kleyweg, R. P., Van Der Meché, F. G., & Schmitz, P. I. (1991). Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain‐Barré syndrome. *Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine, 14*(11), 1103-1109.

217. Knaus, W. A., Draper, E. A., Wagner, D. P., & Zimmerman, J. E. (1985). APACHE II: a severity of disease classification system. *Critical Care Medicine, 13*(10), 818-829.

218. Knott, A., Stevenson, M., & Harlow, S. K. (2015). Benchmarking rehabilitation practice in the intensive care unit. *J Intensive Care Soc, 16*(1), 24-30. doi:10.1177/1751143714553901

219. Koch, S., Spuler, S., Deja, M., Bierbrauer, J., Dimroth, A., Behse, F., . . . Weber-Carstens, S. (2011). Critical illness myopathy is frequent: accompanying neuropathy protracts ICU discharge. *J Neurol Neurosurg Psychiatry, 82*(3), 287-293. doi:10.1136/jnnp.2009.192997

220. Koch, S., Wollersheim, T., Bierbrauer, J., Haas, K., Morgeli, R., Deja, M., . . . Weber-Carstens, S. (2014). Long-term recovery In critical illness myopathy is complete, contrary to polyneuropathy. *Muscle Nerve, 50*(3), 431-436. doi:10.1002/mus.24175

221. Koo, K. K. Y., Choong, K., Cook, D. J., Herridge, M., Newman, A., Lo, V., . . . Canadian Critical Care Trials, G. (2016). Early mobilization of critically ill adults: a survey of knowledge, perceptions and practices of Canadian physicians and physiotherapists. *CMAJ open, 4*(3), E448-E454. doi:10.9778/cmajo.20160021

222. Koukourikos, K., Tsaloglidou, A., & Kourkouta, L. (2014). Muscle atrophy in intensive care unit patients. *Acta Informatica Medica, 22*(6), 406.

223. Koutsioumpa, E., Makris, D., Theochari, A., Bagka, D., Stathakis, S., Manoulakas, E., . . . Zakynthinos, E. (2018). Effect of Transcutaneous Electrical Neuromuscular Stimulation on Myopathy in Intensive Care Patients. *Am J Crit Care, 27*(6), 495-503. doi:10.4037/ajcc2018311

224. Kramer, C. L. (2017). Intensive Care Unit–Acquired Weakness. *Neurologic Clinics, 35*(4), 723-736. doi:https://doi.org/10.1016/j.ncl.2017.06.008

225. Kress, J. P., Pohlman, A. S., O'Connor, M. F., & Hall, J. B. (2000). Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med, 342*(20), 1471-1477. doi:10.1056/NEJM200005183422002

226. Kurtoğlu, D. K., Taştekin, N., Birtane, M., Tabakoğlu, E., & Süt, N. (2015). Effectiveness of Neuromuscular Electrical Stimulation on Auxiliary Respiratory Muscles in Patients with Chronic Obstructive Pulmonary Disease Treated in the Intensive Care Unit. *Turkish Journal of Physical Medicine & Rehabilitation/Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi, 61*(1).

227. Lach-Trifilieff, E., Minetti, G. C., Sheppard, K., Ibebunjo, C., Feige, J. N., Hartmann, S., . . . Morvan, F. (2014). An antibody blocking activin type II receptors induces strong skeletal muscle hypertrophy and protects from atrophy. *Molecular and cellular biology, 34*(4), 606-618.

228. Lagasse, R. S., Katz, R. I., Petersen, M., Jacobson, M. J., & Poppers, P. J. (1990). Prolonged neuromuscular blockade following vecuronium infusion. *J Clin Anesth, 2*(4), 269-271. doi:10.1016/0952-8180(90)90107-e

229. Langouche, L., Vanhorebeek, I., Vlasselaers, D., Vander Perre, S., Wouters, P. J., Skogstrand, K., . . . Van den Berghe, G. (2005). Intensive insulin therapy protects the endothelium of critically ill patients. *J Clin Invest, 115*(8), 2277-2286. doi:10.1172/jci25385

230. Larsson, L. (2008). Acute Quadriplegic Myopathy: An Acquired “Myosinopathy”. In N. G. Laing (Ed.), *The Sarcomere and Skeletal Muscle Disease* (pp. 92-98). New York, NY: Springer New York.

231. Latronico, N., & Bolton, C. F. (2011). Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. *Lancet Neurol, 10*(10), 931-941. doi:10.1016/S1474-4422(11)70178-8

232. Latronico, N., Fenzi, F., Recupero, D., Guarneri, B., Tomelleri, G., Tonin, P., . . . Candiani, A. (1996). Critical illness myopathy and neuropathy. *Lancet, 347*(9015), 1579-1582.

233. Latronico, N., Herridge, M., Hopkins, R. O., Angus, D., Hart, N., Hermans, G., . . . Needham, D. M. (2017). The ICM research agenda on intensive care unit-acquired weakness. *Intensive Care Med, 43*(9), 1270-1281. doi:10.1007/s00134-017-4757-5

234. Lecker, S. H. (2003). Ubiquitin-protein ligases in muscle wasting: multiple parallel pathways? *Curr Opin Clin Nutr Metab Care, 6*(3), 271-275. doi:10.1097/01.mco.0000068963.34812.e5

235. Lecker, S. H., Goldberg, A. L., & Mitch, W. E. (2006). Protein Degradation by the Ubiquitin–Proteasome Pathway in Normal and Disease States. *Journal of the American Society of Nephrology, 17*(7), 1807-1819. doi:10.1681/asn.2006010083

236. Lecker, S. H., Solomon, V., Mitch, W. E., & Goldberg, A. L. (1999). Muscle protein breakdown and the critical role of the ubiquitin-proteasome pathway in normal and disease states. *The Journal of nutrition, 129*(1), 227S-237S.

237. Leditschke, I. A., Green, M., Irvine, J., Bissett, B., & Mitchell, I. A. (2012). What are the barriers to mobilizing intensive care patients? *Cardiopulmonary Physical Therapy Journal, 23*(1), 26.

238. Lee, J. K., Choi, S. M., Lee, J., Park, Y. S., Lee, C. H., Yim, J. J., . . . Lee, S. M. (2016). Serum activin‐A as a predictive and prognostic marker in critically ill patients with sepsis. *Respirology, 21*(5), 891-897.

239. Lee, S.-J., & McPherron, A. C. (2001). Regulation of myostatin activity and muscle growth. *Proceedings of the National Academy of Sciences, 98*(16), 9306-9311.

240. Lee, S.-J., Reed, L. A., Davies, M. V., Girgenrath, S., Goad, M. E., Tomkinson, K. N., . . . Holmstrom, J. (2005). Regulation of muscle growth by multiple ligands signaling through activin type II receptors. *Proceedings of the National Academy of Sciences, 102*(50), 18117-18122.

241. Lefaucheur, J. P., Nordine, T., Rodriguez, P., & Brochard, L. (2006). Origin of ICU acquired paresis determined by direct muscle stimulation. *Journal of neurology, neurosurgery, and psychiatry, 77*(4), 500-506. doi:10.1136/jnnp.2005.070813

242. Leite, M. A., Osaku, E. F., Albert, J., Costa, C., Garcia, A. M., Czapiesvski, F. D. N., . . . Duarte, P. A. D. (2018). Effects of Neuromuscular Electrical Stimulation of the Quadriceps and Diaphragm in Critically Ill Patients: A Pilot Study. *Crit Care Res Pract, 2018*, 4298583. doi:10.1155/2018/4298583

243. Levine, B., & Kroemer, G. (2008). Autophagy in the pathogenesis of disease. *Cell, 132*(1), 27-42.

244. Levine, S., Nguyen, T., Taylor, N., Friscia, M. E., Budak, M. T., Rothenberg, P., . . . Kaiser, L. R. (2008). Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *New England journal of medicine, 358*(13), 1327-1335.

245. Levy, M. M., Fink, M. P., Marshall, J. C., Abraham, E., Angus, D., Cook, D., . . . Ramsay, G. (2003). 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med, 31*(4), 1250-1256. doi:10.1097/01.Ccm.0000050454.01978.3b

246. LI, Y.-P., LECKER, S. H., CHEN, Y., WADDELL, I. D., GOLDBERG, A. L., & REID, M. B. (2003). TNF-α increases ubiquitin-conjugating activity in skeletal muscle by up-regulating UbcH2/E220k. *The FASEB Journal, 17*(9), 1048-1057. doi:https://doi.org/10.1096/fj.02-0759com

247. Liddell, E. G. T., & Sherrington, C. S. (1925). Recruitment and some other features of reflex inhibition. *Proceedings of the Royal Society of London. Series B, Containing Papers of a Biological Character, 97*(686), 488-518.

248. Linko, R., Hedger, M. P., Pettilä, V., Ruokonen, E., Ala-Kokko, T., Ludlow, H., & de Kretser, D. M. (2014). Serum activin A and B, and follistatin in critically ill patients with influenza A (H1N1) infection. *BMC infectious diseases, 14*(1), 253.

249. Llano-Diez, M., Fury, W., Okamoto, H., Bai, Y., Gromada, J., & Larsson, L. (2019). RNA-sequencing reveals altered skeletal muscle contraction, E3 ligases, autophagy, apoptosis, and chaperone expression in patients with critical illness myopathy. *Skeletal muscle, 9*(1), 9.

250. Llano-Diez, M., Gustafson, A.-M., Olsson, C., Goransson, H., & Larsson, L. (2011). Muscle wasting and the temporal gene expression pattern in a novel rat intensive care unit model. *BMC Genomics, 12*(1), 602.

251. Llano-Diez, M., Renaud, G., Andersson, M., Marrero, H. G., Cacciani, N., Engquist, H., . . . Larsson, L. (2012). Mechanisms underlying ICU muscle wasting and effects of passive mechanical loading. *Crit Care, 16*, R209. doi:cc11841 [pii]

10.1186/cc11841

252. Lokireddy, S., Mouly, V., Butler-Browne, G., Gluckman, P. D., Sharma, M., Kambadur, R., & McFarlane, C. (2011). Myostatin promotes the wasting of human myoblast cultures through promoting ubiquitin-proteasome pathway-mediated loss of sarcomeric proteins. *American Journal of Physiology-Cell Physiology, 301*(6), C1316-C1324.

253. Long, C. L., Birkhahn, R. H., Geiger, J. W., Betts, J. E., Schiller, W. R., & Blakemore, W. S. (1981). Urinary excretion of 3-methylhistidine: an assessment of muscle protein catabolism in adult normal subjects and during malnutrition, sepsis, and skeletal trauma. *Metabolism, 30*(8), 765-776.

254. Lowe, C. J. M., Barker, K. L., Dewey, M. E., & Sackley, C. M. (2009). Effectiveness of physiotherapy exercise following hip arthroplasty for osteoarthritis: a systematic review of clinical trials. *BMC musculoskeletal disorders, 10*(1), 98.

255. Lush, C. W., & Kvietys, P. R. (2000). Microvascular dysfunction in sepsis. *Microcirculation, 7*(2), 83-101.

256. Machado, A. D. S., Pires-Neto, R. C., Carvalho, M. T. X., Soares, J. C., Cardoso, D. M., & Albuquerque, I. M. (2017). Effects that passive cycling exercise have on muscle strength, duration of mechanical ventilation, and length of hospital stay in critically ill patients: a randomized clinical trial. *J Bras Pneumol, 43*(2), 134-139. doi:10.1590/S1806-37562016000000170

257. Maffei, P., Wiramus, S., Bensoussan, L., Bienvenu, L., Haddad, E., Morange, S., . . . Gregoire, E. (2017). Intensive Early Rehabilitation in the Intensive Care Unit for Liver Transplant Recipients: A Randomized Controlled Trial. *Arch Phys Med Rehabil, 98*(8), 1518-1525. doi:10.1016/j.apmr.2017.01.028

258. Maiden, M. J., Bone, A., & Fitzpatrick, M. (2020). Physical restraint of patients in Australia and New Zealand intensive care units. *Intensive Care Medicine*, 1-3.

259. Malone, D., Ridgeway, K., Nordon-Craft, A., Moss, P., Schenkman, M., & Moss, M. (2015). Physical Therapist Practice in the Intensive Care Unit: Results of a National Survey. *Physical Therapy, 95*(10), 1335-1344. doi:10.2522/ptj.20140417

260. Mammucari, C., Milan, G., Romanello, V., Masiero, E., Rudolf, R., Del Piccolo, P., . . . Sandri, M. (2007). FoxO3 controls autophagy in skeletal muscle in vivo. *Cell Metab, 6*(6), 458-471. doi:10.1016/j.cmet.2007.11.001

261. Marino, F. E., Risbridger, G., & Gold, E. (2015). Activin‐βC modulates cachexia by repressing the ubiquitin‐proteasome and autophagic degradation pathways. *Journal of cachexia, sarcopenia and muscle, 6*(4), 365-380.

262. Martin, A. D., Smith, B. K., Davenport, P. D., Harman, E., Gonzalez-Rothi, R. J., Baz, M., . . . Gabrielli, A. (2011). Inspiratory muscle strength training improves weaning outcome in failure to wean patients: a randomized trial. *Crit Care, 15*(2), R84. doi:10.1186/cc10081

263. Masiero, E., Agatea, L., Mammucari, C., Blaauw, B., Loro, E., Komatsu, M., . . . Sandri, M. (2009). Autophagy is required to maintain muscle mass. *Cell Metab, 10*(6), 507-515. doi:10.1016/j.cmet.2009.10.008

264. Matzuk, M. M., Finegold, M. J., Mather, J. P., Krummen, L., Lu, H., & Bradley, A. (1994). Development of cancer cachexia-like syndrome and adrenal tumors in inhibin-deficient mice. *Proc Natl Acad Sci U S A, 91*(19), 8817-8821.

265. Mayer, K. P., Joseph-Isang, E., Robinson, L. E., Parry, S. M., Morris, P. E., & Neyra, J. A. (2020). Safety and Feasibility of Physical Rehabilitation and Active Mobilization in Patients Requiring Continuous Renal Replacement Therapy: A Systematic Review. *Crit Care Med, 48*(11), e1112-e1120. doi:10.1097/ccm.0000000000004526

266. Mayer, K. P., Thompson Bastin, M. L., Montgomery-Yates, A. A., Pastva, A. M., Dupont-Versteegden, E. E., Parry, S. M., & Morris, P. E. (2020). Acute skeletal muscle wasting and dysfunction predict physical disability at hospital discharge in patients with critical illness. *Critical Care, 24*(1), 637. doi:10.1186/s13054-020-03355-x

267. McCaughey, E. J., Jonkman, A. H., Boswell-Ruys, C. L., McBain, R. A., Bye, E. A., Hudson, A. L., . . . Butler, J. E. (2019). Abdominal functional electrical stimulation to assist ventilator weaning in critical illness: a double-blinded, randomised, sham-controlled pilot study. *Crit Care, 23*(1), 261. doi:10.1186/s13054-019-2544-0

268. McGuinness, L. A., & Higgins, J. P. T. (2020). Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. *Res Synth Methods, n/a*(n/a). doi:10.1002/jrsm.1411

269. McWilliams, D., Jones, C., Atkins, G., Hodson, J., Whitehouse, T., Veenith, T., . . . Snelson, C. (2018). Earlier and enhanced rehabilitation of mechanically ventilated patients in critical care: A feasibility randomised controlled trial. *J Crit Care, 44*, 407-412. doi:10.1016/j.jcrc.2018.01.001

270. Medical Research Council. (1976). *Aids to the examination of the peripheral nervous system, Memorandum No. 45.* Retrieved from London:

271. Meduri, G. U., Schwingshackl, A., & Hermans, G. (2016). Prolonged Glucocorticoid Treatment in ARDS: Impact on Intensive Care Unit-Acquired Weakness. *Frontiers in pediatrics, 4*, 69-69. doi:10.3389/fped.2016.00069

272. Menges, D., Seiler, B., Tomonaga, Y., Schwenkglenks, M., Puhan, M. A., & Yebyo, H. G. (2021). Systematic early versus late mobilization or standard early mobilization in mechanically ventilated adult ICU patients: systematic review and meta-analysis. *Critical Care, 25*(1), 16. doi:10.1186/s13054-020-03446-9

273. Michel, U., Ebert, S., Phillips, D., & Nau, R. (2003). Serum concentrations of activin and follistatin are elevated and run in parallel in patients with septicemia. *Eur J Endocrinol, 148*(5), 559-564.

274. Michie, H. R. (1996). Metabolism of sepsis and multiple organ failure. *World J Surg, 20*(4), 460-464. doi:10.1007/s002689900072

275. Mizushima, N., & Komatsu, M. (2011). Autophagy: renovation of cells and tissues. *Cell, 147*(4), 728-741.

276. Mofarrahi, M., Sigala, I., Guo, Y., Godin, R., Davis, E. C., Petrof, B., . . . Hussain, S. N. (2012). Autophagy and skeletal muscles in sepsis. *PLoS One, 7*(10).

277. Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., . . . Group, P.-P. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev, 4*, 1. doi:10.1186/2046-4053-4-1

278. Morandi, A., Brummel, N. E., & Ely, E. W. (2011). Sedation, delirium and mechanical ventilation: the 'ABCDE' approach. *Curr Opin Crit Care, 17*(1), 43-49. doi:10.1097/MCC.0b013e3283427243

279. Morris, P. E. (2007). Moving our critically ill patients: mobility barriers and benefits. *Crit Care Clin, 23*(1), 1-20. doi:10.1016/j.ccc.2006.11.003

280. Morris, P. E., Berry, M. J., Files, D. C., Thompson, J. C., Hauser, J., Flores, L., . . . Young, M. P. (2016). Standardized Rehabilitation and Hospital Length of Stay Among Patients With Acute Respiratory Failure: A Randomized Clinical Trial. *JAMA, 315*(24), 2694-2702. doi:10.1001/jama.2016.7201

281. Morris, P. E., Goad, A., Thompson, C., Taylor, K., Harry, B., Passmore, L., . . . Haponik, E. (2008). Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med, 36*(8), 2238-2243. doi:10.1097/CCM.0b013e318180b90e

282. Moss, M., Nordon-Craft, A., Malone, D., Van Pelt, D., Frankel, S. K., Warner, M. L., . . . Schenkman, M. (2016). A Randomized Trial of an Intensive Physical Therapy Program for Patients with Acute Respiratory Failure. *Am J Respir Crit Care Med, 193*(10), 1101-1110. doi:10.1164/rccm.201505-1039OC

283. Nadeau, S. E., Wu, S. S., Dobkin, B. H., Azen, S. P., Rose, D. K., Tilson, J. K., . . . Team, L. I. (2013). Effects of task-specific and impairment-based training compared with usual care on functional walking ability after inpatient stroke rehabilitation: LEAPS Trial. *Neurorehabil Neural Repair, 27*(4), 370-380. doi:10.1177/1545968313481284

284. Nakamura, K., Kihata, A., Naraba, H., Kanda, N., Takahashi, Y., Sonoo, T., . . . Morimura, N. (2019). Efficacy of belt electrode skeletal muscle electrical stimulation on reducing the rate of muscle volume loss in critically ill patients: A randomized controlled trial. *J Rehabil Med, 51*(9), 705-711. doi:10.2340/16501977-2594

285. Nanas, S., Kritikos, K., Angelopoulos, E., Siafaka, A., Tsikriki, S., Poriazi, M., . . . Roussos, C. (2008). Predisposing factors for critical illness polyneuromyopathy in a multidisciplinary intensive care unit. *Acta Neurol Scand, 118*(3), 175-181. doi:10.1111/j.1600-0404.2008.00996.x

286. Needham, D. M., Feldman, D. R., & Kho, M. E. (2011). The functional costs of ICU survivorship. Collaborating to improve post-ICU disability. *Am J Respir Crit Care Med, 183*(8), 962-964. doi:10.1164/rccm.201012-2042ED

287. Needham, D. M., & Korupolu, R. (2010). Rehabilitation quality improvement in an intensive care unit setting: implementation of a quality improvement model. *Top Stroke Rehabil, 17*(4), 271-281. doi:10.1310/tsr1704-271

288. Needham, D. M., Korupolu, R., Zanni, J. M., Pradhan, P., Colantuoni, E., Palmer, J. B., . . . Fan, E. (2010). Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. *Arch Phys Med Rehabil, 91*(4), 536-542. doi:10.1016/j.apmr.2010.01.002

289. Needham, D. M., Sepulveda, K. A., Dinglas, V. D., Chessare, C. M., Friedman, L. A., Bingham, C. O., 3rd, & Turnbull, A. E. (2017). Core Outcome Measures for Clinical Research in Acute Respiratory Failure Survivors. An International Modified Delphi Consensus Study. *Am J Respir Crit Care Med, 196*(9), 1122-1130. doi:10.1164/rccm.201702-0372OC

290. Needham, D. M., Sepulveda, K. A., Dinglas, V. D., Chessare, C. M., Friedman, L. A., Bingham, C. O., 3rd, & Turnbull, A. E. (2017). Core Outcome Measures for Clinical Research in Acute Respiratory Failure Survivors. An International Modified Delphi Consensus Study. *American journal of respiratory and critical care medicine, 196*(9), 1122-1130. doi:10.1164/rccm.201702-0372OC

291. Neveu, H., Kleinknecht, D., Brivet, F., Loirat, P., Landais, P., & Failure, F. S. G. o. A. R. (1996). Prognostic factors in acute renal failure due to sepsis. Results of a prospective multicentre study. *Nephrology Dialysis Transplantation, 11*(2), 293-299.

292. Nguyen The, L., & Nguyen Huu, C. (2015). Critical illness polyneuropathy and myopathy in a rural area in Vietnam. *Journal of the neurological sciences, 357*(1-2), 276-281. doi:10.1016/j.jns.2015.08.005

293. Nickels, M. R., Aitken, L. M., Barnett, A. G., Walsham, J., King, S., Gale, N. E., . . . McPhail, S. M. (2020). Effect of in-bed cycling on acute muscle wasting in critically ill adults: A randomised clinical trial. *J Crit Care, 59*, 86-93. doi:10.1016/j.jcrc.2020.05.008

294. Nickels, M. R., Aitken, L. M., Walsham, J., Crampton, L. J., Barnett, A. G., & McPhail, S. M. (2020). Exercise interventions are delayed in critically ill patients: a

cohort study in an Australian tertiary intensive care unit. *Physiotherapy, 109*, 75-84. doi:https://doi.org/10.1016/j.physio.2019.06.011

295. Norrenberg, M., Vincent, J. L., & with the collaboration of the European Society of Intensive Care, M. (2000). A profile of European intensive care unit physiotherapists. *Intensive Care Medicine, 26*(7), 988-994. doi:10.1007/s001340051292

296. Nydahl, P., Gunther, U., Diers, A., Hesse, S., Kerschensteiner, C., Klarmann, S., . . . Kopke, S. (2019). PROtocol-based MObilizaTION on intensive care units: stepped-wedge, cluster-randomized pilot study (Pro-Motion). *Nurs Crit Care*. doi:10.1111/nicc.12438

297. Nydahl, P., Ruhl, A. P., Bartoszek, G., Dubb, R., Filipovic, S., Flohr, H. J., . . . Needham, D. M. (2014). Early mobilization of mechanically ventilated patients: a 1-day point-prevalence study in Germany. *Crit Care Med, 42*(5), 1178-1186. doi:10.1097/ccm.0000000000000149

298. Okada, Y., Unoki, T., Matsuishi, Y., Egawa, Y., Hayashida, K., & Inoue, S. (2019). Early versus delayed mobilization for in-hospital mortality and health-related quality of life among critically ill patients: a systematic review and meta-analysis. *Journal of intensive care, 7*(1), 57. doi:10.1186/s40560-019-0413-1

299. Paddon-Jones, D., Sheffield-Moore, M., Cree, M. G., Hewlings, S. J., Aarsland, A., Wolfe, R. R., & Ferrando, A. A. (2006). Atrophy and impaired muscle protein synthesis during prolonged inactivity and stress. *J Clin Endocrinol Metab, 91*(12), 4836-4841. doi:10.1210/jc.2006-0651

300. Pandey, D. P., Babu, R., & Sharma, U. S. (2013). Electrical Muscle Stimulation (EMS) Preserve Muscle Strength in Critically ill Patients- A Pilot Study. *Indian Journal of Physiotherapy and Occupational Therapy - An International Journal, 7*(3), 71-75. doi:10.5958/j.0973-5674.7.3.068

301. Papazian, L., Forel, J. M., Gacouin, A., Penot-Ragon, C., Perrin, G., Loundou, A., . . . Roch, A. (2010). Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med, 363*(12), 1107-1116. doi:10.1056/NEJMoa1005372

302. Parry, S. M., Berney, S., Granger, C. L., Koopman, R., El-Ansary, D., & Denehy, L. (2013). Electrical Muscle Stimulation in the Intensive Care Setting: A Systematic Review*. *Critical Care Medicine, 41*(10).

303. Parry, S. M., Knight, L. D., Connolly, B., Baldwin, C., Puthucheary, Z., Morris, P., . . . Granger, C. L. (2017). Factors influencing physical activity and rehabilitation in survivors of critical illness: a systematic review of quantitative and qualitative studies. *Intensive Care Medicine, 43*(4), 531-542.

304. Partridge, B. L., Abrams, J. H., Bazemore, C., & Rubin, R. (1990). Prolonged neuromuscular blockade after long-term infusion of vecuronium bromide in the intensive care unit. *Crit Care Med, 18*(10), 1177-1179. doi:10.1097/00003246-199010000-00025

305. Patel, B., Pohlman, A., Hall, J., & Kress, J. (2014). Impact of early mobilization on glycemic control and ICU-acquired weakness in critically ill patients who are mechanically ventilated. *Chest, 146*(3), 583 ‐ 589. Retrieved from https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01072450/full doi:10.1378/chest.13-2046

306. Patman, S., Sanderson, D., & Blackmore, M. (2001). Physiotherapy following cardiac surgery: is it necessary during the intubation period? *Australian journal of physiotherapy, 47*(1), 7 ‐ 16.

307. Pereira, R. M., & Freire de Carvalho, J. (2011). Glucocorticoid-induced myopathy. *Joint Bone Spine, 78*(1), 41-44. doi:10.1016/j.jbspin.2010.02.025

308. Perme, C., Lettvin, C., Throckmorton, T. A., Mitchell, K., & Masud, F. (2011). Early mobility and walking for patients with femoral arterial catheters in intensive care unit: a case series. *Journal of Acute Care Physical Therapy, 2*(1), 32-36.

309. Phillips, D. J., de Kretser, D. M., & Hedger, M. P. (2009). Activin and related proteins in inflammation: not just interested bystanders. *Cytokine & growth factor reviews, 20*(2), 153-164.

310. Podsiadlo, D., & Richardson, S. (1991). The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc, 39*(2), 142-148.

311. Pohlman, M. C., Schweickert, W. D., Pohlman, A. S., Nigos, C., Pawlik, A. J., Esbrook, C. L., . . . et al. (2010). Feasibility of physical and occupational therapy beginning from initiation of mechanical ventilation. *Critical Care Medicine, 38*(11), 2089 ‐ 2094. doi:10.1097/CCM.0b013e3181f270c3

312. Polkey, M. I., Praestgaard, J., Berwick, A., Franssen, F. M., Singh, D., Steiner, M. C., . . . Roubenoff, R. (2019). Activin type II receptor blockade for treatment of muscle depletion in chronic obstructive pulmonary disease. A randomized trial. *American journal of respiratory and critical care medicine, 199*(3), 313-320.

313. Price, D. R., Mikkelsen, M. E., Umscheid, C. A., & Armstrong, E. J. (2016). Neuromuscular Blocking Agents and Neuromuscular Dysfunction Acquired in Critical Illness: A Systematic Review and Meta-Analysis. *Crit Care Med, 44*(11), 2070-2078. doi:10.1097/ccm.0000000000001839

314. Puthucheary, Z. A., Astin, R., Mcphail, M. J. W., Saeed, S., Pasha, Y., Bear, D. E., . . . Montgomery, H. E. (2018). Metabolic phenotype of skeletal muscle in early critical illness. *Thorax, 73*(10), 926-935. doi:10.1136/thoraxjnl-2017-211073

315. Puthucheary, Z. A., Rawal, J., McPhail, M., Connolly, B., Ratnayake, G., Chan, P., . . . Montgomery, H. E. (2013). Acute skeletal muscle wasting in critical illness. *JAMA, 310*(15), 1591-1600. doi:10.1001/jama.2013.278481

316. Rabuel, C., Renaud, E., Brealey, D., Ratajczak, P., Damy, T., Alves, A., . . . Mebazaa, A. (2004). Human septic myopathy: induction of cyclooxygenase, heme oxygenase and activation of the ubiquitin proteolytic pathway. *ANESTHESIOLOGY-PHILADELPHIA THEN HAGERSTOWN-, 101*, 583-590.

317. Raurell-Torredà, M., Arias-Rivera, S., Martí, J., Frade-Mera, M., Zaragoza-García, I., Gallart, E., . . . Delgado, M. E. R. (2021). Care and treatments related to intensive care unit–acquired muscle weakness: A cohort study. *Australian Critical Care*.

318. Rebel, A., Marzano, V., Green, M., Johnston, K., Wang, J., Neeman, T., . . . Bissett, B. (2019). Mobilisation is feasible in intensive care patients receiving vasoactive therapy: An observational study. *Australian Critical Care, 32*(2), 139-146.

319. Reid, C. L., Murgatroyd, P. R., Wright, A., & Menon, D. K. (2008). Quantification of lean and fat tissue repletion following critical illness: a case report. *Crit Care, 12*(3), R79. doi:10.1186/cc6929

320. Reid, J. C., Unger, J., McCaskell, D., Childerhose, L., Zorko, D. J., & Kho, M. E. (2018). Physical rehabilitation interventions in the intensive care unit: a scoping review of 117 studies. *J Intensive Care, 6*, 80. doi:10.1186/s40560-018-0349-x

321. Reid, M. B., Haack, K. E., Franchek, K. M., Valberg, P. A., Kobzik, L., & West, M. S. (1992). Reactive oxygen in skeletal muscle. I. Intracellular oxidant kinetics and fatigue in vitro. *J Appl Physiol (1985), 73*(5), 1797-1804. doi:10.1152/jappl.1992.73.5.1797

322. Reis Miranda, D., Moreno, R., & Iapichino, G. (1997). Nine equivalents of nursing manpower use score (NEMS). *Intensive Care Med, 23*(7), 760-765.

323. Renaud, G., Llano-Diez, M., Ravara, B., Gorza, L., Feng, H. Z., Jin, J. P., . . . Larsson, L. (2013). Sparing of muscle mass and function by passive loading in an experimental intensive care unit model. *J Physiol, 591*(5), 1385-1402. doi:10.1113/jphysiol.2012.248724

324. Rennie, M. J., Wackerhage, H., Spangenburg, E. E., & Booth, F. W. (2004). Control of the size of the human muscle mass. *Annu Rev Physiol, 66*, 799-828. doi:10.1146/annurev.physiol.66.052102.134444

325. Rich, M. M., Bird, S. J., Raps, E. C., McCluskey, L. F., & Teener, J. W. (1997). Direct muscle stimulation in acute quadriplegic myopathy. *Muscle Nerve, 20*(6), 665-673. doi:10.1002/(sici)1097-4598(199706)20:6<665::aid-mus2>3.0.co;2-6

326. Rich, M. M., Teener, J. W., Raps, E. C., Schotland, D. L., & Bird, S. J. (1996). Muscle is electrically inexcitable in acute quadriplegic myopathy. *Neurology, 46*(3), 731-736. doi:10.1212/wnl.46.3.731

327. Rochwerg, B., Oczkowski, S. J., Siemieniuk, R. A., Agoritsas, T., Belley-Cote, E., D'Aragon, F., . . . Alghuroba, M. (2018). Corticosteroids in sepsis: an updated systematic review and meta-analysis. *Read Online: Critical Care Medicine| Society of Critical Care Medicine, 46*(9), 1411-1420.

328. Rock, K. L., Gramm, C., Rothstein, L., Clark, K., Stein, R., Dick, L., . . . Goldberg, A. L. (1994). Inhibitors of the proteasome block the degradation of most cell proteins and the generation of peptides presented on MHC class I molecules. *Cell, 78*(5), 761-771.

329. Ronco, C., Bellomo, R., & Ricci, Z. (2001). Continuous renal replacement therapy in critically ill patients. *Nephrol Dial Transplant, 16 Suppl 5*, 67-72. doi:10.1093/ndt/16.suppl_5.67

330. Rose, D. K., Nadeau, S. E., Wu, S. S., Tilson, J. K., Dobkin, B. H., Pei, Q., & Duncan, P. W. (2017). Locomotor Training and Strength and Balance Exercises for Walking Recovery After Stroke: Response to Number of Training Sessions. *Phys Ther, 97*(11), 1066-1074. doi:10.1093/ptj/pzx079

331. Rothen, H. U., Kung, V., Ryser, D. H., Zurcher, R., & Regli, B. (1999). Validation of "nine equivalents of nursing manpower use score" on an independent data sample. *Intensive Care Med, 25*(6), 606-611.

332. Routsi, C., Gerovasili, V., Vasileiadis, I., Karatzanos, E., Pitsolis, T., Tripodaki, E., . . . Nanas, S. (2010). Electrical muscle stimulation prevents critical illness polyneuromyopathy: a randomized parallel intervention trial. *Crit Care, 14*(2), R74. doi:10.1186/cc8987

333. Russell, A. P. (2010). Molecular regulation of skeletal muscle mass. *Clin Exp Pharmacol Physiol, 37*(3), 378-384. doi:10.1111/j.1440-1681.2009.05265.x

334. Russell, J. A., Rush, B., & Boyd, J. (2018). Pathophysiology of septic shock. *Critical Care Clinics, 34*(1), 43-61.

335. Sander, H. W., Golden, M., & Danon, M. J. (2002). Quadriplegic areflexic ICU illness: selective thick filament loss and normal nerve histology. *Muscle Nerve, 26*(4), 499-505. doi:10.1002/mus.10233

336. Sandri, M., Sandri, C., Gilbert, A., Skurk, C., Calabria, E., Picard, A., . . . Goldberg, A. L. (2004). Foxo transcription factors induce the atrophy-related ubiquitin ligase atrogin-1 and cause skeletal muscle atrophy. *Cell, 117*(3), 399-412. doi:10.1016/s0092-8674(04)00400-3

337. Sarfati, C., Moore, A., Pilorge, C., Amaru, P., Mendialdua, P., Rodet, E., . . . Rezaiguia-Delclaux, S. (2018). Efficacy of early passive tilting in minimizing ICU-acquired weakness: a randomized controlled trial. *Journal of Critical Care, 46*, 37‐43. doi:10.1016/j.jcrc.2018.03.031

338. Savci, S., Degirmenci, B., Saglam, M., Arikan, H., Inal-Ince, D., Turan, H. N., & Demircin, M. (2011). Short-term effects of inspiratory muscle training in coronary artery bypass graft surgery: a randomized controlled trial. *Scand Cardiovasc J, 45*(5), 286-293. doi:10.3109/14017431.2011.595820

339. Schaller, S. J., Anstey, M., Blobner, M., Edrich, T., Grabitz, S. D., Gradwohl-Matis, I., . . . International Early, S.-g. M. R. I. (2016). Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial. *Lancet, 388*(10052), 1377-1388. doi:10.1016/S0140-6736(16)31637-3

340. Schefold, J. C., Bierbrauer, J., & Weber-Carstens, S. (2010). Intensive care unit-acquired weakness (ICUAW) and muscle wasting in critically ill patients with severe sepsis and septic shock. *J Cachexia Sarcopenia Muscle, 1*(2), 147-157. doi:10.1007/s13539-010-0010-6

341. Schefold, J. C., Wollersheim, T., Grunow, J. J., Luedi, M. M., Z'Graggen, W. J., & Weber‐Carstens, S. (2020). Muscular weakness and muscle wasting in the critically ill. *Journal of cachexia, sarcopenia and muscle*.

342. Schiaffino, S., Dyar, K. A., Ciciliot, S., Blaauw, B., & Sandri, M. (2013). Mechanisms regulating skeletal muscle growth and atrophy. *Febs j, 280*(17), 4294-4314. doi:10.1111/febs.12253

343. Schmidt, F., Kny, M., Zhu, X., Wollersheim, T., Persicke, K., Langhans, C., . . . Fielitz, J. (2014). The E3 ubiquitin ligase TRIM62 and inflammation-induced skeletal muscle atrophy. *Critical Care, 18*(5), 545.

344. Schwab, S. J., & Beathard, G. (1999). The hemodialysis catheter conundrum: hate living with them, can't live without them. *Kidney International, 56*, 1-17.

345. Schweickert, W. D., Pohlman, M. C., Pohlman, A. S., Nigos, C., Pawlik, A. J., Esbrook, C. L., . . . Kress, J. P. (2009). Early physical and occupational therapy in

mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet, 373*(9678), 1874-1882. doi:10.1016/S0140-6736(09)60658-9

346. Seo, B., & Shin, W.-S. (2019). Effects of functional training on strength, function level, and quality of life of persons in intensive care units. *Physical Therapy Rehabilitation Science, 8*(3), 134-140.

347. Sharshar, T., Bastuji-Garin, S., Stevens, R. D., Durand, M. C., Malissin, I., Rodriguez, P., . . . Groupe de Reflexion et d'Etude des Neuromyopathies En, R. (2009). Presence and severity of intensive care unit-acquired paresis at time of awakening are associated with increased intensive care unit and hospital mortality. *Crit Care Med, 37*(12), 3047-3053. doi:10.1097/CCM.0b013e3181b027e9

348. Sheean, P. M., Peterson, S. J., Gomez Perez, S., Troy, K. L., Patel, A., Sclamberg, J. S., . . . Braunschweig, C. A. (2014). The Prevalence of Sarcopenia in Patients With Respiratory Failure Classified as Normally Nourished Using Computed Tomography and Subjective Global Assessment. *Journal of Parenteral and Enteral Nutrition, 38*(7), 873-879. doi:https://doi.org/10.1177/0148607113500308

349. Shen, S.-Y., Lee, C.-H., Lin, R.-L., & Cheng, K.-H. (2017). Electric Muscle Stimulation for Weaning from Mechanical Ventilation in Elder Patients with Severe Sepsis and Acute Respiratory Failure–A Pilot Study. *International journal of gerontology, 11*(1), 41-45.

350. Shepherd, S. J., Newman, R., Brett, S. J., & Griffith, D. M. (2016). Pharmacological Therapy for the Prevention and Treatment of Weakness After Critical Illness: A Systematic Review. *Crit Care Med, 44*(6), 1198-1205. doi:10.1097/ccm.0000000000001652

351. Shimizu, N., Yoshikawa, N., Ito, N., Maruyama, T., Suzuki, Y., Takeda, S., . . . Tanaka, H. (2011). Crosstalk between glucocorticoid receptor and nutritional sensor mTOR in skeletal muscle. *Cell Metab, 13*(2), 170-182. doi:10.1016/j.cmet.2011.01.001

352. Showalter, C. J., & Engel, A. G. (1997). Acute quadriplegic myopathy: analysis of myosin isoforms and evidence for calpain-mediated proteolysis. *Muscle Nerve, 20*(3), 316-322. doi:10.1002/(sici)1097-4598(199703)20:3<316::Aid-mus8>3.0.Co;2-e

353. Siu, P. M. (2009). Muscle Apoptotic Response to Denervation, Disuse, and Aging. *Medicine and Science in Sports and Exercise*.

354. Siu, P. M., & Alway, S. E. (2009). Response and adaptation of skeletal muscle to denervation stress: the role of apoptosis in muscle loss. *Frontiers in Bioscience, 14*, 432-452.

355. Skinner, E. H., Berney, S., Warrillow, S., & Denehy, L. (2008). Rehabilitation and exercise prescription in Australian intensive care units. *Physiotherapy, 94*(3), 220-229.

356. Skinner, E. H., Haines, K. J., Berney, S., Warrillow, S., Harrold, M., & Denehy, L. (2015). Usual care physiotherapy during acute hospitalization in subjects admitted to the ICU: an observational cohort study. *Respiratory care, 60*(10), 1476-1485.

357. Smith, D. A. (2018). *The sliding-filament theory of muscle contraction*: Springer.

358. Smith, D. R., Kobrine, A. I., & Rizzoli, H. V. (1977). Absence of autoregulation in peripheral nerve blood flow. *J Neurol Sci, 33*(3), 347-352.

359. Solomon, V., & Goldberg, A. L. (1996). Importance of the ATP-ubiquitin-proteasome pathway in the degradation of soluble and myofibrillar proteins in rabbit muscle extracts. *Journal of Biological Chemistry, 271*(43), 26690-26697.

360. Souza, T. A., Chen, X., Guo, Y., Sava, P., Zhang, J., Hill, J. J., . . . Qiu, Y. (2008). Proteomic identification and functional validation of activins and bone morphogenetic protein 11 as candidate novel muscle mass regulators. *Molecular endocrinology, 22*(12), 2689-2702.

361. Spate, U., & Schulze, P. C. (2004). Proinflammatory cytokines and skeletal muscle. *Curr Opin Clin Nutr Metab Care, 7*(3), 265-269.

362. Standl, T., Annecke, T., Cascorbi, I., Heller, A. R., Sabashnikov, A., & Teske, W. (2018). The Nomenclature, Definition and Distinction of Types of Shock. *Deutsches arzteblatt international, 115*(45), 757-768. doi:10.3238/arztebl.2018.0757

363. Stein, T., & Wade, C. (2005). Metabolic consequences of muscle disuse atrophy. *The Journal of nutrition, 135*(7), 1824S-1828S.

364. Sterne, J. A., Hernan, M. A., Reeves, B. C., Savovic, J., Berkman, N. D., Viswanathan, M., . . . Higgins, J. P. (2016). ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ, 355*, i4919. doi:10.1136/bmj.i4919

365. Sterne, J. A. C., Savovic, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., . . . Higgins, J. P. T. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ, 366*, l4898. doi:10.1136/bmj.l4898

366. Stevens, R. D., Dowdy, D. W., Michaels, R. K., Mendez-Tellez, P. A., Pronovost, P. J., & Needham, D. M. (2007). Neuromuscular dysfunction acquired in critical illness: a systematic review. *Intensive Care Med, 33*(11), 1876-1891. doi:10.1007/s00134-007-0772-2

367. Stevens, R. D., Marshall, S. A., Cornblath, D. R., Hoke, A., Needham, D. M., de Jonghe, B., . . . Sharshar, T. (2009). A framework for diagnosing and classifying intensive care unit-acquired weakness. *Crit Care Med, 37*(10 Suppl), S299-308. doi:10.1097/CCM.0b013e3181b6ef67

368. Stiller, K. (2013). Physiotherapy in intensive care: an updated systematic review. *Chest, 144*(3), 825-847. doi:10.1378/chest.12-2930

369. Synolaki, E., Papadopoulos, V., Divolis, G., Tsahouridou, O., Gavriilidis, E., Loli, G., . . . Sideras, P. (2021). The Activin/Follistatin-axis is severely deregulated in COVID-19 and independently associated with in-hospital mortality. *The Journal of Infectious Diseases*. doi:10.1093/infdis/jiab108

370. Talley, C. L., Wonnacott, R. O., Schuette, J. K., Jamieson, J., & Heung, M. (2013). Extending the benefits of early mobility to critically ill patients undergoing continuous renal replacement therapy: the Michigan experience. *Critical Care Nursing Quarterly, 36*(1), 89-100.

371. Tang, B. M., Craig, J. C., Eslick, G. D., Seppelt, I., & McLean, A. S. (2009). Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis. *Crit Care Med, 37*(5), 1594-1603. doi:10.1097/CCM.0b013e31819fb507

372. Tiao, G., Hobler, S., Wang, J. J., Meyer, T. A., Luchette, F. A., Fischer, J. E., & Hasselgren, P.-O. (1997). Sepsis is associated with increased mRNAs of the ubiquitin-proteasome proteolytic pathway in human skeletal muscle. *The Journal of clinical investigation, 99*(2), 163-168.

373. Timenetsky, K. T., Neto, A. S., Assunção, M. S. C., Taniguchi, L., Eid, R. A. C., Corrêa, T. D., & on behalf of the e, M. g. (2020). Mobilization practices in the ICU: A nationwide 1-day point- prevalence study in Brazil. *PLoS One, 15*(4), e0230971. doi:10.1371/journal.pone.0230971

374. Tipping, C. J., Harrold, M., Holland, A., Romero, L., Nisbet, T., & Hodgson, C. L. (2017). The effects of active mobilisation and rehabilitation in ICU on mortality and function: a systematic review. *Intensive Care Med, 43*(2), 171-183. doi:10.1007/s00134-016-4612-0

375. Tisdale, M. J. (2010). Reversing cachexia. *Cell, 142*(4), 511-512.

376. Tonella, R. M., Ratti, L., Delazari, L. E. B., Junior, C. F., Da Silva, P. L., Herran, A., . . . Falcao, A. L. E. (2017). Inspiratory Muscle Training in the Intensive Care Unit: A New Perspective. *J Clin Med Res, 9*(11), 929-934. doi:10.14740/jocmr3169w

377. Truong, A. D., Fan, E., Brower, R. G., & Needham, D. M. (2009). Bench-to-bedside review: mobilizing patients in the intensive care unit--from pathophysiology to clinical trials. *Crit Care, 13*(4), 216. doi:10.1186/cc7885

378. Uchino, S., Fealy, N., Baldwin, I., Morimatsu, H., & Bellomo, R. (2003). Continuous is not continuous: the incidence and impact of circuit "down-time" on uraemic control during continuous veno-venous haemofiltration. *Intensive Care Medicine, 29*, 575-578.

379. Uchino, S., Kellum, J. A., Bellomo, R., Doig, G. S., Morimatsu, H., Morgera, S., . . . Investigators, B. a. E. S. T. f. t. K. B. K. (2005). Acute renal failure in critically ill patients: a multinational, multicentre study. *JAMA, 294*(17), 813-818.

380. Van den Berghe, G., Schoonheydt, K., Becx, P., Bruyninckx, F., & Wouters, P. J. (2005). Insulin therapy protects the central and peripheral nervous system of intensive care patients. *Neurology, 64*(8), 1348-1353. doi:10.1212/01.WNL.0000158442.08857.FC

381. Vanhorebeek, I., Gunst, J., Derde, S., Derese, I., Boussemaere, M., Güiza, F., . . . Van den Berghe, G. (2011). Insufficient Activation of Autophagy Allows Cellular Damage to Accumulate in Critically Ill Patients. *The Journal of Clinical Endocrinology & Metabolism, 96*(4), E633-E645. doi:10.1210/jc.2010-2563

382. Vanhorebeek, I., Latronico, N., & Van den Berghe, G. (2020). ICU-acquired weakness. *Intensive Care Med, 46*(4), 637-653. doi:10.1007/s00134-020-05944-4

383. Vanpee, G., Hermans, G., Segers, J., & Gosselink, R. (2014). Assessment of limb muscle strength in critically ill patients: a systematic review. *Crit Care Med, 42*(3), 701-711. doi:10.1097/CCM.0000000000000030

384. Vanpee, G., Segers, J., Van Mechelen, H., Wouters, P., Van den Berghe, G., Hermans, G., & Gosselink, R. (2011). The interobserver agreement of handheld dynamometry for muscle strength assessment in critically ill patients. *Crit Care Med, 39*(8), 1929-1934. doi:10.1097/CCM.0b013e31821f050b

385. Vincent, J.-L., Moreno, R., Takala, J., Willatts, S., De Mendonça, A., Bruining, H., . . . Thijs, L. G. (1996). The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. In: Springer-Verlag.

386. Vincent, J. L., Moreno, R., Takala, J., Willatts, S., De Mendonça, A., Bruining, H., . . . Thijs, L. G. (1996). The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med, 22*(7), 707-710. doi:10.1007/bf01709751

387. Von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., Vandenbroucke, J. P., & Initiative, S. (2007). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Preventive medicine, 45*(4), 247-251.

388. Vorona, S., Sabatini, U., Al-Maqbali, S., Bertoni, M., Dres, M., Bissett, B., . . . Goligher, E. C. (2018). Inspiratory Muscle Rehabilitation in Critically Ill Adults. A Systematic Review and Meta-Analysis. *Ann Am Thorac Soc, 15*(6), 735-744. doi:10.1513/AnnalsATS.201712-961OC

389. Wan, X., Wang, W., Liu, J., & Tong, T. (2014). Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol, 14*(1), 135. doi:10.1186/1471-2288-14-135

390. Watson, A. C., Hughes, P. D., Louise Harris, M., Hart, N., Ware, R. J., Wendon, J., . . . Moxham, J. (2001). Measurement of twitch transdiaphragmatic, esophageal, and endotracheal tube pressure with bilateral anterolateral magnetic phrenic nerve stimulation in patients in the intensive care unit. *Critical Care Medicine, 29*(7).

391. Weber-Carstens, S., Schneider, J., Wollersheim, T., Assmann, A., Bierbrauer, J., Marg, A., . . . Koch, S. (2013). Critical illness myopathy and GLUT4: significance of insulin and muscle contraction. *American journal of respiratory and critical care medicine, 187*(4), 387-396.

392. Wieske, L., van Hest, R. M., Witteveen, E., Verhamme, C., Schultz, M. J., van Schaik, I. N., & Horn, J. (2015). Is gentamicin affecting the neuromuscular system of critically ill patients? *Intensive Care Medicine, 41*(4), 727-728. doi:10.1007/s00134-015-3731-3

393. Wieske, L., Witteveen, E., Verhamme, C., Dettling-Ihnenfeldt, D. S., van der Schaaf, M., Schultz, M. J., . . . Horn, J. (2014). Early prediction of intensive care unit–acquired weakness using easily available parameters: A prospective observational study. *PLoS One, 9*(10), e111259.

394. Wilcox, P., Milliken, C., & Bressler, B. (1996). High-dose tumor necrosis factor alpha produces an impairment of hamster diaphragm contractility. Attenuation with a prostaglandin inhibitor. *Am J Respir Crit Care Med, 153*(5), 1611-1615. doi:10.1164/ajrccm.153.5.8630610

395. Williams, N., & Flynn, M. (2013). An exploratory study of physiotherapists' views of early rehabilitation in critically ill patients. *Physiotherapy Practice and Research, 34*(2), 93-102.

396. Winkelman, C. (2004). Inactivity and inflammation: selected cytokines as biologic mediators in muscle dysfunction during critical illness. *AACN Clinical Issues, 15*(1), 74-82. doi:00044067-200401000-00006 [pii]

397. Winkelman, C., Johnson, K. D., Hejal, R., Gordon, N. H., Rowbottom, J., Daly, J., . . . Levine, A. D. (2012). Examining the positive effects of exercise in intubated adults in ICU: a prospective repeated measures clinical study. *Intensive Crit Care Nurs, 28*(6), 307-318. doi:10.1016/j.iccn.2012.02.007

398. Winkelman, C., & Peereboom, K. (2010). Staff-perceived barriers and facilitators. *Crit Care Nurse, 30*(2), S13-16. doi:10.4037/ccn2010393

399. Winkelman, C., Sattar, A., Momotaz, H., Johnson, K. D., Morris, P., Rowbottom, J. R., . . . Levine, A. (2018). Dose of Early Therapeutic Mobility: Does Frequency or Intensity Matter? *Biol Res Nurs, 20*(5), 522-530. doi:10.1177/1099800418780492

400. Witt, N. J., Zochodne, D. W., Bolton, C. F., Grand'Maison, F., Wells, G., Young, G. B., & Sibbald, W. J. (1991). Peripheral nerve function in sepsis and multiple organ failure. *Chest, 99*(1), 176-184.

401. Wolfe, K. S., Patel, B. K., MacKenzie, E. L., Giovanni, S. P., Pohlman, A. S., Churpek, M. M., . . . Kress, J. P. (2018). Impact of Vasoactive Medications on ICU-Acquired Weakness in Mechanically Ventilated Patients. *Chest, 154*(4), 781-787. doi:10.1016/j.chest.2018.07.016

402. Wolfe, K. S., Wendlandt, B. N., Patel, S. B., Patel, B. K., Greenberg, J. A., Pohlman, A. S., . . . Kress, J. P. (2013). Long-term survival and health care utilization of mechanically ventilated patients in a randomized controlled trial of early mobilization. *American journal of respiratory and critical care medicine, 187*.

403. Wollersheim, T., Grunow, J., Carbon, N., Haas, K., Malleike, J., Ramme, S., . . . et al. (2019). Muscle wasting and function after muscle activation and early protocol-based physiotherapy: an explorative trial. *Journal of cachexia, sarcopenia and muscle*. Retrieved from doi:10.1002/jcsm.12428

404. Wollersheim, T., Woehlecke, J., Krebs, M., Hamati, J., Lodka, D., Luther-Schroeder, A., . . . Fielitz, J. (2014). Dynamics of myosin degradation in intensive care unit-acquired weakness during severe critical illness. *Intensive Care Med, 40*(4), 528-538. doi:10.1007/s00134-014-3224-9

405. Worraphan, S., Thammata, A., Chittawatanarat, K., Saokaew, S., Kengkla, K., & Prasannarong, M. (2020). Effects of Inspiratory Muscle Training and Early Mobilization on Weaning of Mechanical Ventilation: A Systematic Review and Network Meta-analysis. *Arch Phys Med Rehabil, 101*(11), 2002-2014. doi:10.1016/j.apmr.2020.07.004

406. Wright, J. M., & Collier, B. (1977). The effects of neomycin upon transmitter release and action. *J Pharmacol Exp Ther, 200*(3), 576-587.

407. Wright, S. E., Thomas, K., Watson, G., Baker, C., Bryant, A., Chadwick, T. J., . . . Baudouin, S. (2018). Intensive versus standard physical rehabilitation therapy in the critically ill (EPICC): a multicentre, parallel-group, randomised controlled trial. *Thorax, 73*(3), 213-221. doi:10.1136/thoraxjnl-2016-209858

408. Yang, T., Li, Z.-Q., Li, H.-L., Zhou, J.-X., & Chen, G.-Q. (2020). Aminoglycoside use and intensive care unit-acquired weakness: A systematic review and meta-analysis. *PLoS One, 15*(3), e0230181.

409. Yang, T., Li, Z., Jiang, L., Wang, Y., & Xi, X. (2018). Risk factors for intensive care unit-acquired weakness: A systematic review and meta-analysis. *Acta Neurol Scand, 138*(2), 104-114. doi:10.1111/ane.12964

410. Yang, T., Li, Z., Jiang, L., & Xi, X. (2018). Corticosteroid use and intensive care unit-acquired weakness: a systematic review and meta-analysis. *Critical Care, 22*(1), 187. doi:10.1186/s13054-018-2111-0

411. Yosef-Brauner, O., Adi, N., Ben Shahar, T., Yehezkel, E., & Carmeli, E. (2015). Effect of physical therapy on muscle strength, respiratory muscles and functional parameters in patients with intensive care unit-acquired weakness. *Clin Respir J, 9*(1), 1-6. doi:10.1111/crj.12091

412. Yousefzadeh-Chabok, S., Khodadadi-Hassankiadeh, N., Saberi, A., Ghanbari Khanghah, A., Zarrabi, H., Yeganeh, M. R., . . . Dehnadi Moghadam, A. (2018). Anxiety, Depression, and Their Related Factors in Patients Admitted to Intensive Care Units. *Caspian Journal of Neurological Sciences, 4*(4), 159-168. doi:10.29252/cjns.4.15.159

413. Z'Graggen, W. J., Lin, C. S., Howard, R. S., Beale, R. J., & Bostock, H. (2006). Nerve excitability changes in critical illness polyneuropathy. *Brain, 129*(Pt 9), 2461-2470. doi:10.1093/brain/awl191

414. Zamir, O., Hasselgren, P. O., von Allmen, D., & Fischer, J. E. (1991). The effect of interleukin-1 alpha and the glucocorticoid receptor blocker RU 38486 on total and myofibrillar protein breakdown in skeletal muscle. *J Surg Res, 50*(6), 579-583. doi:10.1016/0022-4804(91)90045-n

415. Zang, K., Chen, B., Wang, M., Chen, D., Hui, L., Guo, S., . . . Shang, F. (2020). The effect of early mobilization in critically ill patients: A meta-analysis. *Nurs Crit Care, 25*(6), 360-367. doi:10.1111/nicc.12455

416. Zayed, Y., Kheiri, B., Barbarawi, M., Chahine, A., Rashdan, L., Chintalapati, S., . . . Al-Sanouri, I. (2020). Effects of neuromuscular electrical stimulation in critically ill patients: A systematic review and meta-analysis of randomised controlled trials. *Aust Crit Care, 33*(2), 203-210. doi:10.1016/j.aucc.2019.04.003

417. Zhang, G., Zhang, K., Cui, W., Hong, Y., & Zhang, Z. (2018). The effect of early mobilization for critical ill patients requiring mechanical ventilation: a systematic review and meta-analysis. *J Emerg Crit Care Med, 2*(1), 2-9.

418. Zhao, J., Brault, J. J., Schild, A., Cao, P., Sandri, M., Schiaffino, S., . . . Goldberg, A. L. (2007). FoxO3 coordinately activates protein degradation by the autophagic/lysosomal and proteasomal pathways in atrophying muscle cells. *Cell metabolism, 6*(6), 472-483.

419. Zhou, X., Wang, J., Lu, J., Song, Y., Kwak, K., Jiao, Q., . . . Han, H. Q. (2010). Reversal of Cancer Cachexia and Muscle Wasting by ActRIIB Antagonism Leads to Prolonged Survival. *Cell, 142*(4), 531-543.

420. Zhu, X., van Hees, H. W. H., Heunks, L., Wang, F., Shao, L., Huang, J., . . . Ma, S. (2017). The role of calpains in ventilator-induced diaphragm atrophy. *Intensive care medicine experimental, 5*(1), 14-14. doi:10.1186/s40635-017-0127-4

421. Zochodne, D. W., Bolton, C. F., Wells, G. A., Gilbert, J. J., Hahn, A. F., Brown, J. D., & Sibbald, W. A. (1987). Critical illness polyneuropathy. A complication of sepsis and multiple organ failure. *Brain, 110 (Pt 4)*, 819-841.

Appendices

Appendix 3.1 Daily ICU Data Collection Form

Daily ICU Data Collection Form

Date and study ID

Time point

- ☐ Standard ICU day
- ☐ First awakening
- ☐ First sit out of bed session - also complete PFIT form
- ☐ ICU discharge - use ICU Discharge Form INSTEAD

Assessment for wakefulness

Ask the patient in a loud clear voice to do the following activities: tick if performed correctly.
A minimum 3 out of 5 is deemed awake

- ☐ Open/close your eyes
- ☐ Look at me
- ☐ Poke out your tongue
- ☐ Nod your head
- ☐ Raise your eyebrows

Grip strength attempt 1(kg)

If unable, why?

Grip strength attempt 2 (kg)

If unable, why?

Grip strength attempt 3 (kg)

If unable, why?

Standardised grip strength test position
As upright as practicable either on a bed/plinth or sitting in a chair, with backrest support.
Shoulder adducted and neutrally rotated.
Elbow flexed at 90°.
Forearm and wrist in neutral position, with 0-15° of ulnar deviation and 0-30° of wrist extension.
Allow 6 seconds for each contraction, as a delay in peak force generation may occur.

ICU Mobility Scale

Tick the most accurate description of the participant's HIGHEST level of mobilisation in the last 24 hours.

- ☐ (0) Nothing (lying in bed) Passively rolled or passively exercised by staff, but not actively moving
- ☐ (1) Sitting in bed, exercises in bed Any activity in bed, including rolling, bridging, active exercises, cycle ergometry and active assisted exercises, not moving out of bed or over the edge of the bed
- ☐ (2) Passively moved to chair (no standing) Hoist, passive lift or slide transfer to the chair, with no standing or sitting on the edge of the bed
- ☐ (3) Sitting over edge of bed May be assisted by staff, but involves actively sitting over the side of the bed with some trunk control
- ☐ (4) Standing Weight bearing through the feet in the standing position, with or without assistance. This may include use of a standing lifter device or tilt table
- ☐ (5) Transferring bed to chair Able to step or shuffle through standing to the chair. This involves actively transferring weight from one leg to another to move to the chair. If the patient has been stood with the assistance of a medical device, they must step to the chair (not included if the patient is wheeled in a standing lifter device)
- ☐ (6) Marching on spot (at bedside) Able to walk on the spot by lifting alternate feet (must be able to step at least 4 times, twice on each foot), with or without assistance
- ☐ (7) Walking with assistance of 2 or more people Walking away from the bed/chair by at least 5 m assisted by 2 or more people
- ☐ (8) Walking with assistance of 1 person Walking away from the bed/chair by at least 5 m assisted by 1 person
- ☐ (9) Walking independently with a gait aid Walking away from the bed/chair by at least 5 m with a gait aid, but no assistance from another person. In a wheelchair bound person, this activity level includes wheeling the chair independently 5 m away from the bed/chair
- ☐ (10) Walking independently without a gait aid Walking away from the bed/chair by at least 5 m without a gait aid or assistance from another person

Medical Research Council muscle strength grade

Wrist extension	Left	Right	If unable, why?
Elbow flexion	Left	Right	If unable, why?
Shoulder abduction	Left	Right	If unable, why?
Hip flexion	Left	Right	If unable, why?
Knee extension	Left	Right	If unable, why?
Ankle dorsiflexion	Left	Right	if unable, why?

Total score (sum of all scores)

Presence of focal/unilateral neurological deficit

☐ No

☐ If Yes, please provide details

Grade 5: Muscle contracts normally against full resistance.
Grade 4: Muscle strength is reduced but muscle contraction can still move joint against resistance.
Grade 3: Muscle strength is further reduced such that the joint can be moved only against gravity with the examiner's resistance completely removed. As an example, the elbow can be moved from full extension to full flexion starting with the arm hanging down at the side.
Grade 2: Muscle can move only if the resistance of gravity is removed. As an example, the elbow can be fully flexed only if the arm is maintained in a horizontal plane.
Grade 1: Only a trace or flicker of movement is seen or felt in the muscle or fasciculations are observed in the muscle.
Grade 0: No movement is observed.

Sequential [Sepsis-Related] Organ Failure Assessment Score (SOFA Score)

PaO2/FiO2 ratio

- ◯ ≥400
- ◯ <400
- ◯ <300
- ◯ <200 with respiratory support
- ◯ <100 with respiratory support

Platelets, x1000/μL

◯ ≥150 ◯ <150 ◯ <100 ◯ <50 ◯ <20

Bilirubin, μmol/L

◯ <20 ◯ 20-32 ◯ 33-101 ◯ 102-204 ◯ >204

Mean arterial pressure

- ◯ ≥ 70 mm Hg
- ◯ < 70 mm Hg
- ◯ < 5 mcg/kg/min dopamine OR any dose of dubutamine
- ◯ ≤ 0.1 mcg/kg/min noradrenaline OR adrenaline OR 5.1-15 mcg/kg/min dopamine
- ◯ > 0.1 mcg/kg/min noradrenaline OR adrenaline OR >15 mcg/kg/min dopamine

Glasgow Coma Scale score

◯ 15 ◯ 13-14 ◯ 10-12 ◯ 6-9 ◯ <6

Creatinine, μmol/L

- ◯ <110
- ◯ 110-170
- ◯ 171-299
- ◯ 300-400 OR urine output <500 mL/day
- ◯ >400 OR Urine output <200 mL/day

Septic shock criteria (Sepsis-3)

Requiring vasopressors to maintain mean blood pressure of ≥65 mmHg

◯ Yes
◯ No

Serum lactate ≥2 mmol/L

◯ Yes
◯ No

Has the patient received ≥30 ml/kg crystalloid fluid resuscitation?

◯ Yes
◯ No

SIRS, Sepsis, and Septic Shock Criteria (Sepsis-1)

Temperature >38°C or < 36°C

◯ Yes ◯ No

Heart Rate > 90

◯ Yes ◯ No

Respiratory rate > 20 or PaCO2 < 32 mm Hg

◯ Yes ◯ No

White cell count > 12,000/mm3, < 4,000/mm3, or > 10% bands cells

◯ Yes ◯ No

Confirmed source of infection

◯ Yes ◯ No

Lactic Acidosis, oliguria, or acute change in mental status

◯ Yes ◯ No

Sepsis induced hypotension (systolic blood pressure of <90 mm Hg, or a drop of more than 40 mm Hg from baseline)

◯ Yes ◯ No

Has the patient received adequate fluid resuscitation?

◯ Yes ◯ No

Presence of altered function in one or more organ requiring intervention to achieve homeostasis

◯ Yes ◯ No

Patient requiring renal replacement therapy in last 24 hours

◯ Yes ◯ No

Patient requiring mechanical ventilation in last 24 hours

◯ Yes ◯ No

If requiring mechanical ventilation

◯ Invasive mechanical ventilation
◯ Noninvasive mechanical ventilation
◯ N/A patient not on mechanical ventilation

Patient requiring vasopressors in last 24 hours

◯ Yes ◯ No

Patient received systemic corticosteroids in the last 24 hours

◯ Yes ◯ No

Beta2-adrenergic agonist use in last 24 hours

◯ Yes ◯ No

Sedation at time of data collection

◯ Yes ◯ No

Neuromuscular blocking agent use in last 24 hours

◯ Yes ◯ No

Frequency of neuromuscular blocking agent use

◯ Continuous infusion
◯ Bolus
◯ N/A no neuromuscular blocking agent used

Respiratory muscle strength

Is the participant "Awake"

- ◯ Yes - Proceed with Maximal Inspiratory Pressure. Hold NIF button, ask participant to breath out as much as they can, and ask them to breath in as hard as they can. Refer to standard operating procedure for details.
- ◯ No - Test Maximal Inspiratory Pressure if intensivist happy. Hold NIF button for 20 seconds. Refer to standard operating procedure for details.

Is the treating intensivist happy for MIP to be measured?

- ◯ Yes
- ◯ Not applicable, participant is awake
- ◯ No, please state reason given

Maximal inspiratory pressure

If unable to complete, please state why

Is the patient suitable to undergo vital capacity testing on pressure support ventilation with Positive End Expiratory Pressure=5 and Pressure Support=5

- ◯ Yes
- ◯ No, please state why

Vital capacity

If unable to complete, please state why

Nutrition

- ☐ Enteral feeding ONLY (via GI tract)
- ☐ Parenteral feeding ONLY (bypassing GI tract)
- ☐ Enteral AND Parental feeding
- ☐ None

Percentage of daily energy requirement met. (Previous calendar day)
(If feed density is blinded due to TARGET RCT write "TARGET")

Percentage of daily protein requirement met. (Previous calendar day)

Enrollment in TARGET RCT (The augmented versus routine approach to giving energy trial)?

- ◯ Yes
- ◯ No

Appendix 3.2 ICU Discharge Form

ICU Discharge Form

Date and study ID

Assessment for wakefulness

Ask the patient in a loud clear voice to do the following activities: tick if performed correctly.
A minimum 3 out of 5 is deemed awake

- ☐ Open/close your eyes
- ☐ Look at me
- ☐ Poke out your tongue
- ☐ Nod your head
- ☐ Raise your eyebrows

Grip strength attempt 1(kg)

If unable, why?

Grip strength attempt 2 (kg)

If unable, why?

Grip strength attempt 3 (kg)

If unable, why?

Standardised grip strength test position
As upright as practicable either on a bed/plinth or sitting in a chair, with backrest support.
Shoulder adducted and neutrally rotated.
Elbow flexed at 90°.
Forearm and wrist in neutral position, with 0-15° of ulnar deviation and 0-30° of wrist extension.
Allow 6 seconds for each contraction, as a delay in peak force generation may occur.

ICU Mobility Scale

Tick the most accurate description of the participants HIGHEST level of mobilisation in the last 24 hours

- ☐ (0) Nothing (lying in bed) Passively rolled or passively exercised by staff, but not actively moving
- ☐ (1) Sitting in bed, exercises in bed Any activity in bed, including rolling, bridging, active exercises, cycle ergometry and active assisted exercises, not moving out of bed or over the edge of the bed
- ☐ (2) Passively moved to chair (no standing) Hoist, passive lift or slide transfer to the chair, with no standing or sitting on the edge of the bed
- ☐ (3) Sitting over edge of bed May be assisted by staff, but involves actively sitting over the side of the bed with some trunk control
- ☐ (4) Standing Weight bearing through the feet in the standing position, with or without assistance. This may include use of a standing lifter device or tilt table
- ☐ (5) Transferring bed to chair Able to step or shuffle through standing to the chair. This involves actively transferring weight from one leg to another to move to the chair. If the patient has been stood with the assistance of a medical device, they must step to the chair (not included if the patient is wheeled in a standing lifter device)
- ☐ (6) Marching on spot (at bedside) Able to walk on the spot by lifting alternate feet (must be able to step at least 4 times, twice on each foot), with or without assistance
- ☐ (7) Walking with assistance of 2 or more people Walking away from the bed/chair by at least 5 m assisted by 2 or more people
- ☐ (8) Walking with assistance of 1 person Walking away from the bed/chair by at least 5 m assisted by 1 person
- ☐ (9) Walking independently with a gait aid Walking away from the bed/chair by at least 5 m with a gait aid, but no assistance from another person. In a wheelchair bound person, this activity level includes wheeling the chair independently 5 m away from the bed/chair
- ☐ (10) Walking independently without a gait aid Walking away from the bed/chair by at least 5 m without a gait aid or assistance from another person

Medical Research Council muscle strength grade

Wrist extension	Left	Right	If unable, why?
Elbow flexion	Left	Right	If unable, why?
Shoulder abduction	Left	Right	If unable, why?
Hip flexion	Left	Right	If unable, why?
Knee extension	Left	Right	If unable, why?
Ankle dorsiflexion	Left	Right	if unable, why?

Total score (sum of all scores)

Presence of focal/unilateral neurological deficit

☐ No

☐ If Yes, please provide details

Grade 5: Muscle contracts normally against full resistance.
Grade 4: Muscle strength is reduced but muscle contraction can still move joint against resistance.
Grade 3: Muscle strength is further reduced such that the joint can be moved only against gravity with the examiner's resistance completely removed. As an example, the elbow can be moved from full extension to full flexion starting with the arm hanging down at the side.
Grade 2: Muscle can move only if the resistance of gravity is removed. As an example, the elbow can be fully flexed only if the arm is maintained in a horizontal plane.
Grade 1: Only a trace or flicker of movement is seen or felt in the muscle or fasciculations are observed in the muscle.
Grade 0: No movement is observed.

Sequential [Sepsis-Related] Organ Failure Assessment Score (SOFA Score)

PaO2/FiO2 ratio

- ◯ ≥400
- ◯ <400
- ◯ <300
- ◯ <200 with respiratory support
- ◯ <100 with respiratory support

Platelets, x1000/µL

◯ ≥150 ◯ <150 ◯ <100 ◯ <50 ◯ <20

Bilirubin, µmol/L

◯ <20 ◯ 20-32 ◯ 33-101 ◯ 102-204 ◯ >204

Mean arterial pressure

- ◯ ≥ 70 mm Hg
- ◯ < 70 mm Hg
- ◯ < 5 mcg/kg/min dopamine OR any dose of dubutamine
- ◯ ≤ 0.1 mcg/kg/min noradrenaline OR adrenaline or 5.1-15 mcg/kg/min dopamine
- ◯ > 0.1 mcg/kg/min noradrenaline OR adrenaline OR >15 mcg/kg/min dopamine

Glasgow Coma Scale score

◯ 15 ◯ 13-14 ◯ 10-12 ◯ 6-9 ◯ <6

Creatinine, µmol/L

- ◯ <110
- ◯ 110-170
- ◯ 171-299
- ◯ 300-400 OR urine output <500 mL/day
- ◯ >400 OR Urine output <200 mL/day

Septic shock criteria (Sepsis-3)

Requiring vasopressors to maintain mean blood pressure of ≥65 mmHg

◯ Yes
◯ No

Serum lactate ≥2 mmol/L

◯ Yes
◯ No

Has the patient received ≥30 ml/kg crystalloid fluid resuscitation?

◯ Yes
◯ No

SIRS, Sepsis, and Septic Shock Criteria (Sepsis-1)

Temp >38°C or < 36°C

◯ Yes ◯ No

Heart Rate > 90

◯ Yes ◯ No

Respiratory rate > 20 or PaCO2 < 32 mm Hg

◯ Yes ◯ No

WCC > 12,000/mm3, < 4,000/mm3, or > 10% bands cells

◯ Yes ◯ No

Confirmed source of infection

◯ Yes ◯ No

Lactic Acidosis, oliguria, or acute change in mental status

◯ Yes ◯ No

Sepsis induced hypotension (systolic blood pressure of <90 mm Hg, or a drop of more than 40 mm Hg from baseline)

◯ Yes ◯ No

Has the patient received adequate fluid resuscitation?

◯ Yes ◯ No

Presence of altered function in one or more organ requiring intervention to achieve homeostasis

◯ Yes ◯ No

Patient requiring renal replacement therapy in last 24 hours

◯ Yes ◯ No

Patient requiring mechanical ventilation in last 24 hours

◯ Yes ◯ No

If requiring mechanical ventilation

◯ Invasive mechanical ventilation
◯ Noninvasive mechanical ventilation
◯ N/A patient not on mechanical ventilation

Patient requiring vasopressors in last 24 hours

◯ Yes ◯ No

Patient received steroids in the last 24 hours

◯ Yes ◯ No

Beta2-adrenergic agonist use in last 24 hours

◯ Yes ◯ No

Sedation at time of data collection

◯ Yes ◯ No

Neuromuscular blocking agent use in last 24 hours

◯ Yes ◯ No

Frequency of neuromuscular blocking agent use

◯ Continuous infusion
◯ Bolus
◯ N/A no neuromuscular blocking agent used

Nutrition

- ☐ Enteral feeding ONLY (via GI tract)
- ☐ Parenteral feeding ONLY (bypassing GI tract)
- ☐ Enteral AND Parental feeding
- ☐ None

Percentage of daily energy requirement met.
(If feed density is blinded due to TARGET RCT write "TARGET")

Percentage of daily protein requirement met

Enrolled in TARGET RCT (The augmented versus routine approach to giving energy trial)?

- ◯ Yes
- ◯ No

Physical Function in ICU Test

Sit to stand. From sit out of bed position.

- ☐ Unable (0)
- ☐ Assist x 2 (1)
- ☐ Assist x 1 (2)
- ☐ No Assistance (3)

If unable, why?

Cadance (steps/min). Calculated by max number of steps taken and duration of marching.

- ☐ Unable (0)
- ☐ 1-49 (1)
- ☐ 50-79 (2)
- ☐ 80+ (3)

If unable, why?

Shoulder flexion power. Greatest of left OR right

- ☐ Grade 0 (0)
- ☐ Grade 1 (0)
- ☐ Grade 2 (0)
- ☐ Grade 3 (1)
- ☐ Grade 4 (2)
- ☐ Grade 5 (3)

If unable, why?

Knee extension power. Greatest of left OR right

- ☐ Grade 0 (0)
- ☐ Grade 1 (0)
- ☐ Grade 2 (0)
- ☐ Grade 3 (1)
- ☐ Grade 4 (2)
- ☐ Grade 5 (3)

If unable, why?

Total score

Timed Up and Go Test

Measure and mark a 3 meter walkway.
Place a standard height chair (seat height 46cm, arm height 67cm) at the beginning of the walkway.
Regular footwear and customary walking aids should be used.
Instruct the patient to sit on the chair and place his/her back against the chair and rest his/her arms chair's arms.
The upper extremities should not be on the assistive device (if used for walking), but it should be nearby.

Demonstrate the test to the patient.
The patient should walk to a line that is 3 meters away, turn around at the line, walk back to the chair, and sit down. Patients should be instructed to use a comfortable and safe walking speed.
When the patient is ready, say "Go".
The stopwatch should start when you say go, and should be stopped with the patient's buttocks touch the seat.

Timed Up and Go time - If unable to complete please write "unable to complete" here

Gait aid used?

- ◯ No
- ◯ Not applicable, could not complete test
- ◯ Yes. if yes, please state what was used

If unable to complete please state why

Six-Minute Walk Test

Measure and mark a 25 metre walkway. The track should be flat, with minimal blind turns or obstacles. The patient should rest for at least 15 minutes before beginning the 6MWT. Set up chair at start of track as required.
Describe the walking track to the patient and then give the patient the following instructions:

"You are now going to do a six-minute walking test. The object of this test is to walk as quickly as you can for six minutes (around the track; up and down the corridor etc… depending on your track set up) so that you cover as much ground as possible.
You may slow down if necessary. If you stop, I want you to continue to walk again as soon as possible. You will be regularly informed of the time and you will be encouraged to do your best. Your goal is to walk as far as possible in six minutes.
Please do not talk during the test unless you have a problem or I ask you a question. You must let me know if you have any chest pain or dizziness.
When the six minutes is up I will ask you to stop where you are. Do you have any questions?"

Begin the test by instructing the patient to: “Start walking now.”

Use the following standard encouragements during the test:
At minute one: “Five minutes remaining (patient name). Do your best!”
At minute two: “Four minutes remaining (patient name). You're doing well - keep it up!”
At minute three: “Half way - three minutes remaining (patient name). Do your best!”
At minute four: “Two minutes remaining (patient name). You're doing well - keep it up!”
At minute five: “One minute remaining (patient name). Do your best!”

If the Patient Stops During the Six Minutes
Allow the patient to sit in a chair if they wish.
Measure the SpO2% and heart rate.
Ask patient why they stopped.
Record the time the patient stopped (but keep the stop watch running).
Give the following encouragement (repeat this encouragement every 15 seconds if necessary):

“Begin walking as soon as you feel able.”

Monitor the patient for untoward signs and symptoms.

Distance covered

- [ ] 0
- [ ] 25
- [ ] 50
- [ ] 75
- [ ] 100
- [ ] 125
- [ ] 150
- [ ] 175
- [ ] 200
- [ ] 225
- [ ] 250
- [ ] 300
- [ ] 325
- [ ] 350
- [ ] 375
- [ ] 400
- [ ] 425
- [ ] 450
- [ ] 475
- [ ] 500

Notes

Final distance covered to nearest metre - If unable to complete please score "0" here

Gait aid used?

- ◯ No
- ◯ Not applicable, could not complete test
- ◯ Yes. if yes, please state what was used

If unable to complete please state why

Complete infusion drug collection table (attached, print more as required)

- [ ]

If other, write in empty rows. Particularly inotropes and neuromuscular blocking agents

Date														
Day of ICU admission														
Propofol total (mg)														
Propofol hours														
Morphine total (mg)														
Morphine hours														
Midazolam total (mg)														
Midazolam hours														
Dexmedetomidine (mcg)														
Dexmedetomidine hours														
Fentanyl total (mcg)														
Fentanyl hours														
Cisatracurium total (mg)														
Cisatracurium hours														
Noradrenaline total (mcg)														
Noradrenaline hours														
Adrenaline total (mcg)														
Adrenaline hours														
Vasopressin total (units)														
Vasopressin hours														
Dobutamine total (mcg)														
Dobutamine hours														
Dopamine (mcg)														
Dopamine hours														
Actrapid total (units)														
Actrapid hours														

If other, write in empty rows. Particularly inotropes and neuromuscular blocking agents

Date														
Day of ICU admission														
Propofol total (mg)														
Propofol hours														
Morphine total (mg)														
Morphine hours														
Midazolam total (mg)														
Midazolam hours														
Dexmedetomidine (mcg)														
Dexmedetomidine hours														
Fentanyl total (mcg)														
Fentanyl hours														
Cisatracurium total (mg)														
Cisatracurium hours														
Noradrenaline total (mcg)														
Noradrenaline hours														
Adrenaline total (mcg)														
Adrenaline hours														
Vasopressin total (units)														
Vasopressin hours														
Dobutamine total (mcg)														
Dobutamine hours														
Dopamine (mcg)														
Dopamine hours														
Actrapid total (units)														
Actrapid hours														

Appendix 3.3 Hospital Discharge Form

Hospital Discharge Form

Hospital discharge date

Study ID

ICU discharge date

Number of ICU admissions during stay

Hours on invasive mechanical ventilation

Hours of renal replacement therapy in ICU.
If none, score Zero.

CT abdomen during admission?

- ☐ Yes
- ☐ No
- ☐ If yes, check box when CT downloaded

Discharge destination

- ☐ Home
- ☐ Rehabilitation
- ☐ Other acute hospital
- ☐ Residential care facility
- ☐ Deceased
- ☐ Other

Continuation of consent signed

- ○ Yes ○ No ○ N/A
- ○ If no, reason

Timed Up and Go Test

Measure and mark a 3 meter walkway.
Place a standard height chair (seat height 46cm, arm height 67cm) at the beginning of the walkway.
Regular footwear and customary walking aids should be used.
Instruct the patient to sit on the chair and place his/her back against the chair and rest his/her arms chair's arms.
The upper extremities should not be on the assistive device (if used for walking), but it should be nearby.

Demonstrate the test to the patient.
The patient should walk to a line that is 3 meters away, turn around at the line, walk back to the chair, and sit down. Patients should be instructed to use a comfortable and safe walking speed.
When the patient is ready, say "Go".
The stopwatch should start when you say go, and should be stopped with the patient's buttocks touch the seat.

Timed Up and Go time - If unable to complete please write "unable to complete" here

Gait aid used?

- ◯ No
- ◯ Not applicable, could not complete test
- ◯ Yes. if yes, please state what was used

If unable to complete please state why

Six-Minute Walk Test

Measure and mark a 25 metre walkway. The track should be flat, with minimal blind turns or obstacles. The patient should rest for at least 15 minutes before beginning the 6MWT. Set up chair at start of track as required.
Describe the walking track to the patient and then give the patient the following instructions:

"You are now going to do a six-minute walking test. The object of this test is to walk as quickly as you can for six minutes (around the track; up and down the corridor etc… depending on your track set up) so that you cover as much ground as possible.
You may slow down if necessary. If you stop, I want you to continue to walk again as soon as possible. You will be regularly informed of the time and you will be encouraged to do your best. Your goal is to walk as far as possible in six minutes.
Please do not talk during the test unless you have a problem or I ask you a question. You must let me know if you have any chest pain or dizziness.
When the six minutes is up I will ask you to stop where you are. Do you have any questions?"

Begin the test by instructing the patient to: “Start walking now.”

Use the following standard encouragements during the test:
At minute one: “Five minutes remaining (patient name). Do your best!”
At minute two: “Four minutes remaining (patient name). You're doing well - keep it up!”
At minute three: “Half way - three minutes remaining (patient name). Do your best!”
At minute four: “Two minutes remaining (patient name). You're doing well - keep it up!”
At minute five: “One minute remaining (patient name). Do your best!”

If the Patient Stops During the Six Minutes
Allow the patient to sit in a chair if they wish.
Measure the SpO2% and heart rate.
Ask patient why they stopped.
Record the time the patient stopped (but keep the stop watch running).
Give the following encouragement (repeat this encouragement every 15 seconds if necessary):

“Begin walking as soon as you feel able.”

Monitor the patient for untoward signs and symptoms.

Distance covered

- [ ] 0
- [ ] 25
- [ ] 50
- [ ] 75
- [ ] 100
- [ ] 125
- [ ] 150
- [ ] 175
- [ ] 200
- [ ] 225
- [ ] 250
- [ ] 300
- [ ] 325
- [ ] 350
- [ ] 375
- [ ] 400
- [ ] 425
- [ ] 450
- [ ] 475
- [ ] 500

Notes

Final distance covered to nearest metre - If unable to complete please score "0" here

Gait aid used?

- ◯ No
- ◯ Not applicable, could not complete test
- ◯ Yes. if yes, please state what was used

If unable to complete please state why

Medical Research Council muscle strength grade

Wrist extension	Left	Right	If unable, why?
Elbow flexion	Left	Right	If unable, why?
Shoulder abduction	Left	Right	If unable, why?
Hip flexion	Left	Right	If unable, why?
Knee extension	Left	Right	If unable, why?
Ankle dorsiflexion	Left	Right	if unable, why?

Total score (sum of all scores)

Presence of focal/unilateral neurological deficit

☐ No

☐ If Yes, please provide details

Grade 5: Muscle contracts normally against full resistance.
Grade 4: Muscle strength is reduced but muscle contraction can still move joint against resistance.
Grade 3: Muscle strength is further reduced such that the joint can be moved only against gravity with the examiner's resistance completely removed. As an example, the elbow can be moved from full extension to full flexion starting with the arm hanging down at the side.
Grade 2: Muscle can move only if the resistance of gravity is removed. As an example, the elbow can be fully flexed only if the arm is maintained in a horizontal plane.
Grade 1: Only a trace or flicker of movement is seen or felt in the muscle or fasciculations are observed in the muscle.
Grade 0: No movement is observed.

Grip strength attempt 1 (kg)

Grip strength attempt 2 (kg)

Grip strength attempt 3 (kg)

Standardised grip strength test position
As upright as practicable either on a bed/plinth or sitting in a chair, with backrest support.
Shoulder adducted and neutrally rotated.
Elbow flexed at 90°.
Forearm and wrist in neutral position, with 0-15° of ulnar deviation and 0-30° of wrist extension.
Allow 6 seconds for each contraction, as a delay in peak force generation may occur.

Complete pathology data collection table (attached, print more as required)

☐

Date (DD/MM/YYYY)	ICU admission day (Day of admission = day 0)	Creatinine (micromole/L)	Lactate (millimol/L)	Creatine kinase (Units/L)	Glucose (millimol/L)	Notes

Please print out more pages as required

Date (DD/MM/YYYY)	ICU admission day (Day of admission = day 0)	Creatinine (micromole/L)	Lactate (millimol/L)	Creatine kinase (Units/L)	Glucose (millimol/L)	Notes

Please print out more pages as required

Appendix 4.1 Letter to the editor and our response

Jacobs *Critical Care* (2015) 19:205
DOI 10.1186/s13054-015-0781-4

CRITICAL CARE

LETTER OpenAccess

Early mobilization on continuous renal replacement therapy is safe and may improve filter life

Frederic M Jacobs

See related research by Wang *et al.* http://ccforum.com/content/18/4/R161

In their study Wang and colleagues [1] found that mobilization during continuous renal replacement therapy (CRRT) is safe, and did not lead to filter circuit clotting. However, I feel that this work raises two remarks.

First, by delivering CRRT via continuous venovenous hemodiafiltration (CVVHDF) with a dialysate rate of 20 ml/kg/hour, a replacement fluid rate of 15 ml/kg/hour and a low effluent fluid removal rate, the filtration fraction, a major determinant of clotting, may have been lower than the one resulting from continuous venovenous hemofiltration (CVVHF), which is as much used as the CRRT mode [2]. Furthermore, details concerning the blood flow (which impacts filtration fraction) are lacking. Thus, generalization of these results should probably be tempered.

Finally, regarding the exclusion criteria, the use of intermittent hemodialysis may be the best way to ensure daily patient mobilization, at a much lower cost [3].

Authors' response

Yi Tian Wang, Nigel Fealy, Terry P Haines and Elizabeth H Skinner

We read the letter by Jacobs with interest. We agree that a combined dose of 35 ml/kg/hour (incorporating both convective and diffusive clearance) in CVVHDF mode would reduce filtration fraction compared with a pure convective mode such as CVVHF. However, there is no conclusive evidence that filter life is related to filtration fraction, while there is some evidence to the contrary [4]. Our original manuscript agreed that the generalizability of the results should be tempered and stated that we felt large multi-center studies were warranted to confirm the findings [1]. We agree that blood flow rates in the circuit should be collected in such studies, as this may be an independent confounding factor for circuit life and filtration fraction. However, we conducted an additional *post hoc* sensitivity analysis adjusting for blood flow and the effect of the MOVE (movement on vascular catheter evaluation) intervention on filter life was still significant in our cohort (regression co-efficient (robust 95% CI), P value = 14.3 hours (5.3, 23.3), $P = 0.003$).

Moreover, mobilization restrictions placed on patients undergoing CVVHDF via femoral vascath frequently preclude the delivery of evidence-based practice [5, 6], where early mobilization reduces ventilation duration and ICU and hospital length of stay [7]. Whilst intermittent hemodialysis is an alternative method of CRRT delivery, CVVHDF is the therapy of choice in over 50% of Australian ICUs (unpublished data). The aim of our study was to test whether patients subjected to continuous therapies via femoral access could be safely mobilized. We reiterate our conclusions, which were that mobilization of patients undergoing CRRT via femoral vascular access was safe and feasible [1].

Abbreviations
CRRT: Continuous renal replacement therapy; CVHDF: Continuous venovenous haemodiafiltration; CVHF: Continuous venovenous haemofiltration.

Competing interests
The author declares that he has no competing interests.

Correspondence: frederic.jacobs@abc.aphp.fr
Service de Réanimation Polyvalente, Hopital Antoine Béclère AP-HP, 157 rue de la Porte de Trivaux, Clamart 92140, France

Published online: 28 April 2015

References

1. Wang YT, Haines TP, Ritchie P, Walcker C, Ansell TA, Ryan DT, et al. Early mobilization on continuous renal replacement therapy is safe and may improve filter life. Crit Care. 2014;18:R161.
2. Legrand M, Darmon M, Joannidis M, Payen D. Management of renal replacement therapy in ICU patients: an international survey. Intensive Care Med. 2013;39:101–8.
3. Klarenbach S, Manns B, Pannu N, Clement FM, Wiebe N, Tonelli M, et al. Economic evaluation of continuous renal replacement therapy in acute renal failure. Int J Technol Assess Health Care. 2009;25:331–8.
4. Brophy PD, Somers MJ, Baum MA, Symons JM, McAfee N, Fortenberry JD, et al. Multi-centre evaluation of anticoagulation in patients receiving continuous renal replacement therapy (CRRT). Nephrol Dial Transplant. 2005;20:1416–21.
5. Leditschke IA, Green M, Irvine J, Bissett B, Mitchell IA. What are the barriers to mobilizing intensive care patients? Cardiopulm Phys Ther J. 2012;23:26–9.
6. Hodgson CL, Stiller K, Needham DM, Tipping CJ, Harrold M, Baldwin CE, et al. Expert consensus and recommendations on safety criteria for active mobilization of mechanically ventilated critically ill adults. Crit Care. 2014;18:658.
7. Kayambu G, Boots R, Paratz J. Physical therapy for the critically ill in the ICU: a systematic review and meta-analysis. Crit Care Med. 2013;41:1543–54.

Appendix 4.2 Data Collection Form Intervention Day

Data Collection Form Intervention Day

Date: **Time:** **Nursing Shift:**

Date of Vascath insertion: **Vascath type:**

Vascath number (for patient):

Site of vascath insertion: **Vascath sutured?** Yes No

Vascath site: NAD haematoma bruising Oozing Bleeding

Any ordered ultrasound for haematoma: Yes No **Vascath dressed?** Yes No

Catheter dislodgement since insertion: Yes No

Documented day and time of catheter dislodgement: _____

Documented reason for dislodgement: _____

Catheter dislodgement observations documented by (e.g. nursing/medical)_____

Vascular observations distal to Vascath: NAD Abnormal Not done N/A

Suspected presence of thrombosis in upper or lower limb with vascath Yes No

(Circle) Nursing opinion Medical opinion Allied Health opinion

Confirmed presence of thrombosis in upper/lower limb with vascath (Medical) Yes No

Any medical investigations/therapy for thrombosis: Yes No

Any documentation in medical notes of complications with CVVHDF: Yes No

Does the nursing staff think their filter is imminently going to crash? Yes No

How concerned is the nursing staff that the line is going to stop working within the next hour

Extremely Very Moderately Mildly Not at all

How concerned is the nursing staff that the line is going to stop working within the next hour if the patient were to be moved within the descriptions of the study

Extremely Very Moderately Mildly Not at all

Filter Modality: **Filter type:**

Is the filter planned for disconnection today? Yes No

What is the current filter life (in hours)?

Additional notes/comments:

_____

_____

_____

What have been the previous filter lives for this patient (whole admission):

Filter Number	Filter starting time and date	Life (hours)	Electively off? (Y/N)	Reason for filter replacement[a]
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				

[a]Elective (1); Clotted filter circuit (2); Clotted vascath requiring replacement (3); Mechanical filter failure (4); Medical procedure (5); Unknown (6); Other (7) – specify.

Anticoagulation: Type_____ Dose_____

(Heparin, Citrate, Saline flushes, regional heparinization)

Transfusions in last 24 hrs: Hb _____ Platelets_____

Pathology (during continuous renal replacement therapy**)**

Date/Time									
Hb									
Platelets									
Haemocrit									
INR									
APTT									

RASS score:

-5 Unarousable *No response to voice or physical stimulation*
-4 Deep sedation *No response to voice but any movement to physical stimulation*
-3 Moderate sedation *Any movement (but no eye contact) to voice*
-2 Light sedation *Briefly (< 10 seconds) awakens with eye contact, to voice*
-1 Drowsy *Not fully alert, sustained > 10 seconds awakening (with eye contact to voice)*
0 Alert and calm
+1 Restless *Anxious or apprehensive but movements not aggressive or vicious*
+2 Agitated *Frequent non-purposeful movement or ventilator-patient dyssynchrony*
+3 Very agitated *Pulls on or removes tubes, catheter(s) or has aggressive behaviour towards staff*
+4 Combative *Overly combative or violent; immediate danger to staff*

1. Observe patient, are they alert and calm? Does patient behave consistently with +1 to +4?
2. If the patient is not alert, loudly state the patient's name and direct them to open eyes and look at you. Repeat once if necessary. Can prompt to continue looking at speaker.
3. If no response to voice, physically stimulate the patient by shaking their shoulder and then rubbing sternum if no response.

CAM-ICU (assess if RASS score between -3 to +4 inclusive)

Feature 1: Acute Onset or Fluctuating Course	**Score**	**Check here if present**
Is the patient different than his/her baseline mental status? or Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale, GCS, or previous delirium assessment?	**Either question Yes →**	☐
Feature 2: Inattention		
Letter attention test (see training manual for alternate **pictures**) Directions: Say to the patient, *"I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand."* Letters from the following letter list in a normal tone 3 seconds apart **S A V E A H A A R T** Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."	**Number of errors > 2 →**	☐
Feature 3: Altered Level of Consciousness		
Positive if the actual RASS score is anything other than zero.	**RASS anything other than zero →**	☐
Feature 4: Disorganized Thinking		
Yes/No Questions (see training manual for alternate set of questions) 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? **Errors are counted when patient incorrectly answers the question.** **Command** Say to the patient, *"Hold up this many fingers"* (examiner holds two fingers in front of patient) *"Now do the same thing with the other hand"* (not repeating the number of fingers). *If patient is unable to move both arms, for the second part of the command as the patient to *"Add one more finger."* **An error is counted if patient is unable to complete the entire command.**	**Combined number of errors > 1 →**	☐

Overall CAM-ICU **Features 1 plus 2 and either 3 or 4 present = CAM-ICU positive**	**Criteria met→**	☐ CAM-ICU Positive (Delirium Present)
	Criteria not met→	☐ CAM-ICU Negative (No Delirium)

Positional changes in last 24 hours

Supine (hours)	L)sly (hours)	R)sly (hours)	SUIB (hours)	SOOB (hours)	Other (hours)	Total changes of position

Pre Intervention:

Does nursing staff have concerns about the patient moving within the description of the intervention groups? If so, what are their concerns?

_____

_____

_____

_____

Mobilization Data Collection (4 mins in each position – total 20minutes)

Group 1_Non-responsive participants (e.g. not able to participate) – 4 mins each position

	Blood flow (mL/min)	Access pressures	Return pressures	TMP	Alarmed? Number of times	Adverse events	Notes
Supine							
Hip flexion 45°, sustained							
Supine							
Hip flexion 45°, repeated							
Supine							

Group 2_Low Level participants (e.g. unable to stand) – 4 mins each position

	Blood flow (mL/min)	Access pressures	Return pressures	TMP	Alarmed? Number of times	Adverse events	Notes
Supine							
Hip flexion 45°, sustained							
Supine							
SOEOB							
Supine							

Group 3_High Level participants (e.g. able to stand), 4 mins each position

	Blood flow (mL/min)	Access pressures	Return pressures	TMP	Alarmed? Number of times	Adverse events	Notes
Supine							
Standing							
MOS							
SOEOB							
Supine							

Post intervention, how do the nurses feel about how the session went?

_____
_____
_____
_____

Post intervention, does nursing staff have concerns about future, similar patients moving within the description of the intervention groups? If so, what are their concerns?

_____
_____
_____
_____

Post intervention Vascath site:

NAD haematoma Bruising Oozing Bleeding

If adverse event(s) occurred, please record in detail:

_____
_____
_____
_____
_____
_____
_____
_____

Did the filter clot and require removal during the intervention or as a direct result of the intervention?

YES NO

Appendix 5.1 Assessment by an independent statistician

Perelman School of Medicine
University of Pennsylvania

Michael O. Harhay, PhD
Assistant Professor of Epidemiology and Medicine
Director, Palliative and Advanced Illness Research (PAIR)
Center Clinical Trials Methods and Outcomes Lab

April 24, 2021

Dear Critical Care Medicine Editors:

I have been asked to review the paper titled "Physical rehabilitation in the intensive care unit, a systematic review and meta-analysis," currently being considered for publication at CCM.

I wish to declare that I have a prior relationship with the authors. However, I also serve as the Statistical Editor for the *Annals of the American Thoracic Society* and I am confident that I can provide an unbiased assessment on behalf of the authors and the CCM Editors.

I have assessed the study design and statistical analysis as presented. I did not review the code or the source data, as that is atypical in my role as a statistical editor.

My assessment is that the authors have conducted their systematic review and meta-analysis in adherence to the PRISMA document, with clear and concise reporting, and have followed the correct risk of bias and random-effects meta-analysis methodology.

As a result, I believe the inferences from their analysis are appropriate.

I apologize for any missing elements requested by the editors. If necessary, I am available by cell: 609-457-7391, or email: mharhay@pennmedicine.upenn.edu

Sincerely,

Michael

(609) 457-7391
mharhay@pennmedicine.upenn.edu

Department of Biostatistics Epidemiology & Informatics | Perelman School of Medicine University of Pennsylvania

304 Blockley Hall, 423 Guardian Dr.
Philadelphia, PA 19104-6021