Fit for surgery? The impact of muscular and cardiopulmonary function on surgical outcomes after major abdominal surgery

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Fit for surgery? The impact of muscular and cardiopulmonary function on surgical outcomes after major abdominal surgery

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> *"Lo peor no es cometer un error, sino tratar de justificarlo, en vez de aprovecharlo como aviso providencial de nuestra ligereza o ignorancia"*
>
> Santiago Ramon y Cajal. Nobel prize of physiology or medicine in 1895.

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ABSTRACT

Background: Poor physical function predicts outcomes after major abdominal surgery. The aim of this thesis is to assess the ability of perioperative patients' function to prognose adverse surgical outcome and the efficacy of supervised pre-operative exercise programs to reduce adverse surgical outcomes.

Methods: Reliability of ultrasound to measure Vastus Lateralis (VL) size, architecture and quality was assessed. Differences in VL size and quality between hepatobiliary surgery patients, old healthy adults and master athletes (MAs) were assessed. Ability of preoperative cardiopulmonary exercise testing, VL size, architecture and quality assessment, body composition using abdominal computed tomography scans, maximum isometric knee extension, rate of force development during maximum voluntary contraction (MVC) and changes in VL size and architecture during in-hospital recovery to prognose surgical outcome were assessed. Effectiveness of supervised pre-operative exercise programs to improve patient fitness and surgical outcome was assessed with a systematic review and meta-analysis.

Results: Ultrasound images showed varying degrees of intra-rater (Intraclass correlation coefficient [ICC]≥0.824), inter-rater (ICC≥0.520) and inter machine (against magnetic resonance imaging) (ICC≥0.892) reliability. Pre-operative VL quality was lower in hepatobiliary surgery patients compared to healthy older adults and MAs (18.9±6.0, 26.7±4.9 and 28.3±7.0, respectively, $p<0.001$). Pre-operative low Psoas muscle index and high equivalents of carbon dioxide increased the risk of 3-years mortality (Hazard ratio [95% confidence interval]: 2.372 [1.246-4.515], $p=0.009$). Patients who performed two supervised exercise sessions per week before surgery showed higher six-minute walk distance (mean difference between groups [95%CI]: +47 [20-75] m., $p<0.001$) and lower relative risk (RR) of post-operative complications (RR [95%CI]: 0.59 [0.46-0.75], $p<0.001$) compared to patients following usual care (UC). Patients undergoing abdominal aortic aneurysms repair that performed a prehabilitation program showed similar peak oxygen uptake compared to UC group (mean difference between groups [95%CI]: 1.42 [0.51-2.34] $ml\cdot kg^{-1}\cdot min^{-1}$, $p<0.001$).

Conclusion: Cardiopulmonary fitness and psoas muscle mass can predict long-term mortality. Two or more weekly supervised sessions are needed to improve fitness and surgical outcome.

CONTENTS

CHAPTER ONE: INTRODUCTION, AIM AND OBJECTIVES..16

1.1 INTRODUCTION 17

1.2. AIM, OBJECTIVES AND OUTCOMES...22

CHAPTER TWO: LITERATURE REVIEW 25

2.1. INTRODUCTION 26

2.2. MUSCLE AND CARDIOPULMONARY CHARACTERISTICS OF PATIENTS SCHEDULED FOR MAJOR ABDOMINAL SURGERY AND THE RISK OF ADVERSE SURGICAL OUTCOME ASSOCIATED WITH PATIENTS' PHYSICAL FUNCTION 27

2.3. EXERCISE TRAINING DURING AGEING AND AS PRE-OPERATIVE CARE 42

CHAPTER THREE: RELIABILITY AND VALIDITY OF ULTRASOUND-DERIVED VASTUS LATERALIS SIZE, QUALITY AND MUSCLE ARCHITECTURE MEASURES 49

3.1. INTRODUCTION 50

3.2. METHODS..52

3.3. RESULTS..58

3.4. DISCUSSION 61

CHAPTER FOUR: LOWER MUSCLE QUALITY IN PATIENTS PREPARING FOR HEPATOBILIARY SURGERY COMPARED TO AGE-MATCHED MASTER ATHLETES AND HEALTHY NON-ATHLETES 68

4.1. INTRODUCTION 69

4.2. METHODS..70

4.3. RESULTS..72

4.4. DISCUSSION 73

CHAPTER FIVE: VENTILATORY INEFFICIENCY TOGETHER WITH LOW PSOAS MUSCLE MASS INDEX CAN PREDICT PREMATURE MORTALITY AFTER LIVER RESECTION AND PANCREATICODUODENECTOMY 77

5.1. INTRODUCTION 78

5.2. METHODS 79

5.3. RESULTS 83

5.4. DISCUSSION 88

CHAPTER SIX: CHANGES IN VASTUS LATERALIS SIZE AND ARCHITECTURE AFTER IN-HOSPITAL RECOVERY FROM HEPATOBILIARY SURGERY CANNOT PREDICT SHORT-TERM SURGICAL OUTCOMES AND 6-MONTHS MORTALITY 93

6.1. INTRODUCTION 94

6.2. METHODS 96

6.3. RESULTS 100

6.4. DISCUSSION 103

CHAPTER SEVEN: EFFICACY OF SUPERVISED EXERCISE PREHABILITATION PROGRAMS TO IMPROVE MAJOR ABDOMINAL SURGERY OUTCOMES: A SYSTEMATIC REVIEW AND META-ANALYSIS 109

7.1. INTRODUCTION 110

7.2. METHODS 111

7.3. RESULTS 115

7.4. DISCUSSION 138

CHAPTER EIGHT: GENERAL DISCUSSION 145

8.1. MAIN FINDINGS AND IMPLICATIONS 146

8.2. PRE-OPERATIVE RISK ASSESSMENT BASED ON MUSCLE CHARACTERISTICS AND CARDIOPULMONARY FITNESS 148

8.3. PREHABILITATION PROGRAMS TO ENHANCE MAJOR ABDOMINAL SURGICAL OUTCOMES 150

8.4. GENERAL LIMITATIONS 152

8.5. GENERAL CONCLUSION 154

Appendices 156

Appendix 1. Supplementary data (Tables) 156

Appendix 2. Supplementary data (Figures) 157

Appendix 3. Chapter 7 search strategy 160

Appendix 4. Risk of bias assessment of chapter 7 168

Appendix 5. First round of answers to reviewers’ comments **Error! Bookmark not defined.**

REFERENCES 186

LIST OF FIGURES

Figure 1. *Coefficient of variation in frailty index against age (years) from Rockwood et al. (2004). Triangles represent men and circles represent women.* 28

Figure 2. Alignment of muscle fibres with the tendon are mechanically advantageous over pennate muscle fibres. Extracted from Degens et al. (2009). 32

Figure 3. L3-L4 Computed Tomography scan. 35

Figure 4. VO_2 and VCO_2 mechanics during a cardiopulmonary exercise testing before major abdominal surgery. 38

Figure 5. A: Age-related muscle power decline in Master weightlifters (black dots) and old healthy population (white dots). Extracted from Pearson et al. (2022). 43

Figure 6. Forest plot representing differences in VO_2 peak between old healthy adults and master endurance athletes. 44

Figure 7. Theoretical physical function changes over the major abdominal surgery pathway depending on the implementation of a patient prehabilitation exercise program or following the usual care treatment. 47

Figure 8. Ultrasound (A.1, A.2, B.1) and magnetic resonance (B.2) Images of Vastus Lateralis, Vastus Intermedius and Rectus Femoris. 55

Figure 9. Correlations between ultrasound derived measures of single quadriceps muscles (VL, RF and VI) size and quality with magnetic resonance imaging derived quadriceps size and quality measures. 61

Figure 10. Vastus Lateralis muscle thickness and knee extension force in master athletes, old healthy adults and hepatobiliary patients. 72

Figure 11. Flow chart of the patient's selection process. 80

Figure 12. Skeletal muscle segmentation from computed tomography scan. 81

Figure 13. 3-year Survival plot. 88

Figure 14. Differences in Vastus lateralis architecture and cross-sectional area index between baseline and after in-hospital recovery (follow-up) (N=29). 102

Figure 15. Significant correlation between Length of stay in critical care and anaerobic threshold (N=13). 103

Figure 16. Data Extraction Timepoints. 113

Figure 17. PRISMA 2020 flow diagram. 116

Figure 18. 6 minutes walk distance forest plots. 129

Figure 19: Line graph of the mean differences in changes in 6MWD between prehabilitation group and usual care group through the surgery journey. 130

Figure 20. Timed up and go and five times sit to stand forest plots. 131

Figure 21. Forest plot of mean differences of handgrip strength changes (Baseline-Pre-surgery) between prehabilitation and usual care group. 132

Figure 22. Cardiorespiratory capacity forest plots. 133

Figure 23. Forest plot of mean differences of VO_2 peak changes (Baseline-Pre-surgery) between prehabilitation group and usual care group without Blackwell et al. (2020)......... 134

Figure 24. Surgical outcomes forest plots. 136

Figure 25. Forest plot of the risk of severe post-operative complications between prehabilitation group and usual care group. 137

Figure 26. Forest plot comparing the length of stay in hospital between prehabilitation group and usual care group. 138

Figure 27. Diagram of the main findings of the thesis. 148

Figure 28. Intra-rater reliability Bland and Altman plots of ultrasound Vastus Lateralis, Vastus Intermedius and Rectus Femoris size measurements and Vastus Lateralis architecture. 157

Figure 29. Inter-rater reliability Bland and Altman plots of ultrasound Vastus Lateralis, Vastus Intermedius and Rectus Femoris size measurements and Vastus Lateralis architecture. 158

Figure 30. Inter-machine reliability (Ultrasound vs Magnetic resonance imaging) of Vastus Lateralis and Rectus Femoris cross-sectional area measurements and inter-method reliability (Extended field of view ultrasound imaging vs intercept) of Vastus Lateralis architecture, fascicle length and pennation angle Bland and Altman plots. 159

LIST OF TABLES

Table 1. Participant’s characteristics 58

Table 2. Intra-rater and inter-rater reliability assessment 59

Table 3. Patient characteristics. 83

Table 4. Univariate regression model with cardiopulmonary fitness parameters as dependent variables and CT-derived parameters as independent variables. 85

Table 5. Multivariate linear regression analysis. 86

Table 6. Univariate and Multivariate Cox regression models. Cardiopulmonary fitness parameters and CT-derived parameters were used to predict 1-year and 3-year early mortality....................87

Table 7. Baseline patient characteristics 100

Table 8. Vastus Lateralis muscle architecture and cross-sectional area at baseline and at follow-up 102

Table 9. Characteristics of included studies 120

Table 10. Length of stay in hospital. 137

Table 11. Participant’s characteristics. 156

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACSA	Anatomical cross-sectional area
ASA score	American society of anaesthesiologists Physical Status Score
AT	Anaerobic threshold
BMI	Body mass index
CPET	Cardiopulmonary exercise testing
CSA	Cross-sectional area
CT	Computed tomography
CO_2	Carbon dioxide
EFOV	Extended field of view
EWGOSP	European Working Group on Sarcopenia in Older People
HIIT	High intensity interval training
HU	Hounsfield Units
ICC	Intraclass correlation coefficient
IQR	Interquartile range
IMAT	Intramuscular adipose tissue
L_f	Fascicle length
LOS	Length of stay in hospital
MAs	Master athletes
MCID	minimally clinical important difference
MFT	Manchester Royal Infirmary
MQ	Muscle quality
MQ_{ACSA}	Muscle quality using anatomical cross-sectional area
MQ_{MT}	Muscle quality using muscle thickness
MRI	Magnetic Resonance Imaging
MT	Muscle Thickness
MVC	Maximum voluntary contraction
O_2	Oxygen
PCSA	Physiological cross-sectional area
P-CSA	Psoas muscle cross-sectional area
P-index	Psoas muscle index
P-RA	Psoas muscle radio attenuation
POETTS	Perioperative Exercise Testing and Training Society
RA	Radio attenuation
RCT	Randomized controlled trial
RF	Rectus Femoris
RFD	Rate of force development
SAT	Subcutaneous adipose tissue
SM	Skeletal muscle
TUG	Timed up and go
UK	United Kingdom
VAT	Visceral adipose tissue
VE	Minute ventilation
VE/VCO_2 slope	Equivalents of volume of CO_2 expired
VI	Vastus Intermedius
VL	Vastus Lateralis
VO_2 peak	Peak volume of oxygen uptake

CHAPTER ONE: INTRODUCTION, AIM AND OBJECTIVES

1.1 INTRODUCTION

Surgeries performed in North America and Europe account for 59% of the total surgeries performed in the world, despite their relative lower share of the world population (Weiser et al., 2016). Post-operative mortality is lower in upper-middle income countries than in lower income countries (Knight et al., 2021). In 2012, the UK had the 7th highest number of surgeries per 100,000 citizens (Weiser et al., 2016). Moreover, between 2009 and 2014, the number of surgeries in the UK increased by 5.3% and surgery-related mortality was reduced by 0.6% in the 90 days after surgery (Abbott et al., 2017). These data suggest that in countries with a well-developed health system, like the UK, surgical interventions are an effective strategy to prolong and enhance life. Part of this success is due to improved perioperative care systems that prepare the patient prior to a major surgery with specialized care with the aim of reducing the possibilities of major complications that can end up in a fatal adverse event (Knight et al., 2021).

Major abdominal surgeries carry a higher risk of premature mortality when compared with other surgical procedures. While the average risk of premature mortality for surgery lies between 1.1% to 2.3%, depending on the time window accounted for analysis (30 to 90 days respectively) (Abbott et al., 2017), however, for major abdominal surgery the mortality rate is between 2% to 12.7% within the first 90 days after surgery (Krautz et al., 2020, Jakobson et al., 2014). It is important, therefore, for this type of surgery to secure an objective and informed preoperative risk assessment strategy. Not only would this provide fully informed consent to a patient and their families for the potential outcomes of a surgery, but would also provide a planned mobilisation of specialised equipment and professionals to support patient's care to reduce the risk of adverse events in the perioperative period (Kocher et al., 2005).

Healthcare practitioners are aware of the influence of physical functionality or fitness, and age acquired muscle weakness on major abdominal surgical outcomes. Patients with poor physical functionality or fitness tend to have poor surgical outcomes in terms of a longer intensive care stay; a longer length of stay (LOS) in hospital and a higher risk of pulmonary or cardiac complications (Wolters et al., 1996). The age of patients scheduled for major abdominal surgery is typically over 60 years (Jones et al., 2017, Myers et al., 2020), which is a time of life when physiological function has gone through and will continue to go through significant decline with advancing age (Ocana et al., 2021). The main reason for the age-related decline in physical function during life course is the increased time spent sedentary during adulthood (Leyk et al., 2010). However, even when physical activity time is maintained with advancing age, this reduction in physiological function remains (Ganse and Degens, 2021, Hoog Antink et al., 2021) despite the better physiological function in highly active adults (Pearson et al., 2002, Degens et al., 2013).

Muscular and respiratory function decline at a similar rate in master athletes (MAs) and healthy populations (Pearson et al., 2002, Michaelis et al., 2008, Degens et al., 2013) leading to a similar decline in physical function (Ocana et al., 2021) and aerobic and anaerobic power (Bagley et al., 2019). However, as mentioned above, muscular and respiratory function is higher in individuals with a highly active lifestyle (Degens et al., 2013, Pearson et al., 2002, Michaelis et al., 2008) which helps to maintain a good physiological function at later stages in life. Regardless of age and the presence of comorbidities, this research group has observed that volume of training is related with a better recovery of the blood pressure following ischaemic exercise (Zambolin et al., 2022). During ischaemic exercise, there is an occlusion of blood vessels that reduce blood supply to exercising muscles, depriving them of oxygen (O_2) supply and carbon dioxide (CO_2) elimination (Patterson et al., 2019). Similarly, during general anaesthesia, used during major abdominal surgery, there is a reduction in ventilatory response to CO_2 and partial pressure of CO_2, which impair CO_2 exhalation and blood oxygenation (Saraswat, 2015). Taken together, this evidence suggests that there is a capacity for physically active, older adults to better cope with physiologically stressing situations, such as major surgery. Therefore, even the known unstoppable decline of physical function during ageing, remaining physically active with age may maintain a high physiological function and may support in coping with the physiological stress that a major abdominal surgery induces. Hence, it is important to consider patients' pre-operative physical functionality prior to the operation to assess the risk of performing a major surgical procedure.

Patients preparing for major abdominal surgery may experience cachexia which may further exacerbate weight loss and muscle atrophy (Dolly et al., 2020, Fearon et al., 2011). Differences in muscle mass and function between patients schedule for major abdominal surgery and healthy adults with a highly active lifestyle have not yet been fully explored. This data would allow us to determine what disease-related impaired muscle attributes may have an adverse effect on major abdominal surgical outcomes and therefore intervene.

Clinical scientists and practitioners aim to develop physiological measures which are representative of the physical function and response to a physiological stress, to better predict the risk of undergoing major abdominal surgery. Thus, body composition assessment through Computed Tomography (CT) image and cardiopulmonary exercise testing (CPET) have become popular techniques to assess risk pre-operatively. Both techniques have been shown to be effective in peri-operative assessment of patients scheduled for major abdominal surgery. Research has shown that both techniques, body composition assessment through CT scans and CPET, are able to predict the risk of undergoing surgery in a large spectrum of abdominal surgeries, from those patients with vascular impairments (Drudi et al., 2016, Lindström et al., 2019, Perissiou et al., 2022, Rose et al., 2018) to those suffering cancer (Jones et al., 2017, Aleixo et al., 2020, Moran et al., 2016b).

Body composition analysis through CT images is focused on the assessment of quantity and density of abdominal muscle tissue (Jones et al., 2017, Aleixo et al., 2020). Thus, it has been found that low muscle quantity and strength, known as sarcopenia, and low muscle density, known as myosteatosis, are related to poor surgical outcomes after major abdominal surgery; namely, higher rates of premature mortality (Aro et al., 2020) increased post-operative complications (van Dijk et al., 2017) and longer LOS (DiMartini et al., 2013). Furthermore, it seems that when both conditions are found in the same patient, the surgical prognosis worsens (Kroenke et al., 2018, Zhuang et al., 2019). Using the CT scans used to diagnose patients' disease is a powerful strength of this method, as these images are taken routinely as part of the surgical planning and procedure, and therefore does not demand any extra time or activity from patients or practitioners. However, CT images do not take into account contractile properties of the muscle which may play an important role in predicting surgical outcomes, especially if they are assessed in locomotory muscles that are better related with the functional status of patients (Maeda et al., 2020, Christensen et al., 2021) and risk of frailty (Rostron et al., 2021), which is an age-related condition characterized by a decline of the body's physical and psychological reserves (Sternberg et al., 2011) (From this point forward in the thesis, frailty is used to express a state of age-related general muscle weakness product of an age-related decline on physical functionality).

Measures of locomotory muscles, such as Vastus lateralis (VL) have been used to successfully identify patients with muscle weakness preparing for abdominal surgery (Canales et al., 2022) which may increase the risk of adverse events (McIsaac et al., 2020). In addition, the time that patients spent in hospital, during in-hospital recovery, often leads to muscle atrophy (Turton et al., 2016), impairing patients' physical function (Boxer et al., 2010). It remains to be seen if this change in muscle size and architecture can also be used to predict adverse events after surgery. Due to the exposure to radiation during CT scans, tracking the extent of this muscle atrophy is not favourable or feasible to measure these outcomes continuously with CT. Ultrasound imaging is a feasible alternative to CT scans.

Ultrasound imaging can track locomotory muscle size and architecture changes without moving the patient from the bed and exposing them to ionising radiation doses. Recently, ultrasound devices incorporated a function called extended field of view (EFOV) that allows the ultrasound operator to image the whole length and cross-sectional area (CSA) of large muscles. However, to the best of our knowledge the validity of measures to capture VL-CSA has only been tested in one study with 6 participants (Reeves et al., 2004a) and intra-rater and inter-rater reliability to measure muscle CSA and architecture using EFOV ultrasound imaging has only been tested in the hamstrings muscles (Franchi et al., 2020a, Franchi et al., 2020b). Furthermore, VL-CSA is usually captured as a good estimation of quadriceps CSA, but the relationship between both measures has never been evaluated.

As described above, during general anaesthesia, there is a reduction in ventilatory response to CO_2 and partial pressure of CO_2, which impair CO_2 exhalation and blood oxygenation (Saraswat, 2015). Overall, CPET has been extensively used in the field of pre-operative risk assessment to establish the efficiency of the cardiorespiratory machinery to cope with the demands of surgery and recovery (Bigatello and Pesenti, 2019). Similar to those patients with sarcopenia and/or myosteatosis, those patients with low peak O_2 uptake (VO_2 peak) (West et al., 2016), low anaerobic threshold (AT) (Junejo et al., 2012) and high equivalents of volume of CO_2 expired (VE/VCO_2 slope) (Junejo et al., 2014) are at risk of adverse surgical outcomes. Little is known about the relationship between CT and CPET derived measures and the impact of their combined use on surgical outcomes. It has been found that skeletal muscle-RA (SM-RA) (a measure of muscle density) is related with AT and VO_2 peak in hepatopancreatobiliary surgery patients (West et al., 2019b) and only with low AT in colorectal surgery patients

(Berkel et al., 2022b). Furthermore, those hepatopancreatobiliary surgery patients with low VO_2 peak and myosteatosis had lower survival than those with only one of the conditions (West et al., 2019b). Therefore, with limited evidence so far in this field, further research is needed to better ascertain the relation between CT and CPET derived parameters and the power of the combination of these parameters to better prognose surgical outcomes.

All the evidence so far points to a better surgical prognosis in those patients with a higher cardiorespiratory and musculoskeletal fitness before surgery. Therefore, it is reasonable to suggest that exercise programs before surgery may positively impact on surgical outcomes if they are able to promote muscular and cardiopulmonary adaptations in the short amount of time available from surgery notification to surgery performance. Some meta-analyses already show that exercise prehabilitation programs can reduce the rate of post-operative complications (Heger et al., 2020, Hughes et al., 2019, Moran et al., 2016a, Lambert et al., 2021) and LOS (Heger et al., 2020, Hughes et al., 2019, Moran et al., 2016a). However, the assessment of the efficacy of these programs to improve fitness and functionality on patients has not yet been explored extensively, with some meta-analysis reporting an improvement on physical function (Waterland et al., 2020) and others not (Hughes et al., 2019, Lambert et al., 2021). It remains to be evaluated if exercise prehabilitation programs can promote improvements on muscle size, function and cardiorespiratory capacity. There is also a high heterogeneity between studies exploring the effects of prehabilitation programs depending on the supervision of exercises. Different studies have reported a greater efficiency of supervised exercise compared to unsupervised exercise to promote physiological adaptations that enhance physical function (LaCroix et al., 2017b, Bäck et al., 2015). Thus, the effect of supervised or unsupervised exercise before surgery should be evaluated to ascertain the optimal type and dose of exercise to positively influence surgical outcomes.

Due to the difficulty to standardize for type and intensity of exercise between studies when pooling the data to meta-analyse, an evaluation of the effect of frequency of supervised training sessions per week is needed to start modelling the ideal training stimulus. This is important to understand, due to the length of time between surgery notification and surgery performance being 4-6 weeks (Fulop et al., 2021, Bousquet-Dion et al., 2018, Barberan-Garcia et al., 2017), a tight schedule to promote physiological adaptations on patients (Hickson et al., 1977, Hughes et al., 2018).

1.2. AIM, OBJECTIVES AND OUTCOMES

The aim of this study is to assess the ability of existing and novel perioperative patients' fitness evaluation in prognosis of adverse outcome following hepatobiliary surgery and the efficacy of pre-operative supervised exercise programs to enhance patients' fitness and to improve adverse major abdominal surgical outcomes. This will be achieved by addressing four main objectives, each with distinct outcomes.

Objective 1. To assess the validity and intra-rater and inter-rater reliability of ultrasound imaging and EFOV ultrasound imaging to assess muscle size and muscle architecture. It is hypothesized that VL size and quality will be representative of the whole quadriceps size and quality and ultrasound imaging will show a good inter-machine (ultrasound imaging vs magnetic resonance imaging [MRI]), intra-rater and inter-rater reliability. This objective is addressed in the findings presented in chapter 3.

Primary outcomes

I. Validity of the use of VL, Rectus Femoris (RF) and VL+RF-CSA and VL, Vastus intermedius (VI) and VL+VI muscle thickness (MT) to estimate the whole quadriceps CSA. Validity of the use of VL, VI, RF, VL+RF or VL+VI muscle quality (MQ) to estimate whole quadriceps quality.
II. Inter-machine reliability of measures of CSA of individual muscles of the quadriceps (VL and RF) (EFOV ultrasound imaging *vs* MRI).

Secondary outcomes

I. Intra-rater and inter-rater reliability of VL, VI and RF size measured with ultrasound and EFOV ultrasound imaging and VL architecture parameters (MT, fascicle length [L_f] and pennation angle).

Objective 2. To compare VL-MT and knee extension force between patients waiting for hepatobiliary surgery of ≥60 years with age-matched healthy adults and age-matched highly active adults MAs. It is hypothesized that VL size and knee extension force will be reduced in patients waiting for hepatobiliary surgery compared to healthy adults and MAs This objective is addressed in the findings presented in chapter 4.

Primary outcomes

I. Differences in VL-MT and knee extension force between the three groups mentioned in this objective.

Objective 3. To analyse muscle size, muscle function and cardiorespiratory fitness of patients waiting for hepatobiliary surgery and assess the relationship between muscle size, muscle function and cardiorespiratory fitness with surgical outcomes. It is hypothesized that measures of muscle size and muscle function will be related with hepatobiliary surgery outcomes with an additive effect and muscle size and function measures will be related with cardiopulmonary fitness. This objective is addressed in the findings presented in chapter 5 and 6.

Primary outcomes

I. Retrospective preoperative assessment of body composition through CT images and cardiopulmonary fitness during a cycle-ergometer CPET of patients waiting for hepatobiliary surgery and its relationship with surgical outcomes (30-day, 90-day, 1-year and 3-year survival, post-operative complications, LOS).

II. Preoperative assessment of VL-MT, VL-MQ, VL architecture, maximum voluntary isometric contraction (MVC) during a knee extension, rate of force development (RFD) during a knee extension MVC, body composition through CT images and cardiopulmonary fitness during a cycle-ergometer CPET of hepatobiliary surgery patients to predict surgical outcomes (30-day, 90-day, 6-months survival, post-operative complications, LOS).

III. Changes in VL-MT and architecture mentioned in the II bullet point between pre-operative Anaesthetic Clinic (baseline) and at hospital discharge (follow-up data collection timepoint) in hepatobiliary surgery patients and its relationship with surgical outcomes (30-day, 90-day, 6-months survival, post-operative complications, LOS).

Secondary outcomes

I. Relation of muscle size, body composition by CT imaging with cardiopulmonary fitness.

Objective 4. To meta-analyse published evidence about the efficiency of supervised exercise prehabilitation programs and its potential positive impact on surgical outcomes (30-day, 90-

day survival, post-operative complications, LOS). It is hypothesized that supervised prehabilitation programs will enhance cardiopulmonary fitness, muscle size, muscle function and physical function and will positively influence surgical outcomes and accelerate the recovery of physical function after surgery. Additionally, frequency of supervised training sessions will be a training variable that influences the promotion of adaptations to training before surgery. This objective will be addressed in chapter 7.

Primary outcomes

I. Differences in changes of cardiorespiratory fitness, muscle function, muscle size and physical function between patients performing a supervised prehabilitation program and those following the usual care pathway at the end of the prehabilitation program (first follow-up time point, usually the week of the surgery), 4 weeks after surgery (second follow-up time point) and 8 weeks after surgery (third follow-up time point).

II. Differences in surgical outcomes between supervised prehabilitation program patients and usual care patients.

Secondary outcomes

I. Influence of the frequency of supervised training sessions per week to promote cardiorespiratory fitness, muscle function, muscle size and physical function improvements during the prehabilitation available time.

CHAPTER TWO: LITERATURE REVIEW

2.1. INTRODUCTION

It is generally accepted that physical activity aids to live longer, healthier and with better quality of life (Blair et al., 1989). We know that even though physical activity cannot stop the age-related decline of physiological systems, a well-trained adult shows a more efficient muscular (Pearson et al., 2002) and cardiopulmonary system (Rogers et al., 1990) than a sedentary adult. Sedentary older adults are at higher risk of frailty (Kehler and Theou, 2019), diminishing their ability to cope with physiological stressing situations like an abdominal surgery.

The major surgery journey starts with the pre-operative anaesthetic clinic. The aim of this clinic is to assess the suitability of patients to undergo major surgery. Chronological age is an easy factor to identify, however, its use as a risk factor for post-operative complications is limited (Wolters et al., 1996). The identification of other comorbidities such as renal insufficiency, anaemia, bronchopulmonary diseases or the class of operation show a higher risk ratio (RR) for post-operative complications than age (Wolters et al., 1996). In addition, poor physical function shows an RR of 1.6 to 4.2 for the rate of post-operative complications based on the *'American society of anaesthesiologists Physical Status Score'* (ASA score). Thus, objective physical function assessment has been incorporated as a form of surgery risk assessment to preoperative clinics. It has also been observed that low muscle mass and poor cardiopulmonary fitness are related to poor surgical outcomes (Moran et al., 2016b, Jones et al., 2017).

During major abdominal surgery while patients are sedated with the use of drugs in general anaesthesia, mechanical ventilation is often used (Ruszkai and Szabó, 2020). Mechanical ventilation allows the anaesthetist to control the concentration of CO_2 in blood through the manipulation of patients' breathing mechanics. The control of CO_2 concentration while under general anaesthesia is important because a high acidosis will increase the risk of longer hospital LOS (Lawton et al., 2019b). CO_2 blood concentration can be reduced by increasing a patient's tidal volume or respiratory rate, what facilitates gas exchange at the lung (Mora Carpio and Mora, 2022). However, this technique increases the risk of pulmonary post-operative complications, a common occurrence in major abdominal surgeries (Miskovic and Lumb, 2017). Post-surgery, when mechanical ventilation is removed, patient's respiratory system is again required to effectively extract and exhale CO_2 to maintain pH balance. This becomes complicated if the preoperative cardiopulmonary fitness of patients is poor, due to potential difficulties in effectively extracting and exhaling CO_2 spontaneously. The odds of experiencing post-operative pulmonary complications are higher in patients with poor cardiopulmonary fitness (Steffens et al., 2021a). Moreover, those patients with higher metabolic acidosis during the intensive care stay had an increased risk of premature mortality (Samanta et al., 2018). During the in-hospital recovery patients drastically reduce physical activity, which can result in a decline of muscle mass and impair muscle function (Di Girolamo et al., 2021), further increasing the age-related muscle weakness(Jolley et al., 2016) that may be accentuated if preoperative physical function was already poor (Kehler and Theou, 2019).

Thus, in view of these findings, researchers and clinicians are beginning to explore the capacity of exercise before surgery to promote physiological adaptations, which may improve surgical prognosis (Hughes et al., 2019, Heger et al., 2020). This literature review examines the potential physiological explanations to the following questions: why poor physical function may negatively impact surgical outcomes; what are the most common measures used to ascertain the physical function of a patient; and finally, what strategies do clinicians have available to enhance patients' fitness before surgery.

2.2. MUSCLE AND CARDIOPULMONARY CHARACTERISTICS OF PATIENTS SCHEDULED FOR MAJOR ABDOMINAL SURGERY AND THE RISK OF ADVERSE SURGICAL OUTCOME ASSOCIATED WITH PATIENTS' PHYSICAL FUNCTION

Low physical function can increase the odds of adverse outcome after major surgery by up to four times compared to age (Wolters et al., 1996). This is somehow surprising as the age-related decline of physiological systems is widely demonstrated (Loe et al., 2013, Delmonico et al., 2009). With age, there is a reduction in the variability of the frailty index within individuals (Rockwood et al., 2004) which shows an increasing likelihood of acquired muscle weakness with advancing age (Figure 1). In other words, in an older population, the chances of finding a person with low muscle function are higher than within the middle-age population. This variability in the frail index through the lifespan suggests that aging does not follow the same pattern in every individual. Hence, chronological age is a limited parameter to represent physiological ageing. However, age is a stochastic process that damages physiological structures and functions systematically during the lifespan, which increases, as mentioned, the risk of acquired muscle weakness with advancing age (Rockwood et al., 2004, Romero-Ortuno and Kenny, 2012). Therefore, as the majority of patients scheduled for major abdominal surgery are over the age of 60 years (Jones et al., 2017, Johnson et al., 2021, Nally et al., 2019, Knight et al., 2021, Krautz et al., 2020), it is important to study ageing in human physiological systems to understand the underpinning processes that increases the risk of acquired muscle weakness with age. This will aid healthcare professionals in creating effective preoperative risk assessment strategies (Wynter-Blyth and Moorthy, 2017) based on the physical functionality of patients (Jones et al., 2017, Moran et al., 2016b).

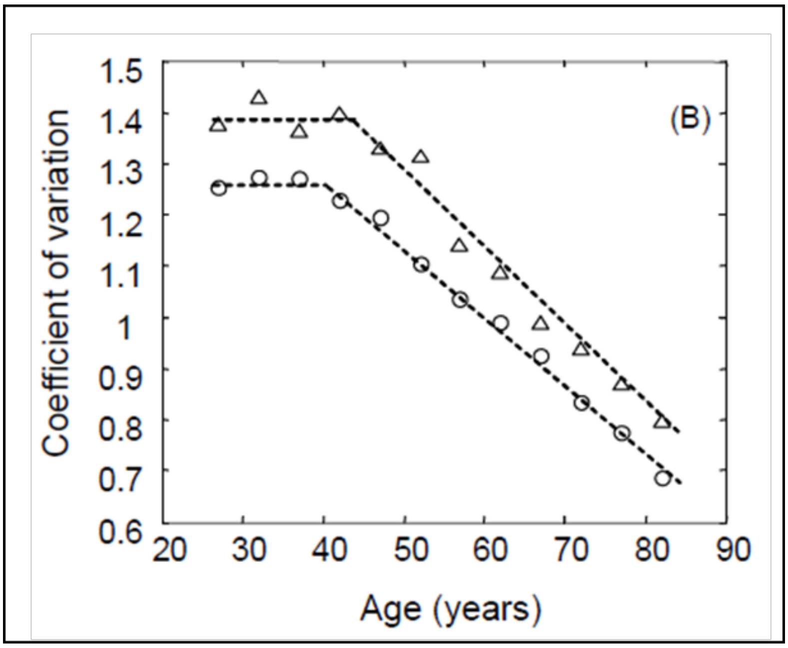


Figure 1. *Coefficient of variation in frailty index against age (years) from Rockwood et al. (2004). Triangles represent men and circles represent women.*

2.2.1. Age-related skeletal muscle conditions associated with patients waiting for major abdominal surgery.

2.2.1.1. Sarcopenia and age-related muscle changes

Weak individuals are characterised by a cumulative decline in many physiological systems that leads to a reduced physiological function and muscle weakness (Clegg et al., 2013). On occasions, researchers and healthcare professionals have linked frailty and sarcopenia (Cesari et al., 2014), defining the latter as the biological substrate of frailty (Landi et al., 2015). During years sarcopenia has been defined as the age-related loss of muscle mass (Rosenberg, 1997).

However, it is suggested that age-related muscle weakness is multifactorial (Zoladz, 2019), and the definition of sarcopenia has a more holistic meaning nowadays. The European Working Group on Sarcopenia in Older People (EWGSOP) defines Sarcopenia as a condition characterised by low muscle strength and low muscle mass or quality (Cruz-Jentoft et al., 2019). Indeed, the working group go on to suggest the evaluation of handgrip strength as the first assessment to diagnose sarcopenia, followed by an assessment of muscle mass to confirm the presence of sarcopenia. Sarcopenia, as a measure of low muscle index or psoas muscle index (P-index), is found in more than 50% of patients scheduled for a major abdominal surgery and increases the risk of adverse outcome event (Jones et al., 2017, Kim et al., 2017) and premature mortality (Beaudart et al., 2017) after surgery. Therefore, understanding the underpinning mechanisms of sarcopenia is important for healthcare professionals involved in the perioperative care of patients preparing for major abdominal surgery.

With age, there is a loss of muscle mass (Wilkinson et al., 2018) that reduces the overall strength of an individual (Zoladz, 2019). While in young adults the relationship between muscle CSA and force generating capacity of muscle seems to be directly related (Bamman et al., 2000), it is not clear in older adults (Sallinen et al., 2008). Therefore, if the relationship between force generating capacity and muscle CSA is not linear, some physiological changes that impair the contractile capacity of the remaining muscle occurs and should be evaluated to understand the mechanisms that lead to the general muscle weakness associated with age. A longitudinal study with 3,075 healthy older adults (aged 70-79 years), found that strength generating capacity of knee extensor muscles declined 2-5 times faster than CSA of thigh muscles (Delmonico et al., 2009) over 5-years. Delmonico et al. (2009) attributed, in part, this decline in force generating capacity to a higher intra- and inter-muscular adipose tissue accumulation that impairs muscle contractility, in line with previous studies (Goodpaster et al., 2001, Goodpaster et al., 2000, Visser et al., 2005). Thus, they described a reduction in MQ, the ratio between maximum voluntary force generation capacity and CSA of muscle, as the determinant of age-related muscle weakness. A more recent 5-year longitudinal study (McPhee et al., 2018) that included 40 sarcopenic older adults (mean age 71 years, appendicular lean mass <7.26 kg·m^{-2} for men and <5.50 kg·m^{-2} for women as criterion for sarcopenia) found that, in contrast to Delmonico et al. (2009), the associated muscle weakness with old age in sarcopenia was due to a loss in muscle mass and not to a reduction in MQ. McPhee et al. (2018) calculated the CSA of the thigh muscles only quantifying CSA of knee extensor muscles, providing a more accurate MQ quantification than Delmonico et al. (2009) that used the CSA of the whole thigh. In addition, Mcphee et al. (2018) used the physiological CSA (PCSA) which takes into account the architecture of the muscle that is altered with age and reduces muscle functionality (Narici et al., 2003). Apart from the methodological differences, the difference in results might be due to the different populations recruited in each study. While Delmonico et al. (2009) included well-functioning adults, McPhee et al. (2018) included sarcopenic patients. However, it seems probable that in Delmonico et al. (2009) may have indeed included sarcopenic patients based on the definition for sarcopenia that McPhee et al. (2018) uses in their study. A recent meta-analysis found a 30.4% prevalence of sarcopenia in older adults under the definition used by McPhee et al. (2018) (Mayhew et al., 2019). Thus, even with the methodological strengths of McPhee et al. (2018), given the large difference in population number between studies and the high probability that Delmonico et al. (2009) also included sarcopenic older adults, the role of MQ in age-related muscle weakness cannot be ignored. This is especially true in the major abdominal preoperative population, where intramuscular adipose tissue (IMAT) infiltration is observed in half of the patients (Zhuang et al., 2019, Czigany et al., 2020, Aro et al., 2020, Srpcic et al., 2020), and its impact on contractile properties of muscle tissue has been reported in a number of studies (Goodpaster et al., 2001, Shaver et al., 2022, Visser et al., 2005). In the context of preoperative risk assessment, patients' preoperative MQ has not yet been evaluated as a marker of physiological resilience. This measure may well aid in better stratifying the risk of undergoing major abdominal surgery.

2.2.1.2. Myosteatosis

Myosteatosis is a condition characterised by low muscle tissue density (Correa-de-Araujo et al., 2017) that is associated with high IMAT infiltration (Goodpaster et al., 2000). In some observations, this condition is associated with sarcopenia (Cruz-Jentoft et al., 2019), but this is not a general finding (Zhuang et al., 2019). Furthermore, myosteatosis may have different effects on muscle tissue function which makes this condition worthy of study in parallel with sarcopenia.

In the muscle, we find intermuscular fat and fat infiltration, commonly utilized as energy within the muscle, within the myocytes (Correa-de-Araujo et al., 2017). Fat infiltration is most likely the key factor in reducing muscle density, leading to reduced Hounsfield units(HU) when myosteatosis is assessed by CT and an increased greyscale when MRI and ultrasound are used for assessment (Aubrey et al., 2014, Kim and Kim, 2021) (assessment of myosteatosis is further discussed below). Similar to sarcopenia, myosteatosis has been associated with a loss of overall strength that affects physical function, compromising mobility (Marcus et al., 2012, Visser et al., 2002). In addition, myosteatosis may also alter muscle metabolism, increasing the risk of insulin resistance (Kim and Kim, 2021, Correa-de-Araujo et al., 2017). The accumulation of adipose tissue in the muscle may lead to a vicious cycle in which IMAT infiltration, lipid oxidation, and insulin resistance amplify one another (Roden, 2005), creating a disruption in oxidative metabolism (Dolly et al., 2020) and impairing cardiopulmonary capacity (Jun et al., 2013). In combination, these factors may indeed lead to an increased risk of frailty (Fung et al., 2018).

2.2.1.3. Muscle architecture

As mentioned above, age-related changes in muscle architecture have an impact on the force and power-generating capacity of the muscle (Zoladz, 2019). With age, there is a reduction in the pennation angle of muscle fibres (Narici et al., 2003, Zoladz, 2019) that, all else staying the same, will enhance, rather than reduce the speed of contraction and force-generating capacity of a muscle. This is because the transmission of force from the muscle to the tendon is more effective the more the fascicles are aligned with the tendon (Zoladz, 2019, Degens et al., 2009) (Figure 2). In addition to the reduction in pennation angle there is also an age-related reduction in L_f (Narici et al., 2003). These architectural changes are a consequence of muscle fibre atrophy, where the atrophied fibres will decrease the angle of pennation to maintain their footprint on the aponeuroses. Architectural changes are thus largely, what Gould calls, Spandrels (Gould and Lewontin, 1979) and not adaptations in their own right, but a consequence of other adaptations (here muscle fibre atrophy).

Thus, as illustrated in Figure 2, the architectural adaptations during ageing result in an increased shortening velocity, and force and power generating capacity that attenuate the loss of power and weakness consequent to muscle atrophy due to muscle fibre loss and atrophy. The reduction in strength and power as a consequence of muscle wasting is accentuated by a preferential atrophy of the faster and more powerful type II fibres (McPhee et al., 2018), intrinsic reduction of contraction speed of muscle fibres (Korhonen et al., 2006), and loss in stiffness of the tendon (Maganaris et al., 2004).

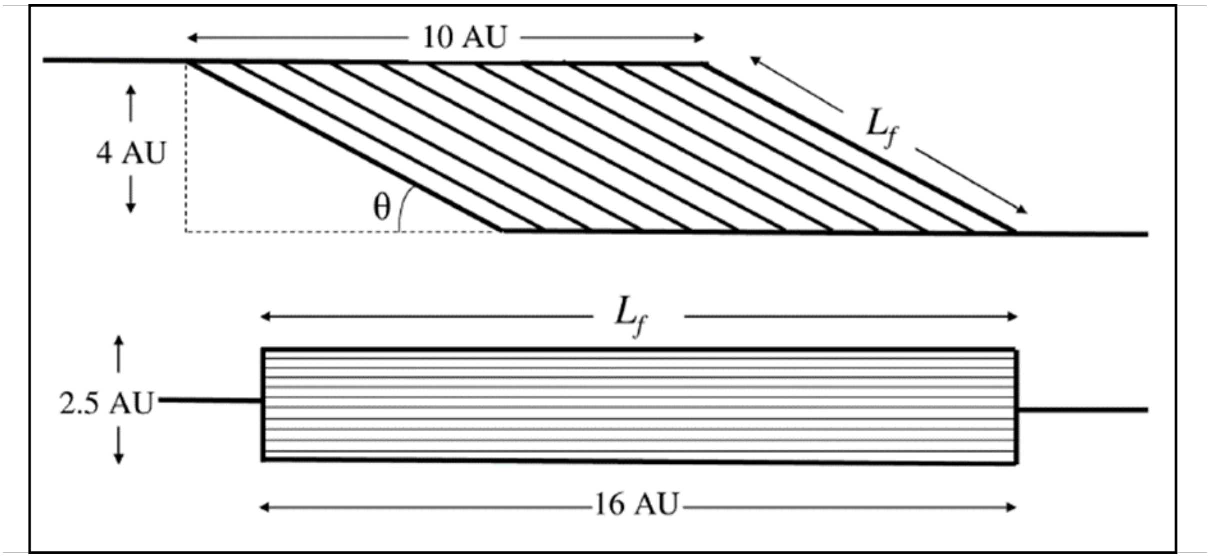


Figure 2. Alignment of muscle fibres with the tendon are mechanically advantageous over pennate muscle fibres. Extracted from Degens et al. (2009).

*"Power is determined by the shortening velocity and force. We assume that the angle of pennation (ı) is 30^o in the pennate muscle (the assertion applies to any angle). The volume of both muscles is 40 arbitrary units (AU), where the depth is 1 AU. The thickness of the pennate muscle is 4 AU and the length of the aponeurosis with fibres attached is 10 AU. The fascicle length (Lf) of the parallel muscle is 16 AU and the thickness (and, in this case, the physiological cross-sectional area, PCSA), is 2.5 AU. To calculate the PCSA of the pennate muscle we first calculate Lf as: (muscle thickness) 4AU * sin30^o=8AU. The PCSA of the pennate muscle is subsequently calculated as muscle volume/Lf: 40AU/8AU=5AU. For the calculation of force and velocity of the muscle we assume that the force-velocity characteristics of the fibres are the same in both muscles. The tendon forces of the pennate and parallel muscles are as follows:*
*Pennate: 5AU * cos30^o=4.33AU Parallel: 2.5AU * cos0^o=2.5AU*
Hence, the pennate muscle produces 1.73 x (4.33/2.5) as much force as the parallel muscle. For the shortening velocity the following applies:
*Pennate: 8AU * cos30^o=6.93AU Parallel: 16AU * cos0^o=16AU.*
Hence, the pennate muscle shortens at 0.43 x (6.93/16) the velocity of the parallel muscle. Multiplying these two factors (0.43 x 1.73) shows that the pennate muscle in this example produces only 74% of the power of a parallel muscle of the same volume" (Degens et al., 2009).

Specific force is the quotient between muscle force and muscle physiological CSA (PCSA). While anatomical CSA (ACSA) is the area of the cross-section of the muscle perpendicular to its longitudinal axis, PCSA is the area of the cross section perpendicular to its fibres, or muscle volume divided by L_f. In parallel muscles (Figure 2) ACSA and PCSA are the same, however in a pennate muscle (Figure 2) the ACSA (4AU, Figure 2) is significantly smaller than the PCSA

(5 AU, Figure 2). Hence the force per cross-sectional area, specific tension or muscle quality, is larger when using the ACSA than when using the PCSA. In other words, using the ACSA overestimates the actual specific tension (Figure 2). The force output measured at the tendon is also dependent on the pennation angle, where part of the fascicle force is not in the line of pull, but perpendicular (see legend Fig. 2). To calculate the specific force of a muscle, we must therefore divide the force by the cosine of the pennation angle, as depicted in Figure 2.

Besides architecture of the muscle, the force output, and hence specific tension, is also affected by 1) the ability to voluntary recruit the muscle of interest, 2) the co-activation of the antagonist muscles, 3) tendon moment arm and 4) the amount of non-contractile tissue in the muscle (the first 3 measures are out of the scope of this thesis and the amount of non-contractile tissue in a muscle is explained below). It should be noted that little change has been observed during ageing and disease in voluntary activation and antagonist co-activation. For instance, in patients with neurological disorders associated with muscle weakness isometric knee extension was not associated with a significant increase in co-activation of antagonists (Busse et al., 2006) and voluntary activation is minimally, if at all, affected during age-related muscle weakness (Degens et al., 2009).

While consideration of all these factors will provide an as accurate as currently possible estimate of the quality (force generating capacity) of the muscle tissue *per se (Erskine et al., 2009)* this comprehensive approach is time consuming, expensive and requires specific expertise. In addition, the many measures required to calculate the specific tension will result in an accumulation of error, as reflected by the 4x higher intra-rater coefficient of variation for the PCSA than ACSA (Erskine et al., 2009), which can be even higher when more than one assessor is calculating PCSA. While the comprehensive method gives a more realistic representation of the force generating capacity of contractile tissue, the higher variation in PCSA than ACSA makes the ACSA more suitable for longitudinal comparative studies, and even more so when time to perform specific tension assessments is limited and equipment, like an MRI, is not available.

2.2.1.4. Muscle mass, muscle density and muscle architecture measurements. Determining Sarcopenia and Myosteatosis

The EWGSOP suggests three specific steps to diagnose sarcopenia (Cruz-Jentoft et al., 2019). Despite this, there is still a lack of standardization of what measurements to use and cut-off values to implement. Handgrip assessment is the first suggested measure to diagnose sarcopenia. Based on a study that pooled handgrip strength data from twelve British studies including 49,964 participants (Dodds et al., 2014), EWGOSP suggested ≤27 kg for men and ≤16 kg for women as cut-offs in handgrip strength for the determination of sarcopenia. If the patient shows a handgrip strength below these cut-offs, the amount of muscle mass requires further assessment.

One of the most used and reliable methods to assess the amount of muscle mass is dual-energy X-ray absorptiometry (DXA). One of the most reported cut-offs is appendicular lean mass <7.26 $kg{\cdot}m^{-2}$ for men and <5.5 $kg{\cdot}m^{-2}$ for women (Mayhew et al., 2019), used by Mcphee, et al. (2018). In the context of preoperative risk assessment, abdominal CT scans at the level of Lumbar 3-4 (L3-L4) is more popular, most likely as these scans are obtained routinely to diagnose patients' disease. The assessment of sarcopenia using CT scans lack of standardization and different abdominal muscles and cut-offs are suggested to be used in the literature (Jones et al., 2017, Kim et al., 2017). Two methods of assessing muscle size appear to be reliable in a number of different studies, the assessment of total abdominal SM and the assessment of total psoas area normalized to the height (m^2). For total abdominal SM assessment, an index of ≤52.4 $cm^2{\cdot}m^{-2}$ for men and ≤38.5 $cm^2{\cdot}m^{-2}$ for women is consistently reported in the literature (Prado et al., 2008, Jones et al., 2017). However, there are less frequent reports around optimal cut-offs for total psoas area. Hamaguchi, et al (2016) proposes 2 SDs below the mean values found in the observed population (≤6.36 $cm^2{\cdot}m^{-2}$ for men and ≤3.92 $cm^2{\cdot}m^{-2}$ for women) (Hamaguchi et al., 2016), others suggests, sex specific cut-offs based on percentiles of the studied population (Kim et al., 2017, Hajibandeh et al., 2019).

Finally, EWGSOP propose the assessment of physical functionality of patients diagnosed with sarcopenia to evaluate the severity of the condition. Timed up and go (TUG) and gait speed are recommended by the EWGSOP with cut-offs of <0.8 $m{\cdot}s^{-1}$ gait speed for men and women and <20 s for men and women in the case of TUG (Cruz-Jentoft et al., 2019). It should be noted, that even though this specific diagnostic pathway is suggested, it is often observed that during the preoperative risk assessment clinic, only muscle mass through CT scans is assessed. It can be assumed that this is due to time constraints and there is usually no further assessment performed.

Similar to sarcopenia, myosteatosis can be evaluated using imaging techniques. CT, MRI, and ultrasound imaging can be used to assess muscle density. While ultrasound cannot be compared between studies, as the measure of myosteatosis is based on the grey scale of the image (Kim and Kim, 2021) and different ultrasound machines do not standardize image contrast, MRI and CT can. Furthermore, MRI and CT scans can quantify the amount of IMAT inside the muscle. CT imaging is the most used clinically and reported in the literature for preoperative risk assessment of myosteatosis. CT measures muscle density based on HU, a quantitative measurement of the radiodensity of biological tissues (DenOtter and Schubert, 2022). Cut-offs of ≤38.5 HU for patients with a body mass index (BMI) of <25 kg·m^{-2} and ≤33 HU for patients with a BMI of >25 kg·m^{-2} are the most frequently reported in the literature to determine whether a patient shows myosteatosis (Aleixo et al., 2020).

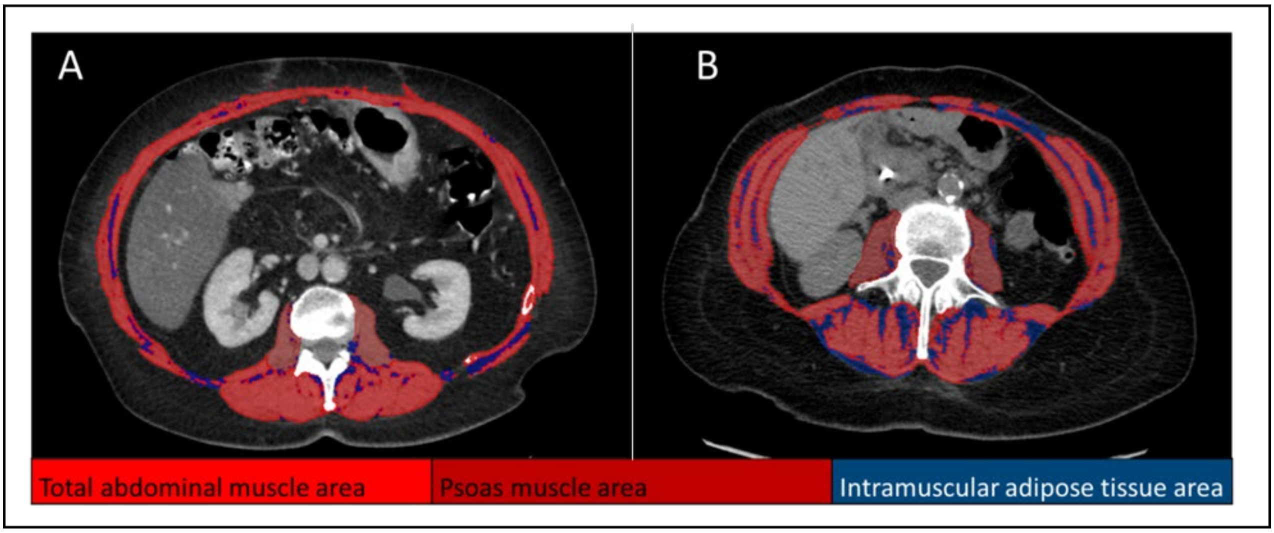


Figure 3. L3-L4 Computed Tomography scan.

Muscle tissue area is divided by the height^2 to quantify muscle tissue index and determine sarcopenia (>7.54 cm·m^{-2} for male and >5.97 cm·m^{-2} for female, based on chapter 5 thresholds).

Mean Hounsfield Units (HU) inside muscle tissue area is quantified to determine myosteatosis (<41 HU for patients with a BMI <25 kg·m^{-2} and <33 for patients with a BMI >25 kg·m^{-2} (Aleixo et al., 2020)). A. 65 years old female scheduled for hepatobiliary surgery without sarcopenia (Psoas muscle index=6.5 cm·m^{-2}) and without myosteatosis (HU=38.7 and BMI=35.7 kg·m^{-2}). B. 75 years old female scheduled for hepatobiliary surgery with sarcopenia (Psoas muscle index=5.0 cm·m^{-2}) and myosteatosis (HU=25.7 and BMI=20.6 kg·m^{-2}), therefore under risk of poor major abdominal surgical outcome.

Ultrasound longitudinal images are used to assess MT, L_f and pennation angle. Thanks to the portability of ultrasound devices, they are useful tools in assessing muscle mass and architecture in field studies, such as for bed-side measurements in the hospital where CT and MRI scans cannot be taken due to clinical, time or logistical constraints. These measurements do however come with their own technical limitations. Ultrasound probes, usually, have a width of ~5cm and long muscles, like VL, has fascicles with a length of more than 5 cm. Thus, assuming that the MT of the muscle is the same along its length, and fascicles are a straight line, methods based on trigonometry have been used to estimate L_f (Brennan et al., 2017). Recently, some ultrasound devices have offered an EFOV mode that can capture the whole CSA and length of the muscle, and with it the whole L_f. This measure has been demonstrated to be more representative than those based on trigonometrical estimation, as muscles do not have the same MT along their length and fascicles can present with a concave or convex curvature. When using ultrasound to assess muscle mass and architecture it is therefore instructive to evaluate the inter-rater reliability and intra-rater reliability of ultrasound operators to secure reliable and comparable data (scope of chapter 3).

2.2.2 Age-related decline in cardiopulmonary fitness

Cardiopulmonary fitness is reduced with age, contributing to an increased age-related acquired weakness (Layton et al., 2017, Sugie et al., 2017). Cardiopulmonary fitness can be evaluated with a maximal CPET which evaluates the capacity of the cardiopulmonary system of a patient to deal with physiological stress. Thus, appropriate cardiopulmonary capacity during CPET predicts the readiness of the cardiopulmonary fitness of a patient to face such stressing situations, like major surgeries (Steffens et al., 2021a). Overall, VO_2 peak represents the maximum capacity of the cardiopulmonary system of an individual. VO_2 peak is usually defined as the peak of VO_2 consumption (L/min) at the end of the CPET (Wasserman, 2012). It has been reported to decline to a rate of ~10%-15% per decade (Pollock et al., 1974, Tanaka et al., 1997, Pollock et al., 1997) from the age of 25-30 years old (Loe et al., 2013) and the decline accelerates to a rate of ~20% from the 7th decade (Fleg et al., 2005). Maximum heart rate and stroke volume reductions with advancing age have been proposed as the mechanism for this decline in VO_2 peak, however this does not match the decline of VO_2 peak with advancing age (Fleg et al., 2005, Fleg et al., 1995), which suggests that the reduction in VO_2 peak might be related to an impairment in VO_2 peak by a concurrent reduction of muscle tissue in advancing age. A previous study that estimated muscle mass through 24-h urinary creatinine excretion, found that half of the decline of VO_2 peak with age could be explained by the loss of muscle mass with age (Fleg and Lakatta, 1988). This may be explained by the physiological changes in muscle tissue explained above, namely, there is a reduction of type I fibres (McPhee et al., 2018) in the muscle and the remaining muscle may experience IMAT infiltration which is related with low cardiopulmonary capacity (Correa-de-Araujo et al., 2017).

Another important measure of cardiopulmonary fitness is lactate threshold (LT). LT is defined as the point at which the accumulation of lactate loses a steady growth and increases drastically (Wasserman, 2012). There are different ways of identifying this point with a CPET. In a CPET, LT can be identified observing the behaviour of VO_2 consumption against volume of air expired (VE) during the test without the need of assessing blood lactate concentration. At the beginning of the test, it is observed that VO_2 increases quickly to meet with the oxygen demands of the sudden exercise. Soon, after this quick increase, the VO_2 remains steady until exercise reaches a certain intensity in which VO_2 increases drastically, this point is named AT and it correlates very well with LT (Wasserman, 2012). AT is automatically determined by most modern CPET systems as the VO_2 consumption ($L \cdot min^{-1}$) at the breakpoint in the VCO_2-VO_2 relationship (Weissman et al., 2003). AT is also known as cardiopulmonary reserve and its determination is clinically important. A patient with a low absolute AT will not be able to cope with stressing situations efficiently, due to a disproportionate accumulation of lactate. Uncontrolled high levels of lactate may lead into an inadequate oxygen utilization and/or delivery by the cells which results in cell hypoxia and ultimately, cell death (Kraut and Madias, 2014). There are opposing research outcomes as to whether there is a reduction in the relative percentage of VO_2 peak at which AT occurs with advancing age (Iredale and Nimmo, 1997, Mattern et al., 2003). Whatever the case may be, AT is stable at the same relative percentage of VO_2 peak during adult life and it is most likely the reduction of VO_2 peak with age which leads to an absolute lower AT. A lower absolute AT with age indicates a lower capacity of older adults to properly supply oxygen to physiological systems. This means that under the effect of general anaesthesia when patients may not spontaneously ventilate (Saraswat, 2015), cells will obtain energy through anaerobic metabolic pathways, increasing drastically the accumulation of lactate.

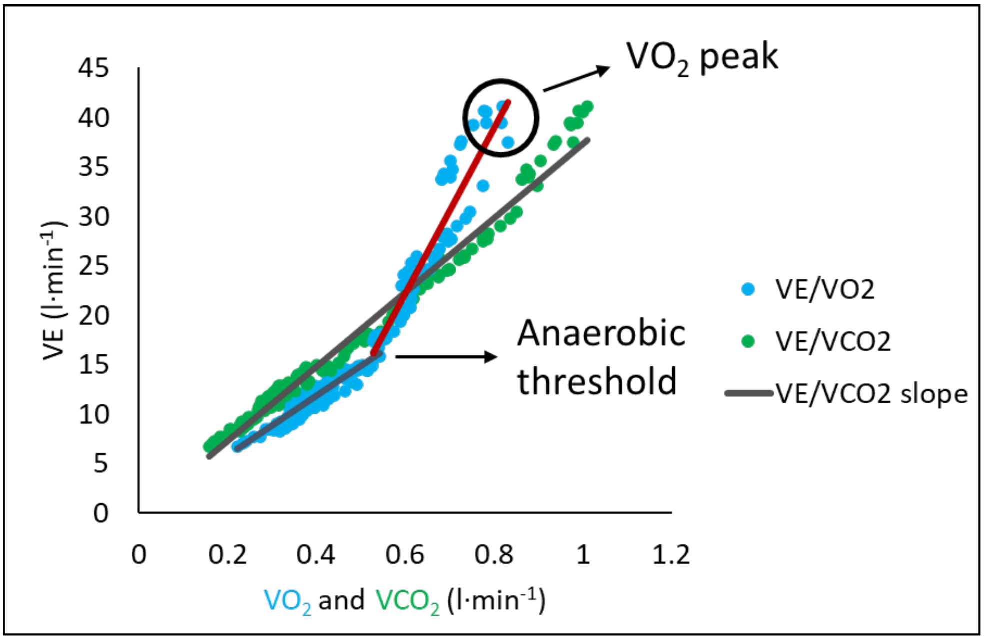


Figure 4. VO_2 and VCO_2 mechanics during a cardiopulmonary exercise testing before major abdominal surgery.
The data used for the figure was extracted from a 75-year-old woman waiting for major abdominal surgery with an AT of 9.8 mL·kg-1·min-1, a VO2 peak of 15.30 mL·kg-1·min-1 and a VE/VCO2 slope of 37.4. Based on cut-off values reported by Moran et al. (2016) and cut-offs reported in chapter 5 for VE/VCO2 slope the patient shows poor AT, VO2 peak and high VE/VCO2 and therefore, the patient is under risk of poor abdominal surgical outcome.
VE: volume of air expired; VO2: volume of oxygen; VCO2: volume of carbon dioxide.

The VE/VCO_2 slope is another relevant measure to observe during a clinical CPET. VE/VCO_2 slope reflects an increase in ventilatory response to blood CO_2 , with the aim of expiring the increased production of CO_2 with increasing exercise intensity (Wasserman, 2012). VE/VCO_2 slope is calculated as the ratio of minute ventilation (VE) and CO_2 production (VCO_2) (Weissman et al., 2003). This measure gives an indication as to the ability of the cardiopulmonary system to properly respond to increasing CO_2 production during hypoxia. Ultimately, this is an insight as to the ability of the cardiopulmonary system to cope with a drop in blood pH (acidosis) with increasing lactate accumulation during hypoxia (Anderson and Rhodes, 1991, Hirakoba et al., 1996). With age, the VE/VCO_2 slope increases, which indicates an inefficiency of the cardiopulmonary system to eliminate CO_2 under hypoxic conditions (Brischetto et al., 1984). One of the reasons for this age-related increase in VE/VCO_2 slope may be an increased ventilatory dead space that impairs gas exchange during ventilation (Brischetto et al., 1984, Miller and Tenney, 1956). Ventilatory dead space represents the volume of air that does not participate in gas exchange. Every individual shows some degree of respiratory dead space due to anatomical characteristics of the conducting zone respiration and represents approximately the 30% of the maximum air that can be inspired in a minute (Sharma and Goodwin, 2006). In addition to this anatomical dead space, there is the physiological dead space that represents alveolar dead space, which is considered negligible in healthy people (Intagliata et al., 2022). The physiological dead space is lower with age, which in addition to a reduction in respiratory muscle strength, reduces pulmonary function and decreases sensitization of airway receptors to $PaCO_2$, reducing the respiratory response to CO_2 accumulation (Sharma and Goodwin, 2006). Taken together, this increases the risk of general acidosis in various systems risking the patient's life in the immediate term, and may ultimately determine their surgical recovery (Kraut and Madias, 2014). The increased ventilation with lower intensities during CPET in older populations is most likely a product of compensation for this ventilatory dead space (Brischetto et al., 1984). Thus, an increased quotient of VE/VCO_2 represents an inefficiency of the ventilatory response to exhale CO_2 as the concentration of CO_2 in the air expired remains similar, even with an increased VE.

2.2.3. Associations of sarcopenia, myosteatosis and cardiopulmonary fitness with major abdominal surgical outcomes. Effect of in-hospital recovery on muscle mass and function.

It is well documented that an older population who experience general muscle weakness are at an elevated risk of premature mortality compared to more robust older adults. Older adults with sarcopenia without co-morbidity has a premature mortality hazard ratio of 1.2 (95%CI=1.09-1.34) compared to those older adults without sarcopenia and the hazard ratio increased to up to 2 (95%CI=1.71-2.34]) if older adults experience an underlying co-morbidity, such as cardiovascular diseases, cancer or liver disease (Xu et al., 2022, Koon-Yee Lee et al., 2021). Older adults with high IMAT infiltration in the thigh have a premature mortality hazard ratio of up to 1.3 (95%CI=1.21-1.36) compared to those with low IMAT infiltration, and similarly those older adults with higher MQ (the ratio between force production with thigh CSA) had a reduced premature mortality hazard ratio of 0.9 (95%CI=0.83-0.95) compared to those with lower MQ (Reinders et al., 2016). When myosteatosis was found in patients with cancer, the all-cause mortality hazard ratio increased to up to 1.7 (95%=1.58-1.90) compared to those experiencing cancer without myosteatosis (Aleixo et al., 2020). This increased risk of premature mortality on adults with sarcopenia and myosteatosis with and without co-morbidity attracted the attention of healthcare professionals and researchers to prognose surgical outcomes based on muscle characteristics. The risk ratios of suffering post-operative complications after major abdominal surgery are 1.6 (95%CI=1.24-4.15) in patients with abdominal CT-determined sarcopenia compared to those without sarcopenia (Jones et al., 2017). Patients scheduled for major abdominal surgery with sarcopenia have a risk ratio of up to 2.1 (95%CI=1.02-4.17), 1.6 (95%CI=1.36-1.91), 1.5 (95%CI=1.33-1.58) and 1.3 (95%CI=1.11-1.42) for mortality at 30-days, 1-year, 3-years and 5-years respectively, compared to those patients without sarcopenia (Jones et al., 2017, Hajibandeh et al., 2019). Hazard ratios of overall mortality are 1.8 in patients scheduled for major abdominal surgery with CT-determined myosteatosis compared to those that does not have myosteatosis (Aleixo et al., 2020, MacCormick et al., 2022). It seems evident that CT-determined sarcopenia and myosteatosis increase the chances of adverse event after major abdominal surgery. Despite this, it remains to be seen which condition can better predict surgical outcomes, or perhaps the combination of both conditions is more effective in determining surgical outcomes, as a cohort study has reported previously (Zhuang et al., 2019).

As well as measures of muscle mass and muscle density, muscle function is an important factor that contributes to the overall weakness and therefore, may increase the risk of poor major abdominal surgical outcome. Handgrip strength as an expression of overall muscle function is an important factor that contributes to the overall weakness with age (Cruz-Jentoft et al., 2019). In addition, handgrip strength is associated to poor surgical outcomes (Sultan et al., 2012). However, health outcomes such as psychological factors and nutritional status are better associated to knee extension force than handgrip strength (Yeung et al., 2018a). Thus, it might be probable that muscle function of the lower limb could better predict major abdominal surgical outcomes. This has not yet been explored and is assessed in the work presented in chapter 6.

Depending upon the surgical procedure performed, length of stay in hospital (LOS) after major abdominal surgery is around 9 days (chapter 7). Therefore, it is important to understand the impact of this bed rest on muscle tissue, as changes in muscle tissue may influence post-operative outcomes during and after the in-hospital recovery period. A meta-analysis assessing changes in muscle mass and knee extension force after 5-14 days of bed rest in adults >60 years old showed that leg muscle mass and knee extension power is negatively affected by bed rest. However, only knee extension power was statistically significantly associated with the bed rest days, suggesting that the effect of the amount of bed rest days has a variable influence on muscle mass within older adults. (Di Girolamo et al., 2021).

This suggests that the mechanisms by which muscle power is lost after bed rest varies between individuals and they are not only dependent on muscle mass. This bed rest effect on muscle tissue can be extrapolated to the effects seen during in-hospital recovery after major abdominal surgery. In-hospital recovery drastically reduces physical activity in patients. This may also involve a period in critical care, where patients are in total bed rest and possibly mechanically ventilated. After the in-hospital recovery, patients may acquire a generalized muscle weakness that may be present even 24 months after hospital discharge (Jolley et al., 2016). This phenomenon induce a general muscle weakness that increase the likelihood of having a persistent reduction of physical activity (Kehler and Theou, 2019) which creates a vicious cycle in favour of a general acquired weakness. Thus, it remains to be seen if changes in muscle mass and function after in-hospital recovery will have a negative impact on surgical outcomes, such as premature mortality in the long term.

General anaesthesia reduces central ventilatory drive (Saraswat, 2015), which leads to poor tissue oxygenation and the incapacity of the patient to properly excrete CO_2. Just by changing the body position from upright to supine the resting lung volume is reduced by 0.8-1 L and an additional reduction of 0.4-0.5 L is observed under the effects of general anaesthesia due to a reduction of the respiratory muscle tone (Hedenstierna and Edmark, 2015). Most of the patients will show atelectasis during general anaesthesia which is a collapsed of a partial space of the lungs. Additionally, a mechanism called “shunt dead space” may occur, what augments lung dead space and increase the arterial partial pressure of CO_2 (Hedenstierna and Edmark, 2015). This mechanism, among others, increased the risk of hypoxemia, which reduces the transfer of O_2 to cells to obtain energy and push cells to obtain energy using the anaerobic metabolism pathways (Bigatello and Pesenti, 2019). It has been observed that blood lactate concentration increases from the moment of the induction of general anaesthesia and persists post-operatively, increasing the risk of longer stay in intensive care unit (Lawton et al., 2019b). Thus, during the last decade, healthcare professionals started assessing patients’ preoperative cardiopulmonary fitness to assess the risk of undergoing major abdominal surgery. A recent meta-analysis has shown a VO_2 peak of +0.84-2.28 $mL \cdot kg^{-1} \cdot min^{-1}$ in those patients without post-operative complications and +2.78 $mL \cdot kg^{-1} \cdot min^{-1}$ in in-hospital survivors compared to patients that experience post-operative complications and suffered premature mortality, respectively. In contrast, those patients with post-operative complications had similar AT and VE/VCO_2 slope. However, when comparing patients with major and minor complications and in-hospital mortality those patients experiencing minor complications had and increased AT by 2.15 $mL\cdot kg^{-1}\cdot min^{-1}$ and in-hospital survivors had an increased AT of 2.27 $mL\cdot kg^{-1}\cdot min^{-1}$ (Steffens et al., 2021a). Another systematic review that collected data from cardiopulmonary fitness assessment prior to major abdominal surgery concluded that poor VO_2 peak and AT was associated with higher rate of premature mortality and intensive care length (Moran et al., 2016b).

There is a strong evidence base that suggests a clear relationship between low? muscle mass, poor muscle function, and low cardiopulmonary fitness with poor surgical outcomes independently. Despite this, there is a low number of studies assessing muscle characteristics and cardiopulmonary fitness together to assess surgery risk. West et al. (2019) found that those patients with myosteatosis and low VO_2 peak had higher 1-year mortality hazard ratio compared to those patients without myosteatosis and high VO_2 peak (West et al., 2019b). More studies are needed to assess the predictive power of considering CT-derived muscle parameters and cardiopulmonary fitness to predict surgical outcomes. Furthermore, the relationship between IMAT infiltration in relation to muscle mass has not yet been explored, this could present an enhanced measure compared to the traditional mean HU of abdominal muscle tissue. Overall HU, in a CT scan may present variation within patients depending on the protocol used to capture CT scans (Kim and Kim, 2021). Thus, a quotient between SM and IMAT may control for this variation to better determine muscle tissue composition.

2.3. EXERCISE TRAINING DURING AGEING AND AS PRE-OPERATIVE CARE

As described above, there is a clear relationship between muscle mass, muscle function and cardiopulmonary fitness with surgical outcomes. Therefore, exercise training may present an effective intervention to enhance muscular and cardiopulmonary systems in older populations, as well as improving the prognosis of patients schedule for major abdominal surgery.

2.3.1. Master athletes

MAs have been proposed as a model of healthy ageing, due to their high levels of physical activity. MAs also present with greater muscle mass (Peterson et al., 2011), muscle function (Pearson et al., 2002) and cardiorespiratory fitness (McKendry et al., 2018) (Figure 5 and

Figure 6) compared to older healthy adults. This better preservation of physiological system function translates into higher physical function (Maden-Wilkinson et al., 2015, Ocana et al., 2021, Walker et al., 2021). This suggests that a sustained physical activity during life may better prepare patients to face major surgeries with a higher chance of successful recovery, due to the relationships described above between muscle mass, muscle function and cardiorespiratory fitness with surgical outcomes. However, not every patient arrives to the pre-operative clinic with a sustained active lifestyle and some patients are in the late stages of life. The older population possesses less physiological plasticity to physiological adaptations (Peterson et al., 2011) to improve physical function, something that was examined in the Heritage study in which parents showed less response to aerobic training compared to their offspring (Bouchard et al., 1999). However, even though this loss of plasticity to physiological adaptations during the late stages of life, a recent study showed that the age of exercise training onset is irrelevant, with the benefits of an exercise stimulus still providing effective improvement in physiological function (Piasecki et al., 2019) in the older population. This evidence supports the use of physical activity in aiding improving surgical outcomes at whatever stage in life, even though physical practice was not present during the youth and a person’s middle-age.

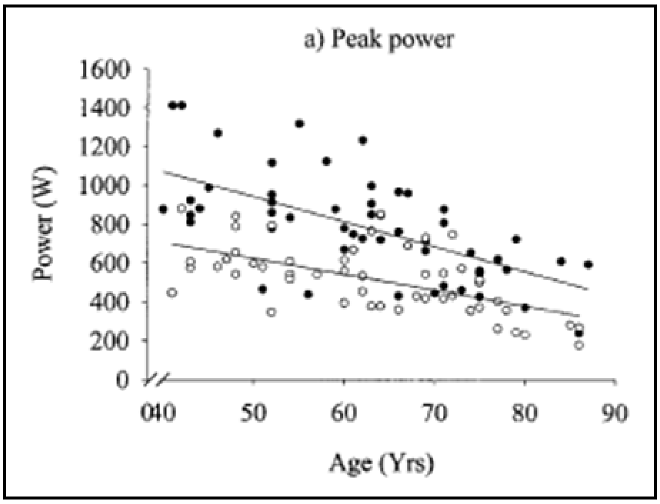


Figure 5. A: Age-related muscle power decline in Master weightlifters (black dots) and old healthy population (white dots). Extracted from Pearson et al. (2022).

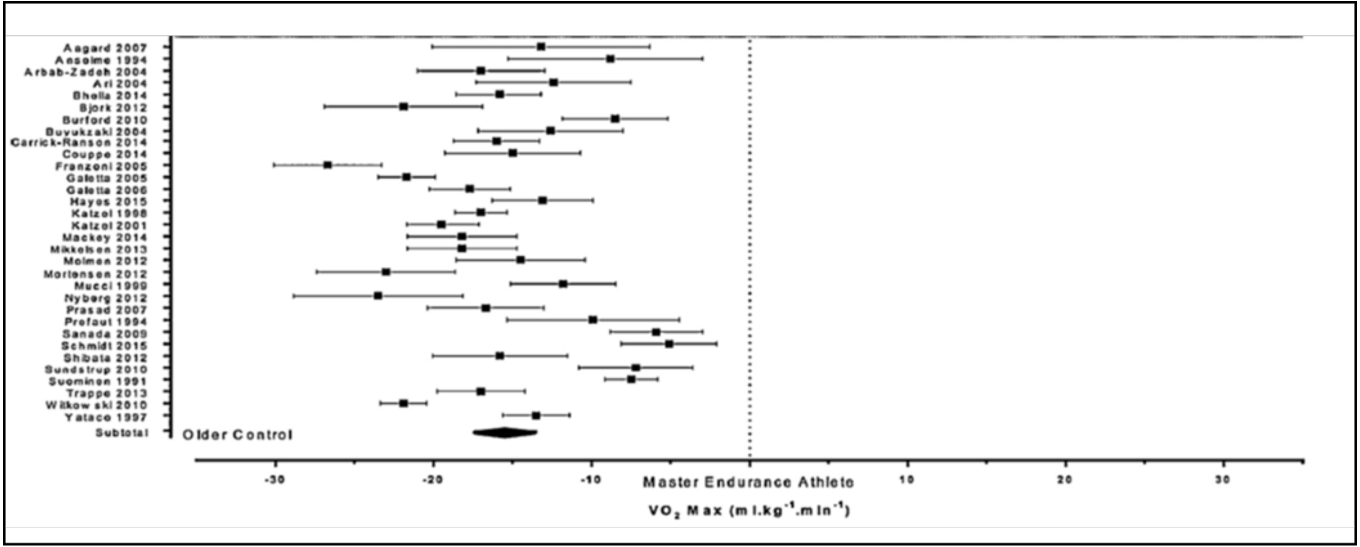


Figure 6. Forest plot representing differences in VO_2 peak between old healthy adults and master endurance athletes. The dot line represents zero difference between old healthy adults with master athletes. Extracted from Mckendry et al. (2018).

In the previous section, the effect of physical activity on physical function in middle-age and older populations irrespective of the age of exercise training onset was described. Nevertheless, it is important to ascertain what type of exercise, volume and level of intensity may produce more effective adaptations in muscle tissue to plan effective training programs. A meta-analysis showed that resistance training with heavy loads is the most effective way to promote strength and lean mass gain in older adults (Peterson et al., 2011, Steib et al., 2010). Similarly, resistance training with low weights can promote strength gains as a result of neuromuscular adaptations (Steib et al., 2010). In addition, progressive training seem crucial to get the most from resistance training and promote greater enhancements of strength compared to non-progressive resistance training (Steib et al., 2010). Sets per session of training are linearly associated with larger gains of lean mass in older adults (Peterson et al., 2011) and one session of resistance training per week seem to be enough to promote effective adaptations in the muscular system of older adults (DiFrancisco-Donoghue et al., 2007, Taaffe et al., 1999). Another meta-analysis showed that overall 8-12 weeks of resistance training is the minimum time to promote gains on muscle mass in older adults, but 12 weeks secures muscle growth (Chen et al., 2021). Thus, high intensity resistance training, once per week during 8-12 weeks with a progressive training plan appears to be an effective strategy to promote muscle growth and improve strength in older adults. In the next section, the methods by which training theory is currently applied to exercise training before surgery with the aim of improving surgical prognosis will be described.

Resistance training may also help to improve different muscle characteristics and physical function tests in sarcopenic people. After resistance training, sarcopenic patients improved appendicular muscle mass, handgrip strength, lower-limb strength, TUG, balance and gait speed compared to control groups (Talar et al., 2021, Chen et al., 2021). Moreover, the benefits of resistance training on sarcopenic population remained even after the age of 70 years old (Chen et al., 2021). These benefits were reported in two meta-analysis in which the length of the exercise period ranged 10 to 48 weeks with a session frequency ranging 2 to 3 times per week (Talar et al., 2021) and 8 to 36 weeks with a session frequency ranging 1 to 3 sessions per week (Chen et al., 2021). Furthermore, when resistance and endurance training is combined, IMAT accumulation is seemingly reduced (Tuñón-Suárez et al., 2021, Ramírez-Vélez et al., 2021). One of these studies found a relationship between the effect of exercise on IMAT with loss of body weight and total fat mass (Tuñón-Suárez et al., 2021), which may be due an improved fatty oxidation rate induced by exercise (Bagley et al., 2016). These benefits were reported in two meta-analyses in which the length of exercise ranged 8 to 52 weeks with a session frequency ranging 2 to 6 sessions per week (Tuñón-Suárez et al., 2021) and 10 to 48 weeks with a session frequency ranging 2 to 6 sessions per week (Ramírez-Vélez et al., 2021).

2.3.3. Aerobic training during middle and old ages

Aerobic fitness may improve the key cardiopulmonary fitness parameters that have a relationship with surgical outcomes. Therefore, if aerobic training is effective in promoting clinically relevant adaptations in the cardiopulmonary system of middle-age and older populations, it might be used to enhance major abdominal prognosis. A meta-analysis including studies with old healthy population with more than 60 years old found that walking for a mean of 23 weeks, 3 times a week for at least 40 minutes can increase VO_2 peak by 3.5 (95%CI=1.83-5.17) $mL \cdot kg^{-1} \cdot min^{-1}$ compared to a control group (Huang et al., 2005). Other forms of training may be more effective and reduce the time of adaptation to gain the same improvement on VO_2 peak values. A meta-analysis (Poon et al., 2021) including a population with an age ranging 40 to 75 years old, that performed moderate continuous endurance training (MCET) and high intensity interval training (HIIT), found that MCET and HIIT may promote an enhancement of 1.34 (95%CI=0.45-2.23) mL·kg^{-1}·min^{-1} and 2.26 (95%CI=1.50-3.02) mL·kg^{-1}·min^{-1} in VO_2 peak, respectively. From this evidence, HIIT seem to promote greater improvements on VO_2 peak compared with moderate endurance training for a long period with a moderate weekly frequency (Huang et al., 2005), Poon et al. 2021 (length of exercise ranged 2 to 8 weeks with a frequency ranging 3 to 4 days) showed that in less than half of the training time, reported by Huang et al. (2005), HIIT is able to promote similar improvement on VO_2 peak. Additionally HIIT may better promote cardiovascular and metabolic adaptations, compared to MCET, such as increase heart ejection fraction, reduce arterial stiffness or reduce insulin resistance (Marriott et al., 2021). Similarly, in a group of healthy individuals with an age ranging between 53 to 74 years old it was found that LT can be improved between 2 to 4.1 mL·kg^{-1}·min^{-1} after 12 weeks of training with a frequency of 2 sessions per week of interval training (Ahmaidi et al., 1998, Fabre et al., 1997).

The effects of aerobic training on VE/VCO_2 are usually reported in the literature for clinical populations due to the measurement's close relationship with clinical outcomes. Prado et al. (2016) published a review of the effect of aerobic training on VE/VCO_2 slope. They found that different studies reported a reduction of VE/VCO_2 slope in patients with heart diseases (Prado et al., 2016). However, other studies with heart failure patients have reported the lack of effect of aerobic training on VE/VCO_2 slope (Myers et al., 2012, Busin et al., 2021). This contradiction may be due to the length of the training program. While patients in Myers et al. (2012) and Busin et al. (2021) did a training with a length of 8-10 weeks in patients with a mean age of 55-64 years, other studies with a length of 15-16 weeks of training in patients with a mean age of 60-61years found a reduction in the VE/VCO_2 slope (Scarpa, 2018, Gademan et al., 2008).

2.2.4. Prehabilitation exercise programs before major abdominal surgery

The aim of prehabilitation exercise programs is to promote adaptations in the muscular and cardiovascular system before the surgery to enhance the surgical prognosis. Thus, as seen in Figure 7, those patients performing a prehabilitation exercise program may improve their physical functionality before surgery and not see a physical performance reduction as the one expected in a usual care pathway patients. In addition, patients performing prehabilitation programs may see their physical function to recover to baseline values faster compared to those patients following the usual care pathway, due to an enhanced physical function at baseline after exercise.

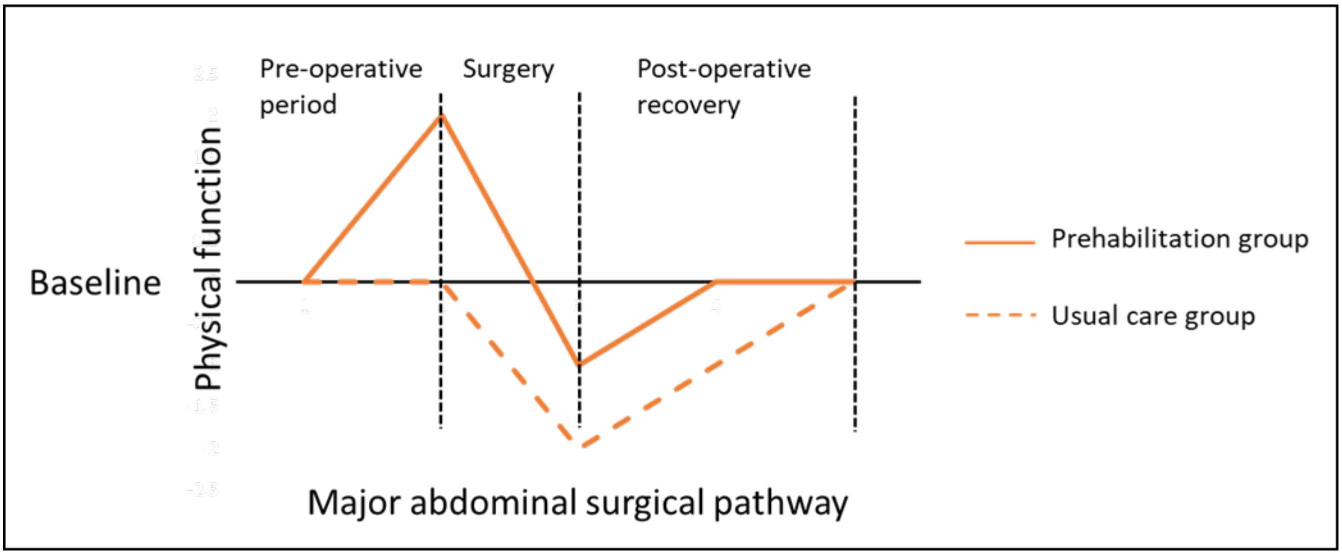


Figure 7. Theoretical physical function changes over the major abdominal surgery pathway depending on the implementation of a patient prehabilitation exercise program or following the usual care treatment.

The usual time between surgery notification and surgery performance is 4-6 weeks (Fulop et al., 2021, Bousquet-Dion et al., 2018, Barberan-Garcia et al., 2017). Due to the training time required to promote adaptations in the muscular and cardiovascular systems as described above the ability to positively impact surgical outcomes poses a real challenge. Hence, in the prehabilitation research area, there are opposing findings. A recent meta-analysis that included the largest number of randomized controlled trials (RCTs) in the literature exploring the effect of prehabilitation exercise programs on the cardiovascular system and physical function before major abdominal surgery (Waterland et al., 2021), found that patients that performed a prehabilitation program improved their 6 minute-walk distance (6MWD), but it was inconclusive as to whether this improves VO_2 peak, before surgery, compared to usual care patients. This exercise adaptation tended to reduce pulmonary complications and reduce the LOS but the overall rate of post-operative complications and premature mortality remained unchanged between groups. Another meta-analysis found that prehabilitation programs are unable to promote improvements on 6MWD before surgery, could not reduce the rate of post-operative complications, and premature mortality but there was a tendency to have the LOS reduced, compared to the usual care patients (Lambert et al., 2021). In contrast to Waterland et al. (2021) and Lambert et al. (2021), other meta-analysis reported that prehabilitation programs are able to reduce the rate of post-operative complications compared to usual care (Hughes et al., 2019, Heger et al., 2020, Moran et al., 2016a).

It should be noted that within the above referenced meta-analysis there is a large heterogeneity between studies that may be due to the nature of the prehabilitation programs, except for Waterland et al (2021) the rest of the meta-analysis included multimodal prehabilitation programs (inclusion of psychological and nutritional support a part of the exercise program) and unimodal programs (including only exercise before surgery). When Waterland et al. (2021) performed a subgroup analysis to assess differences in the effect size between unimodal and multimodal programs, only multimodal programs significantly improved 6MWD in the prehabilitation patients compared to the usual care group rate of pulmonary complications and overall complications remained similar between both uni- and multi-modalities of prehabilitation. Another source of heterogeneity between studies is the supervision of the exercise. All referenced meta-analysis included supervised, semi-supervised and unsupervised exercise programs, which may cause the discrepancy between studies. The effect of exercise on physiological systems in old and clinical population is reduced when the exercise is unsupervised (Lacroix et al., 2017a, Vemulapalli et al., 2015). In fact, a published guideline on pre-operative exercise programs before major abdominal surgery advises to supervise exercise sessions where possible (Tew et al., 2018). Thus, it remains unclear what the effects of prehabilitation programs are when only data from randomized trials where patients performed at least one session of supervised exercise.

The effect of the quantity of supervised exercise on physiological adaptations, strength gains and surgical outcomes is unclear. It is vital therefore, to determine whether patients performing prehabilitation exercise programs recover their physical function after surgery faster than those who do not perform prehabilitation exercise. In addition, when meta-analysis was performed to ascertain the effect of prehabilitation exercise programs on cardiopulmonary fitness, the number of included studies was low (Waterland et al., 2021). Taken together, it is therefore instructive to perform further meta-analysis including only RCTs in which patients in the prehabilitation group perform at least one supervised exercise session per week to clearly understand the potential benefits of prehabilitation programs. Additionally, the optimal training stimulus to gain benefit from the prehabilitation programs is yet to be determined.

CHAPTER THREE: RELIABILITY AND VALIDITY OF ULTRASOUND-DERIVED VASTUS LATERALIS SIZE, QUALITY AND MUSCLE ARCHITECTURE MEASURES

What it is known	What it will be assessed
- EFOV ultrasound images can capture the CSA and the whole L_f of the VL accurately.	- Whether EFOV ultrasound images of VL show good intra-rater, inter-rater and inter-machine (US *vs* MRI) reliability. - Whether ultrasound measures of VL size are representative of the whole quadriceps CSA.

3.1. INTRODUCTION

While there is a strong relationship between the mass and force generating capacity of a muscle (Reggiani and Schiaffino, 2020), this relationship is not linear. This is reflected, for instance, by early increases in force generating capacity during resistance training that are not accompanied by a commensurate increase in muscle mass (Degens et al., 2009, Ozaki et al., 2015, Schoenfeld et al., 2015). Clearly, there are other factors than just muscle mass that determine the force generating capacity of a muscle, such as the proportion of non-contractile material (Goodpaster et al., 2001), muscle architecture (Degens et al., 2009), and the ability to voluntary activate a muscle (Gabriel et al., 2006). Therefore, to assess the contractile properties of the actual muscle tissue, these factors need to be considered. One measure that tries to consider these limitations of muscle mass *per se* is MQ, defined as the force produced per unit of muscle tissue CSA (Delmonico et al., 2009). Even though MQ, still does not consider neuromuscular factors to assess muscle contractility, it does consider IMAT infiltration. Adipose tissue occupies space in the muscle and reduces its contractile capacity (Delmonico et al., 2009, Goodpaster et al., 2001). Therefore, normalising strength to a measure of muscle size estimates the contractile quality of the muscle tissue.

Often quadriceps muscle size and MQ are assessed due to its implication in locomotory activities as walking or running (Maeda et al., 2020, Christensen et al., 2021), cycling (Martin et al., 2000, Martin et al., 2007), and jumping (Ward et al., 2018). Indeed, quadriceps MQ appears to be a rather important measure, as studies on sarcopenia have seen that a poor MQ is associated with higher risk of premature mortality (Reinders et al., 2016).Hence, measures of quadriceps size and MQ have become relevant as an estimate of the physical functionality of patients and community dwelling adults due to its relationship with adverse outcomes in different clinical settings (Wolters et al., 1996, Ezzatvar et al., 2021, Cooper et al., 2010).

The Gold Standard for *In vivo* measurements of quadriceps size requires expensive equipment, such as MRI, or participants to be exposed to radiation in the case of CT imaging (Tosato et al., 2017). These measures are also not practical at the bedside or in the patients' home setting. Ultrasound imaging may, however, present a practical and cost-effective tool, free of radiation exposure that can be implemented in a bedside (Canales et al., 2022) and home setting to assess quadriceps MQ size and architecture. It is important therefore, to assess the inter-rater, intra-rater, and inter-machine reliability (ultrasound *vs* MRI) of ultrasound images before its implementation in research and clinical studies.

It is, however, time consuming to assess size and architecture of every individual muscle of the quadriceps. It is therefore, encouraging that VL size and architecture may be a good representation of the whole quadriceps (Erskine et al., 2009). In addition, the MRI CSA at 50%-60% of the muscle length can provide a good estimate of muscle volume (Morse et al., 2007), suggesting that measuring VL-MT and VL-CSA at 50% muscle length may provide a good representation of the quadriceps muscle as a whole. Furthermore, previous studies have reported a good reliability of CSA measures of the quadriceps muscles when measured with ultrasound EFOV images at 50% of the femur length compared to CT images (Noorkoiv et al., 2010a) or MRI, even when it is used to assess changes after training interventions (Ahtiainen et al., 2010).

EFOV ultrasound imaging allows the acquisition of the whole fascicle even in long muscles, which improves the accuracy of L_f assessment compared to conventional ultrasound techniques that do not normally capture the entire fascicle (Noorkoiv et al., 2010b, Franchi et al., 2020b). The intra-rater reliability and comparison of EFOV against conventional methods (Brennan et al., 2017) to quantify L_f imaging has been explored for the biceps femoris (Franchi et al., 2020b) and VL (Noorkoiv et al., 2010b) successfully.

Despite the plentiful evidence indicating the reliability of ultrasound for muscle size and architecture measurements, the experience of ultrasound assessors should be accounted for when assessing imaging for this purpose. Inexperienced ultrasound operators may show a larger intra-rater error than experienced users (Franchi et al., 2020a). Therefore, it is important to assess the reliability of inexperienced ultrasound operators before commencing data collection for clinical studies or for use in clinical practice. Chapter 6 assessed longitudinal changes in muscle size and architecture in patients undergoing abdominal surgeries, therefore the results presented in this chapter are important, as they suggest reference values about the intra-rater error of the ultrasound operator of that study, which allows an appropriate interpretation of the possible changes in muscle size and architecture observed in that study. In addition, this chapter show reference values about the relationship of single quadriceps muscles size and quality with the whole quadriceps size. These relationships are important of understanding the extent that measures of single quadriceps muscle size and quality (measures included in the next chapters) represent the whole quadriceps size and quality.

Thus, the primary objective of this study was to evaluate the inter-machine (*vs* MRI) intra- and inter-rater reliability of individual quadriceps size and architecture measures when assessed by ultrasound. Additionally, to what extent ultrasound measures of muscle size and MQ measures from individual muscles of the quadriceps are representative of the whole quadriceps size and MQ was assessed. The study therefore has the following objectives: 1) to assess the validity of ultrasound-based measures of MQ and size of individual quadriceps muscles, VL, VI and RF against MRI-based measures of quadriceps MQ and size, 2) assess the intra-rater and inter-rater reliability ultrasound operators to evaluate muscle size of VL, VI and RF, and muscle architecture of VL using conventional ultrasound images and EFOV ultrasound images and 3) assess the agreement between conventional ultrasound images measures and EFOV ultrasound images to measure L_f and pennation angle.

3.2. METHODS

3.2.1. Study design

This study was approved by the ethics committee of Manchester Metropolitan University (Ref. 17493). Twenty-six participants were recruited (12 women and 14 men) with a mean age of 29±4 years from the population in Manchester (UK). Participants attended one assessment session of ~2 hours. Muscle images were taken with ultrasound and MRI, and a MVC knee extension was recorded during the session. Sample size was planned to be 30 participants based on previous studies that assessed the reliability of muscle ultrasound measures (Nijholt et al., 2017). This decision was taken due to time constraints in the required start of experimental studies with patients. Data from 26 participants were included in the study due to university facilities access limitations due to the COVID-19 pandemic.

3.2.2. Muscle imaging acquisition and analysis

Two inexperienced assessors (one never collected a thigh ultrasound picture and the other had limited experience collecting longitudinal ultrasound images) collected EFOV and conventional ultrasound images (Esaote, MyLab™Gamma portable ultrasound) using a linear array transducer (3.0 MHz. - 13.0 MHz, model: Esaote SL1543). Ultrasound images were taken with the patient seated with hip and knee at 90°. Conventional longitudinal ultrasound images of the VL and VI were taken at 50% of femur length (distance between greater trochanter and lateral condyle) to capture VL and VI-MT. Images were considered appropriate when superficial and deep aponeuroses appeared parallel in the image (Figure 8A.1). EFOV images of the whole length of VL (from origin -greater trochanter- to the insertion -tibial tubercle) were taken to capture the whole length of the fascicle (Figure 8A.2). Transverse EFOV images along the thigh circumference at 50% VL length were taken to capture the CSA of VL and RF (Figure 8B.1).

Ultrasound measurements of both assessors were compared for inter-rater reliability. Assessors were not present in the room when the counterpart was taking the images. For intra-rater reliability one of the assessors (PD) took the same images separated by one hour during the session. Any mark on the participants thigh that could indicate to the assessor the exact position where the images were taken the first time was removed before taking the images a second time. The second set of ultrasound images was used to assess the reliability between ultrasound conventional images *vs* EFOV ultrasound images to quantify L_f and pennation angle.

A 0.25-T MRI scanner (G-scan, Esaote Biomedica, Genoa, Italy) was used to collect transverse images (Turbo-3D T1-weighted protocol with consecutive 2.8-mm thick slices (McPhee et al., 2018) at 50% of the VL length (Figure 8B.2). VL-CSA and RF-CSA acquired with MRI were used compared with EFOV-derived VL-CSA and RF-CSA. Furthermore, the whole quadriceps CSA was also computed to assess the relation between individual quadriceps muscles size (VL-CSA, VL-MT, RF-CSA, VI-MT and VL+RF CSA and VL+VI MT).

All image analysis was performed with ImageJ v.1.8.0_172 for windows. Each of the assessors analysed all images to assess inter-rater reliability of both acquisition and analysis. VL-MT and VI-MT (both in mm) were considered as the shortest distance between the superficial and deep aponeuroses (Figure 8A.1). VL-MT and VI-MT were given as the mean of three measurements in three different pictures captured by conventional ultrasound imaging. The length of the two most visible fascicles at the middle section of the VL length was measured for each image. For EFOV ultrasound images, L_f (in mm) was computed as the total length of the selected fascicles from superficial to deep aponeuroses and for conventional ultrasound images L_f was computed using the intercept method (Brennan et al., 2017) (Figure 8A.1 and Figure 8A.2).

The pennation angle (in ^{0}) of these two selected fascicles was measured as the angle between the fascicles and the deep aponeurosis (Figure 8A.1 and Figure 8A.2). Three images were analysed to obtain six measurements of L_f and pennation angle. The smallest and the biggest measures were discarded, and the mean of the rest was computed for further analysis. VI L_f and VI pennation angle were not measured, as VI fascicles were not easily visible in every participant. VL-CSA, RF-CSA and quadriceps CSA acquired with EFOV ultrasound imaging and MRI were given as the mean measure of three different images (Figure 8B.1 and 8B.2). VL-CSA was defined as the area inside the VL superficial and deep aponeurosis. In some muscles the presence of connective tissue inside the VL muscle may lead to confusion while outlining the VL-CSA. In those cases, the VL deep aponeurosis was considered as the last bright line of connective tissue in the image before the external matrix of the femur (Figure 8B.1 and Figure 8B.2 for an illustration how VL inner connective tissue may lead to outline confusion). When the lateral or proximal edge of the VL was not entirely visible, a straight line was drawn from the last visible part of the VL edge to the first visible part of the deep aponeurosis. These decisions were taken to ensure consistency in tracing and calculation of the VL-CSA, even though this approach leads to an unrealistic VL anatomical shape. For comparison, Figure 8B.1 shows with the solid line the real outline of the VL and with the dotted line how the VL was outlined, illustrating the overestimation of the VL-CSA (in 10 subsamples we saw this was approximately 12% (range: 3 to 27%).

VI and VM-CSAs were not computed in ultrasound images because lateral-medial aponeurosis of these muscles was difficult to identify in some participants. They were computed in MRI images to calculate the quadriceps CSA.

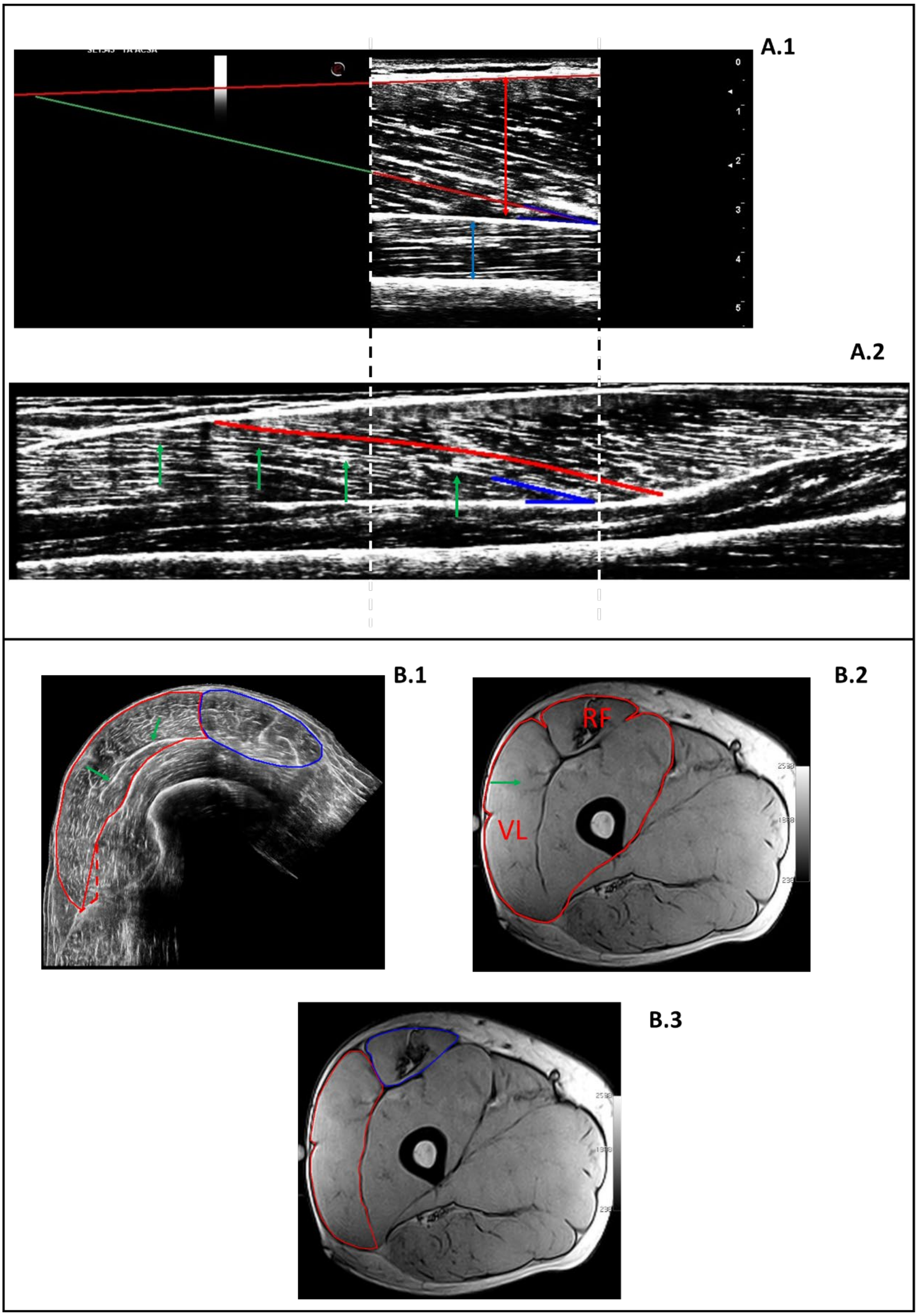


Figure 8. Ultrasound (A.1, A.2, B.1) and magnetic resonance (B.2) Images of Vastus Lateralis, Vastus Intermedius and Rectus Femoris.

RF: Rectus Femoris; VL: Vastus Lateralis.

It should be noted that A.1. longitudinal size and depth are not scaled to A.2. longitudinal size and depth, and in addition the fascicles outlined in A.1 are not the same fascicles as those outlined and pointed in A.2. 'A.1) Vastus Lateralis thickness at

50% length of the femur length (red arrow) Vastus Intermedius thickness at 50% of the femur length (blue arrow). Intercept method to quantify fascicle length (Brennan et al., 2017). The red line in the muscle shows the visible part of the fascicle and the green line the non-visible estimated part. The Blue angle represents pennation angle. The red line at the top of the image represents the aponeuroses and the extrapolated part of the aponeuroses. A.2) Fascicle length quantification using extended field of view ultrasound imaging (red line). The blue angle represents pennation angle of a different fascicle that can be followed using the green arrows. B.1) Vastus Lateralis cross-sectional area (area inside red edges) and Rectus Femoris cross-sectional area (area inside blue edges) using extended field of view ultrasound imaging. The dotted line indicates the VL-CSA according to the methods followed in this thesis and the solid line indicates the correct VL-CSA (Sarto et al., 2021) (Refer to Section 3.4 for further information about the VL-CSA measure in this thesis). B.2) Quadriceps cross sectional area by MRI. Green arrows in B.1 and B.2 indicate inner connective tissue in the VL. B.3) Vastus Lateralis cross-sectional area (area inside red edges) and Rectus Femoris cross-sectional area (area inside blue edges) using extended field of view ultrasound imaging.

3.2.3. Maximum isometric knee extension contraction acquisition and analysis

At the end of the session participants sat on a customized dynamometry chair (Manchester Metropolitan University, Manchester) with knee and hip angle at 90^0 to measure the force during a MVC of the knee extensors. A strap around the hip secured the participants firmly to the chair during the contractions. A load cell (TEDEA, HUNTLEIGH, model n^o 615) was strapped to the ankle, right above the malleolus, to measure the force exerted, after being calibrated against a known weight before the warm-up of every participant. Participants performed a ramp warm-up with 9 submaximal isometric contractions, 3 at 100 N, 3 at 150 N and 3 at 200 N before performing 3 MVC. Between each MVC there was a rest period of at least 1 minute.

The force signal was collected at a rate of 1000 Hz with a 2-channel power lab (PL2062, ADinstruments). Force data was processed with Lab chart Pro (v. 8.19, ADinstruments). The force signal was smoothed with a moving average of 0.5 seconds. The maximum value of the three maximum knee extensions after smoothing was collected as MVC (in N) for further analysis.

3.2.4. Muscle quality quantification

Quadriceps-MQ was calculated as the ratio between MVC with quadriceps-CSA measured by MRI. Ultrasound-derived measures of MQ were calculated using six different ratios for further assessment of associations with quadriceps MQ: 1) VL-MQ_{ACSA} was the ratio between MVC and VL-CSA, 2) RF MQ_{ACSA} was the ratio between MVC and RF-CSA, 3) VL+RF MQ_{ACSA} was the ratio between MVC and VL+RF-CSA, 4) VL MQ_{MT} was the ratio between MVC and VL-MT, 5) VI MQ_{MT} was the ratio between MVC and VI-MT and 6) VL+VI MQ_{MT} was the ratio between MVC and VL+VI-MT.

3.2.5. Statistical analysis

All statistical analysis was performed using SPSS (v. 27, IBM). Normal distribution assessment was completed with the Shapiro-Wilk test. Pearson correlations were calculated between quadriceps CSA acquired with MRI with VL-MT, VL+VI-MT, VL-CSA and VL+RF-CSA acquired with ultrasound. Pearson and Spearman correlations were calculated between quadriceps-MQ acquired with MRI with US-derived measures of MQ. The value R^2 was used to understand to what extent the whole quadriceps size and MQ can be explained by individual quadriceps muscles.

95% Limits of agreement (differences between methods lying between the mean±1.96 SD with an assumption of constant mean and SD error, LOA) (Bland and Altman, 1986, Bland and Altman, 1999) and Intraclass Correlation (ICC) (Koo and Li, 2016) were calculated to assess 1) inter-machine reliability (US *vs.* MRI); 2) inter-rater and intra-rater reliability of VL-MT and CSA, RF-CSA, VI-MT and VL muscle architecture using conventional ultrasound (Brennan et al., 2017) and EFOV ultrasound imaging 3) Agreement between EFOV ultrasound and conventional ultrasound images. A two-way mixed model and absolute agreement type of test was used to calculate ICC. ICC values higher than 0.75 indicate good reliability, and values higher than 0.9 indicate excellent reliability (Koo and Li, 2016).

To further evaluate whether the ultrasound image collection and analysis (outlining) of the VL resulted in a consistent outlining of the VL-CSA, the coefficient of variation for the same investigator (PDO) was calculated.

3.3. RESULTS

Participant and muscle characteristics are reported in Table 1 and Table 2.

Table 1. Participant's characteristics

Participant's Characteristics (N=26)	
Body mass (kg)	69.6±14.5
Height (m)	1.71±0.10
BMI (kg·m^2)	23.7±3.3
Quadriceps CSA MRI (mm^2)	7172±1776
VL CSA MRI (mm^2)	2511±613
RF CSA MRI (mm^2)	935±320
MVC (N)	438±140
Quadriceps quality (N·mm^{-2})	0.06 (0.053-0.067)
VL MQ$_{MT}$ (N·mm^{-1})	17.6±4.9
VI MQ$_{MT}$ (N·mm^{-1})	25.8 (20.6-31.3)
VL+VI MQ$_{MT}$ (N·mm^{-1})	10.6±3.0
VL MQ$_{ACSA}$ (N·mm^{-2})	0.17 (0.16-0.18)
RF VL MQ$_{ACSA}$ (N·mm^{-2})	0.52± 0.10
VL+RF VL MQ$_{ACSA}$ (N·mm^{-2})	0.13±0.02

Data presented as mean±SD or median (IQR)

CSA: Cross-sectional area; MRI: magnetic resonance imaging; MQ$_{ACSA}$: Muscle quality using anatomical cross-sectional area; MQ$_{MT}$: Muscle quality using muscle thickness; MVC: Maximum voluntary contraction; RF: Rectus femoris; VI: Vastus intermedius; VL: Vastus lateralis.

3.3.1. Inter, intra-rater and inter -machine reliability of ultrasound imaging

Inter-rater, intra-rater and inter-machine reliability are reported in Table 2 followed by Bland and Altman LOA plots in Figure 28, Figure 29 and Figure 30.

For both EFOV ultrasound and conventional ultrasound imaging the intra-rater reliability for VL-MT, VI-MT, VL-CSA, RF-CSA and VL L$_f$ and pennation angle was good to excellent based on ICC values (Table 2).

EFOV ultrasound imaging showed a good to excellent inter-rater reliability for VL-CSA, RF-CSA and VL L_f and pennation angle, but for conventional ultrasound imaging, the inter-rater reliability of VL L_f and pennation angle was poor based on ICC values.

VL-CSA and RF-CSA inter-machine reliability (EFOV US imaging *vs* MRI) was assessed as good to excellent based on ICC values. When methods to quantify L_f and pennation angle were compared (EFOV US imaging *vs* conventional US imaging with intercept method), conventional ultrasound imaging with intercept method tend to overestimate L_f and underestimate pennation angle based on the 95% LOA. In addition, the coefficient of variation in VL-CSA derived from ultrasound images was 4.5%.

Table 2. Intra-rater and inter-rater reliability assessment

Intra-rater reliability						
Parameter	*1st measure*	*2nd measure*	*Mean bias*	*LLOA*	*ULOA*	*ICC [CI 95%]*
VL thickness (mm)[a]	24.8±4.2	24.5±4.4	-0.25	-2.13	1.63	0.987 [0.971-0.994]
			0.99	0.92	1.06	
VI thickness (mm)	16.3±3.4	15.3±2.5	0.01	-3.8	3.8	0.826 [0.576-0.928]
L_f (mm) (EFOV acquisition)	123±17	122±16	-0.4	-11.0	10.1	0.972 [0.938-0.988]
Pennation angle (^{0}) (EFOV acquisition)	13.1±2.6	12.0±2.3	-1.1	-4.4	2.1	0.824 [0.474-0.931]
L_f (mm) (Conventional US acquisition)	137±23	133±24	-4	-33	26	0.883 [0.741-0.947]
Pennation angle (^{0}) (Conventional US acquisition)	10.6±2.5	10.5±2.4	-0.05	-3.2	3.1	0.884 [0.739-0.948]
VL CSA US (mm^2)	2526±673	2496±744	-30.5	-372	311	0.985 [0.968-0.993]
RF CSA US (mm^2)	853±263	830±248	-26.9	-186	132	0.973 [0.939-0.988]
Inter-rater reliability (assessor 1 vs. assessor 2)						
	Assessor 1	*Assessor 2*	*Mean bias*	*LLOA*	*ULOA*	*ICC [CI 95%]*
VL thickness (mm)	24.8±4.2	23.7±3.5	-1.1	-4.7	2.5	0.924 [0.780-0.969]
VI thickness (mm)	16.3±3.4	15.52±3.71	-0.72	-5.43	3.99	0.869 [0.708-0.941]
L_f (mm) (EFOV acquisition)	123±17	123±15	2	-4	7	0.979 [0.953-0.990]

Pennation angle $(^0)$ (EFOV acquisition)	13±3	14±3	1.7	-3.0	5.3	0.767 [0.442-0.899]
L_f (mm) (Conventional US acquisition)	135±22	120±15	-15	-47	17	0.644 [-0.023-0.861]
Pennation angle $(^0)$ (Conventional US acquisition)	10.5±2.3	11.4±1.8	0.84	-3.7	5.4	0.520 [-0.009-0.779]
VL CSA US (mm^2)	2526±673	2641±674	73.3	-268	415	0.980 [0.951-0.991]
RF CSA US (mm^2)	853±263	935±320	-51.47	-386	283	0.857[0.680-0.936]
Inter-machine reliability (US *vs.* MRI)						
	Assessor 1	*MRI*	*Mean bias*	*LLOA*	*ULOA*	*ICC [CI 95%]*
VL CSA (mm^2)	2526±673	2511±613	-32.9	-552	486	0.957 [0.904-0.981]
RF CSA (mm^2)	853±263	935±320	73.9	-266	414	0.892 [0.743-0.954]
Inter-method reliability (EFOV US imaging *vs.* conventional US imaging with intercept method)						
	EFOV US	Conv. US	*Mean bias*	*LLOA*	*ULOA*	*ICC [CI 95%]*
L_f (mm)	122±16	135±22	13	-36	62	0.207 [-0.490-0.612]
Pennation angle $(^0)$	12.5±2.3	10.5±2.3	-2.0	-7.1	3.2	0.420 [-0.151-0.725]

Data presented as mean±SD or mean [95% confidence interval].

Conv: Conventional; CSA: Cross-sectional area; EFOV: extended field of view; ICC: Intraclass correlation coefficient; LLOA: Lower limit of agreement; MRI: Magnetic resonance imaging; ULOA: Upper limit of agreement; US: Ultrasound; RF: Rectus femoris; VI: Vastus intermedius; VL: Vastus lateralis.

[a] LOA are presented in absolute values and coefficient between two measures because heteroscedasticity was observed for this parameter (Figure 29A).

3.3.2. Relationship of Vastus Lateralis size and quality with quadriceps cross-sectional area and quality

Quadriceps-CSA as measured by MRI was strongly associated with ultrasound measured VL-CSA ($p<0.001$, $R^2=0.87$), moderately associated with VL-MT ($p<0.01$, $R^2=0.66$) and RF-CSA ($p<0.01$, $R^2=0.62$) and poorly associated with VI-MT ($p<0.01$, $R^2=0.31$) (Figure 9A and Figure 9B). When RF-CSA was added to VL-CSA the correlation coefficient with quadriceps-CSA did not notably change ($p<0.01$, $R^2=0.86$). When VI-MT was added to VL-MT the correlation coefficient increased ($p<0.01$, $R^2=0.76$) (Figure 9A and Figure 9B). Similarly, quadriceps-MQ was strongly associated with VL-MQ_{ACSA} ($p<0.01$, $R^2=0.79$) and VL-MQ_{MT} ($p<0.01$, $R^2=0.74$). The correlation coefficient was reduced in the case of associations between quadriceps MQ with VI-MQ_{MT} ($p<0.01$, $R^2=0.63$) and even more with RF-MQ_{ACSA} (p<0.01

R^2=0.27). The correlation coefficient did not notably change when RF-CSA was added to VL-CSA to calculate VL+RF-MQ_{ACSA} ($p<0.01$, R^2=0.78) and VI-MT to VL-MT to calculate VL+VI-MQ_{MT} ($p<0.01$, R^2=0.77) (Figure 9C and Figure 9D).

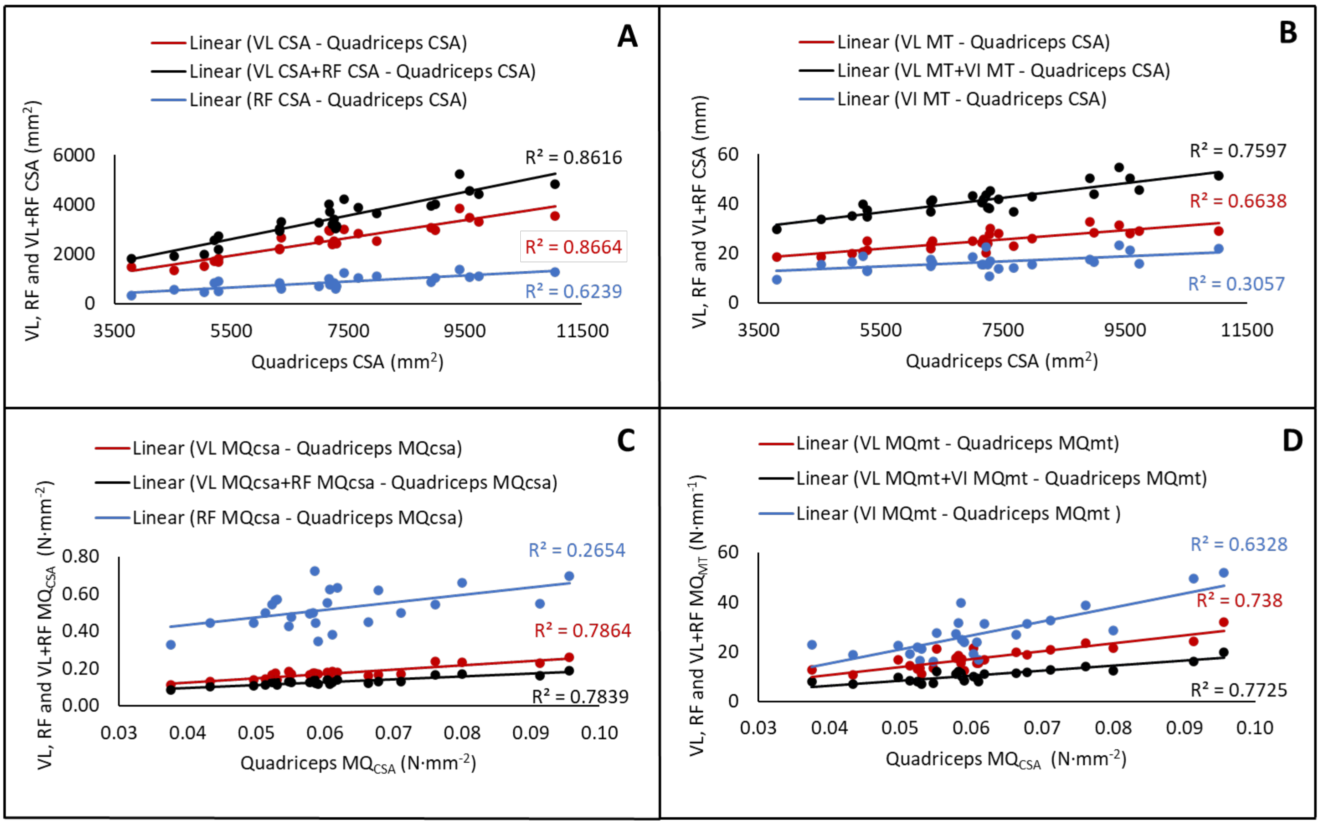


Figure 9. Correlations between ultrasound derived measures of single quadriceps muscles (VL, RF and VI) size and quality with magnetic resonance imaging derived quadriceps size and quality measures.

A) Correlation between quadriceps cross-sectional area acquired by magnetic resonance imaging with VL CSA, VL+RF CSA and RF CSA acquired by Ultrasound extended field of view imaging; B) Correlation between quadriceps CSA acquired by magnetic resonance imaging with VL thickness, VL+VI thickness and VI thickness acquired by US imaging; C) Correlation between quadriceps quality using CSA by magnetic resonance imaging with VL quality, VL+RF quality and VI quality using CSA by ultrasound extended field of view imaging. D) Correlation between quadriceps quality using CSA by magnetic resonance imaging with VL quality, VL+VI quality and VI quality and using muscle thickness by ultrasound imaging.

Vastus Lateralis; VI: Vastus Intermedius; RF: Rectus Femoris; MQ_{mt}*: Muscle quality using muscle thickness;* MQ_{ACSA}*: Muscle quality using anatomical cross-sectional area.*

3.4. DISCUSSION

Ultrasound measurements of VL-CSA and RF-CSA showed an excellent inter-machine correlation according to the ICC scores, but the LOAs showed the degree of error between the MRI and ultrasound measures of CSA when interpreting results in longitudinal studies. In addition, VL-CSA, VL-MT and VL L_f and pennation angle using EFOV ultrasound images showed a good to excellent intra-rater and inter-rater reliability, based on the ICC scores, but the LOAs should be considered when interpreting changes in these parameters. Measurements of VL-MQ_{ACSA} and size using ultrasound imaging can be used as good representations of overall quadriceps MQ_{ACSA} and quadriceps size assessed by MRI.

All muscle architecture and size measures reported in this study showed good to excellent intra-rater reliability based on the ICC scores, similar to previous studies (Pardo et al., 2018, Franchi et al., 2018, Betz et al., 2021, Reeves et al., 2004a, Bemben, 2002, Raj et al., 2012, Franchi et al., 2020b, Noorkoiv et al., 2010b, Noorkoiv et al., 2010a). Furthermore, the low intra-rater coefficient of variation when analysing VL-CSA ultrasound images shows that the criteria used to acquire and measure VL-CSA described in the methods of this chapter was consistent between measurements. However, it should be noted that the coefficient of variation reported in this study for VL-CSA derived via ultrasound was ~3 times higher than that reported for the quadriceps ACSA measured with MRI (Erskine et al., 2009). This higher variability in ultrasound-derived ACSA will lead to a higher chance of false negative changes in ACSA in response to e.g., training or disuse when derived from ultrasound compared to those derived from MRI, and reduce the chance of finding significant differences during longitudinal studies (chapter 6).

A measure of specific force (Reeves et al., 2004b), was not tested for reliability in this chapter because in chapter 6 it was decided to use VL-ACSA and VL-MQ using ACSA, rather than PCSA. Previously, a variability of >8% for specific force has been reported (Erskine et al., 2009). Even if a simplified version of this measure was implemented, where MVC was normalized to PCSA only, the variability of the measure would be ~4 times higher than that when using ACSA (Erskine et al., 2009). Using ultrasound images, this variability will inevitably be higher, as ultrasound images are not as clear as MRI images, and compounded by errors in the L_f needed for the calculation of PCSA. For these reasons and our aim to assess changes in VL size and MQ after in-hospital recovery, follow-up measures were VL-ACSA and VL-MQ that are not compounded by errors in L_f.

The inter-rater reliability was largely similar, however L_f and pennation angle quantified using conventional ultrasound imaging showed low inter-rater reliability. This contrasts with a previous study that reported a good inter-rater reliability of gastrocnemius architecture with conventional US imaging (König et al., 2014). The difference may be due to the setup of the study. While König et al. (2014) used a custom-built probe holder, this was not the case in the present study. In addition, the custom-built probe holder was placed by the same operator that therefore secured a standardized probe angle position that reduced variation in L_f and pennation angle between measurements.

It was found that the intercept method overestimated L_f and underestimated pennation angle. This is somewhat surprising as the concave curvature of VL fascicles are expected to result in longer L_f using EFOV US images, as the intercept method consider fascicles as a straight line (Franchi et al., 2020a). This surprising finding might be explained by the lower pennation angle in conventional US imaging that geometrically will result, at a given MT, in a larger L_f, and due to a reduced MT close to the origin and insertion of VL that discounts the assumption of MT being similar along the length of the muscle in conventional methods. Given that the EFOV has a better inter and intra-rater reliability, and one can see the whole fascicle, it is recommended to use EFOV ultrasound imaging to assess muscle architecture when available.

In the context of this thesis, the inter- and intra-rater error in the ultrasound derived measures are interpreted based on muscle architecture and size adaptations found in previous longitudinal studies. For instance, to be able to assess hypertrophy or atrophy, the changes in VL size should exceed the mean error and LOAs observed here for inter-rater and intra-rater reliability. The increase in VL-CSA after 12-14 weeks of resistance training amounted to up to +360 mm^2 and that of VL-MT up to 2 mm (Franchi et al., 2018, Reeves et al., 2009, Junior et al., 2017), while after 10 days of intensive care atrophy of the VL-MT was up to 3.5 mm (Turton et al., 2016), all exceeding the mean bias found for inter- and intra-rater variability and lying outside the ULOA, in the case of hypertrophy studies, and the LLOA, in the case of atrophy studies. It should be noted that the CSA training changes observed in the literature is inside the error observed between ultrasound and MRI measures therefore these two methods should not be used interchangeably in the same study to compare measurements. The VL L_f and pennation angle can increase by up to 16 mm and 5.8°, respectively after 10-14 weeks of resistance training (Santanielo et al., 2020, Reeves et al., 2009) or be reduced 25mm and 3.1° respectively after 10 days of intensive care (Turton et al., 2016). These changes are larger the mean bias and lie outside of the LLOA and the ULOA in the case of hypertrophy and atrophy changes, respectively, for intra and inter-rater reliability of EFOV ultrasound imaging. Therefore, intra and inter-rater error in the ultrasound derived measures should not prevent assessors from observing changes in VL muscle size and architecture in longitudinal studies due to atrophy or hypertrophy, as previously reported (Ahtiainen et al., 2010), however results from this type of studies should be interpreted carefully.

As the proportional contribution of each muscle to the total quadriceps-CSA varies along the length of the quadriceps muscle and adapts regionally to exercise (Morse et al., 2007, Franchi et al., 2018), it is necessary to standardize the site of size determinations to circumvent any potential site bias. Previous evidence suggests that the ultrasound derived measures of VL-MQ and size at 50% of femur length while patients are sitting with hip and knee at 90^o (Ocana et al., 2021, McPhee et al., 2018, Reeves et al., 2009, Franchi et al., 2018, de Boer et al., 2008) correlate well with quadriceps-MQ and size at full knee extension as determined with MRI, which agrees with a previous study (Noorkoiv et al., 2010a).

The correlations found in this study aligned with those found by Erskine et al, 2009 when a more accurate measure of specific force was used to assess whether VL specific force could represent the whole quadriceps specific force. From all ultrasound muscle size derived measures, VL-CSA and VL-MQ_{ACSA} showed the highest R^2 with quadriceps-CSA and quadriceps-MQ determined by MRI. However, not every ultrasound device has the option of EFOV imaging to capture VL-CSA. Even though ultrasound VL-MT and VL-MQ_{MT} also provide a good representation of quadriceps-CSA and quadriceps-MQ as measured by MRI, it may be further improved when VI-MT and other muscles of the quadriceps are included. It should be noted that correlations were moderate and therefore, VL does not totally represent the whole quadriceps CSA and MQ. Therefore, ultrasound derived measures of VL size and quality may be used as a proxy representative measure of the size and quality of the quadriceps that can be readily applied in a clinical and field setting where MRI is not available.

3.4.1. Considerations

After completion of the analyses of the VL-CSA for this chapter and chapter 6 it was found that the VL was outlined incorrectly, as presented in Figure 8 B.1. The size of this error is illustrated by the LOAs reported in Table 2 for inter-machine reliability. This error should be considered by the reader when interpreting the results in chapter 6.

When possible, only one assessor should acquire the images and perform their analysis as intra-rater reliability showed a lower 95% LOA than inter-rater reliability. Similarly, to assess muscle architecture EFOV ultrasound imaging should be chosen over conventional ultrasound images. In addition, when EFOV ultrasound images is available VL-CSA at 50% of relative femur length is the most representative measure of quadriceps-CSA. In the same sense VL-MQ_{ACSA} was the most representative measure of quadriceps-MQ.

In this study images were acquired at 50% relative femur length. Acquisition of images at a lower or higher relative femur length may vary the associations presented here (Morse et al., 2007) between individual quadricep muscles size and MQ with total quadriceps size and MQ due to the anatomical shape of individual muscles of the quadriceps group.

This chapter was conceived to better understand the potential error of the ultrasound measurements performed in chapter 6, to inform interpretation of the longitudinal changes found in VL size and quality. Knowing that the PCSA has a ~4 times larger coefficient of variation than the ACSA (Erskine et al., 2009), MQ derived from ACSA may be a better measure than that derived from the PCSA for comparative purposes even though the actual MQ is overestimated. Only the measure VL-MT when assessed intra-rater reliability showed signs of heteroscedasticity when observing Bland-Altman plots (Appendix 2, Figure 29). Therefore, it can be assumed that the mean bias and SD of error for intra-rater, inter-rater and inter-machine reliability remains constant independently of the size of the measures but for VL-MT, thus higher intra-rater error maybe found when assessing bigger muscles. Therefore, in Table 2 VL-MT LOA for intra-rater reliability is also reported as coefficient between the two measures.

Assessors taking images were inexperienced in the use of MRI and ultrasound devices, therefore the learning process of data collection should be taken into consideration when interpreting this data. The LOA presented here may be reduced when assessors acquire experience with the ultrasound and MRI devices. Thus, the longitudinal ultrasound imaging data presented in chapter 6 may be subject to a reduced intra-rater error effect than reported here. Despite this, the LOA presented in this study will be used in the interpretation of the findings of studies in this thesis.

3.4.2. Limitations

When collecting MRI images, participants had the knee fully extended, while during ultrasound image acquisition the knee was in a 90° flexed position. Given that muscle volume does not change with contraction or length changes (Swammerdam, 1693), such differences in position will have an impact on VL CSA, observing a larger quadriceps CSA when the knee is extended. This may explain why the mean bias of RF measurements was positive, however in the case of VL the mean bias was negative. Therefore, even though the effect of the knee position should be acknowledged as a limitation that may impact the error between MRI and ultrasound imaging measures, due to the opposite direction of the mean bias found in RF and VL measures, this effect may be negligible when concluding whether ultrasound imaging was reliable, based on the data of this particular study.

The results of this this study are exploratory, statistical power was not calculated. The number of participants in the study was based on previous studies that measured the reliability of muscle ultrasound images (Franchi et al., 2020b, Pardo et al., 2018, Ahtiainen et al., 2010).

It should be noted that data collection of this study was performed during the COVID-19 pandemic when there were restrictions to access lab facilities and complete human studies. Due to these restrictions, it was not possible to recruit the expected number of participants (N=30). Furthermore, due to the mentioned instability on rules about granted lab access, intra-rater reliability had to be assessed with intra-sessions repeated measures (Franchi et al., 2020a) to avoid the loss of follow-up data. Intra-rater reliability muscle ultrasound images has been assessed with intra-session repeated measures previously (Franchi et al., 2020a).

3.4.3. Conclusions

Ultrasound derived measures of VL size and architecture show a good correlation with MRI-derived values, but there is significant error as seen by the LOAs in ultrasound-derived values that should be considered when interpreting changes in VL size. The method used to outline the VL-CSA in this thesis consistently overestimated VL-CSA. Therefore, when interpreting changes in VL size (chapter 6), the systematic overestimation of VL ACSA should be considered.

All size and architectural parameters using EFOV images show a good to excellent intra-rater and inter-rater reliability based on ICC values. Individual ultrasound derived measures of VL-MQ and size at 50% relative femur length can be used as a good estimation of quadriceps-MQ and size in remote or clinical settings where MRI is unavailable or impractical to assess quadriceps MQ and size.

CHAPTER FOUR: LOWER MUSCLE QUALITY IN PATIENTS PREPARING FOR HEPATOBILIARY SURGERY COMPARED TO AGE-MATCHED MASTER ATHLETES AND HEALTHY NON-ATHLETES

What it is known	What will be assessed
- VL ultrasound images demonstrate good inter-rater, intra-rater and inter-machine reliability. In addition, measurement of the VL architecture and thickness accurately represents the quadriceps-CSA. - MAs are a good model of healthy ageing due to their high levels of physical activity that preserve the function of their physiological systems in advancing age. - Patients waiting for major abdominal surgery with lower physical function are under higher risk of adverse surgical outcomes.	- Whether VL size and function are different between MAs, an old healthy population and patients waiting for major abdominal surgery.

4.1. INTRODUCTION

Reduced muscle function can lead to general weakness in old age (Angulo et al., 2020) and is closely related with an increased risk of poor surgical outcomes (Wolters et al., 1996). Muscle size and function are therefore an important factor to consider when planning major abdominal surgery, as the majority of patients are over 60 years old (Myers et al., 2020), a point in life at which muscle size and function has started to or already undergone significant decline. Age-related loss of muscle mass can be accelerated in the presence of disease in the form of cachexia (Fearon et al., 2011), something common in hepatobiliary surgery patients (Tanji et al., 2022, Bachmann et al., 2008)

The age-related reduction in force generating ability of muscle tissue is mainly attributable to muscle atrophy, but the ability to produce force of the remaining muscle is also reduced (Zoladz, 2019, Delmonico et al., 2009). This may be caused by a number of factors, such as loss and atrophy of type II fibres (McPhee et al., 2018), IMAT infiltration (Goodpaster et al., 2000, Goodpaster et al., 2001) and an increased proportion of denervated muscle fibres (Degens, 2018). The above-mentioned age-related muscle changes may lead to Sarcopenia. These two conditions impair muscle morphology and function and have been seen to be related to poor major abdominal surgical outcomes (Aleixo et al., 2020, Jones et al., 2017).

Even though age-related decline in muscle function cannot be stopped (Ocana et al., 2021), MAs show greater muscle size (Piasecki et al., 2019) and function (Pearson et al., 2002), combined with better cardiopulmonary fitness (McKendry et al., 2018), than their sedentary counterparts. Thus, MAs are assumed to have a highly active lifestyle during life, making them a good model for healthy muscle ageing (Gremeaux et al., 2012, Lepers and Stapley, 2016, Geard et al., 2017, Hawkins et al., 2003).

The assessment of sarcopenia in hepatobiliary surgery patients is mainly based on muscle MRI or CT (Jones et al., 2017). These clinically applied measures do not consider the force generating capacity of the muscle that has been suggested to be a more important factor than muscle mass affecting general quality of life of the older person (Delmonico et al., 2009). It is not surprising then, to observe that muscle function correlates more strongly with physical functionality in older healthy adults (Maden-Wilkinson et al., 2015) and sport performance in MAs (Ocana et al., 2021) than with muscle size.

It remains to be seen whether muscle mass and muscle function of patients scheduled for hepatobiliary surgery, differ from that of old healthy adults and MAs. Understanding these differences between healthy and clinical populations may allow us to better identify those patients at a higher risk of poor surgical outcome as a result of accentuated loss of functionality. It is therefore suggested that the assessment of muscle size and muscle function could identify patients at risk of adverse surgical outcomes, and aid in the deployment of mitigation strategies in a patient treatment pathway to reduce the loss of muscle mass and function.

To understand disease-related muscle changes in hepatobiliary surgery patients, a comparison of muscle structure and function with that of age-matched counterparts who undergo habitual physical activity as part of activities of daily living, or indeed regular exercise training was conducted in this study. This analysis may inform clinical practice in providing normative values for VL muscle thickness and knee extension force at a given age in a healthy *vs.* clinical population. Therefore, the aim of this study was to assess differences in muscle size and/or force between patients scheduled for hepatobiliary surgery, age-matched highly active MAs, and habitually active older adults. It was hypothesized that muscle size and knee extension force are significantly lower in patients scheduled for hepatobiliary surgery than in MA and age-matched healthy people.

4.2. METHODS

4.2.1. Study design

The data collection for this study was approved by the ethical committees NHS Northwest ethics committee (IRAS project ID: 215638) of the Manchester Metropolitan University ethics committee (Ref. 08-09-25’) and University of Jyväskylä ethics committee and validated by the Manchester Metropolitan University ethics committee (Ref. 47608). VL ultrasound images (US) and MVC force were collected from patients scheduled for hepatobiliary surgery at the Manchester Royal Infirmary (MFT) NHS trust during the preoperative anaesthetic consultation. Ultrasound VL images and MVC from age-matched MAs and healthy adults were extracted from previously published data collected from Master track and field sprinters at thew University of Jyväskylä (Korhonen et al., 2009, Cristea et al., 2008) and age matched participants from the Myoage project (McPhee et al., 2018, McPhee et al., 2013).

4.2.2. Participants

All participants included in this study were men aged over ≥60 years. Patients scheduled for hepatobiliary surgery due to cancer that did not have any neuromuscular diseases that would preclude the ability to perform a maximum knee extension and did not undergo neoadjuvant treatment or surgery in the preceding 6 weeks, were recruited from the anaesthetic preoperative assessment clinic at the MFT. This included data from male patients over 60 years old recruited for the study reported in chapter 6.

Data from older healthy adults was obtained from the British population recruited for the myoage project (McPhee et al., 2013). They were active adults that did not compete in any competitive sporting events (McPhee et al., 2013). Old healthy adults were excluded from the study if they had cardiovascular (controlled hypertension was allowed), metabolic, musculoskeletal, neurological or mental conditions, or body mass index <18 or >32 kg/m2 (McPhee et al., 2018).

Data from MAs was obtained from a previous study that recruited sprinters of the Finnish Track and Field Organizations (Cristea et al., 2008, Korhonen et al., 2009). MAs competed systematically in national and international competitions. MAs with cardiovascular, metabolic, musculoskeletal, neurological, or mental health conditions or body mass index <18 or >32 $kg \cdot m^{-2}$ were excluded for this study.

4.2.3. Muscle imaging and maximum knee extension isometric contraction force

Ultrasound images of the VL were taken at 50% of femur length with a linear array transducer of 5 cm in the three cohorts. Image analysis was performed following the same procedures in the three cohorts. ImageJ was used to determine VL-MT (in mm) which was considered the shortest distance between the superficial and deep aponeuroses. The ultrasound device used to collect VL images was the same between patients and old healthy adults (Esaote, MyLab™Gamma portable ultrasound, linear array transducer of 3.0 MHz. - 13.0 MHz, model: Esaote SL1543) but different for MAs' data collection (Cristea et al., 2008, Korhonen et al., 2009).

MVC (in N) during knee extension was recorded with participants sitting on a dynamometry chair with a 90^{o} knee angle for the three cohorts. The chair used to collect the data of patients and old healthy adults was the same while the chair used to collect the data of MAs was different. The dynamometry used to measure force production was different for each cohort.

4.2.5. Statistical analysis

IBM SPSS v27 was used for statistical analysis. The Shapiro Wilk test was used to assess data normality. Data were compared between groups using a one-way ANOVA. Bonferroni-corrected post-hoc t-tests were used to locate significant differences between specific groups.

4.3. RESULTS

Participant's characteristics are reported in appendix 1, Table 11. Body mass was higher in patients (Mean differences [95%CI] vs MAs=10.5 Kg [6.3 to 14.7]) and old healthy adults (Mean differences [95%CI] vs. MAs=7.9 Kg [2.6 to 13.1]) than in MAs ($p \leq 0.019$). The BMI was 11% higher in patients compared to MAs (Mean differences [95%CI] vs MAs=10.5 $kg \cdot m^{-2}$ [1.8 to 4.5], $p<0.01$) but did not differ significantly between old healthy adults and MAs ($p=0.084$). MVC was 37% lower in patients compared to old healthy adults (Mean differences [95% CI] vs MAs= -193 N [-268 to -156]) and 40% MAs (Mean differences [95%CI] vs old healthy adults= -212 N [-242.45 to -142.99]) ($p<0.01$) and did not differ significantly between old healthy adults and MAs ($p=1.000$). VL-MT did not differ significantly between groups (Figure 10A; $p=0.065$).

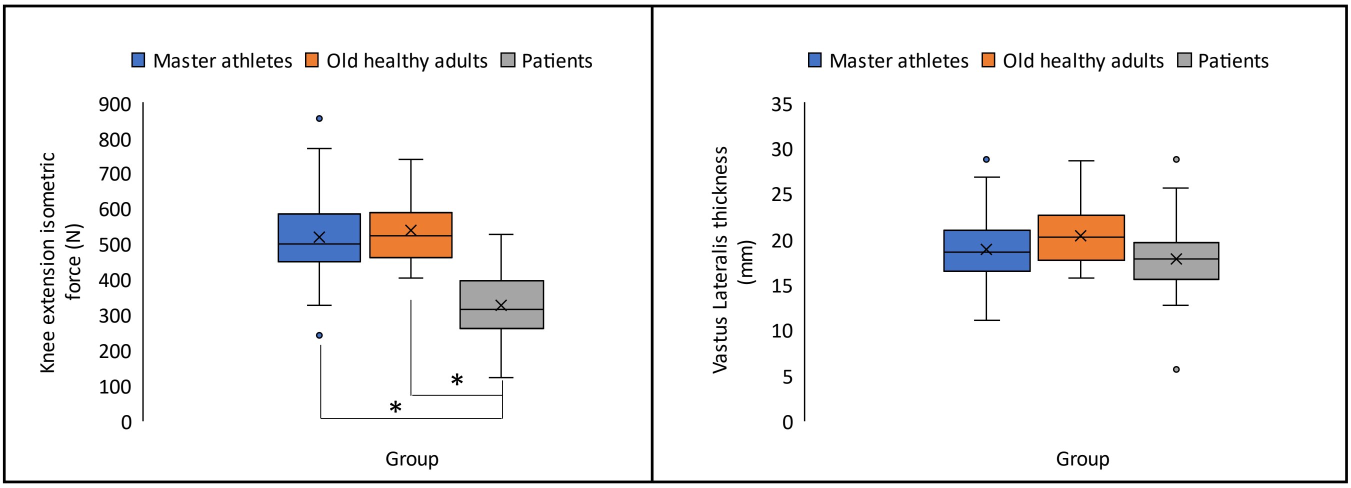


Figure 10. Vastus Lateralis muscle thickness and knee extension force in master athletes, old healthy adults and hepatobiliary patients.

A. Comparison of Vastus Lateralis muscle thickness between groups. B. Comparison of Vastus Lateralis muscle quality between groups.

**Denotes significant difference between groups.*

4.4. DISCUSSION

The main observation of the present study is that patients had a lower force generating capacity, despite similar muscle size, to that seen in age-matched MAs and healthy non-athletes. These findings highlight the importance of considering maximal muscle force generating capacity, rather than muscle size only, given the significance of muscle function for surgical outcomes (Wolters et al., 1996). VL knee extension force may better estimate the risk of surgical outcome of patients waiting for hepatobiliary surgery (scope of chapter 6) and other similar clinical populations affected by disease-related muscle weakness than muscle size.

It has been widely reported that low physical function leads to poor surgical outcomes (Wolters et al., 1996, Jones et al., 2017, Moran et al., 2016b). Given that physical function is determined by muscle function (Maden-Wilkinson et al., 2015, Ocana et al., 2021), assessment of muscle characteristics, such as muscle mass and muscle tissue composition before major abdominal surgery has become useful to prognose surgical outcomes (Jones et al., 2017, Aleixo et al., 2020). This is especially important as patients scheduled for major abdominal surgery are usually over the age of 60 (Johnson et al., 2021, Nally et al., 2019, Krautz et al., 2020), some of whom will suffer from sarcopenia, myosteatosis and weight loss disease-related (Cruz-Jentoft et al., 2019, Fearon et al., 2011).

While patients undergoing cancer upper gastrointestinal surgery due to cancer with stable weight showed similar muscle fibre diameter as other elective abdominal procedure without disease-related weight-loss (Boehm et al., 2020), patients with cachexia (Fearon et al., 2011) or sarcopenia (Zhang et al., 2020), do have smaller muscle fibres when compared to weight stable patients (Boehm et al., 2020). The patients in our study were not sarcopenic or cachectic, as suggested by their normal VL-MT compared to age-matched MAs and healthy non-athletes. Even so, in patients we observed a significantly lower force generating capacity compared to old healthy adults and MAs. It is not possible to determine whether this lower muscle force generating capacity is a direct consequence of the disease or an indirect consequence, where the disease may cause a reduction in habitual physical activity due to fatigue (Jeejeebhoy, 2012, Strasser, 2008) among other factors such as cachexia related disease (Fearon et al., 2011). Whatever the immediate cause of this lower knee extension force, it supports the notion that assessment of knee extension force is more informative than VL size to fully determine acquired muscle weakness and prognosis of surgical outcomes (scope of chapter 6).

Perhaps somewhat surprising was that knee extension force and MT was similar in healthy controls and MAs. This observation does not stand alone. Previously, a similar MT has been seen between old healthy adults and strength-based MAs (Sallinen et al., 2008). In another study, fibre CSA appears to be similar between MAs and old healthy population (Messa et al., 2020). However, in contrast to the findings presented here, Sallinen et al. (2008) showed higher muscle force generating capacity in strength-based MAs compared to old healthy adults. This may be explained by a lower force generating ability in the sprint MAs included in this study compared to strength-based MAs (Häkkinen and Keskinen, 1989).

A similar knee extension force between old healthy adults and MAs do not support the idea that an increased regular physical activity during adult life may enhance the force generating capacity of a muscle. The old healthy adults included here practiced regular physical activity as part of their daily lives, but without competing in athletic events (McPhee et al., 2013). Less active or sedentary behaviour, without disease, may provide a lower muscle function in old healthy adults compared to MAs, confirming that muscle force can be enhanced with healthy physical activity at late stages of life, as seen in previous studies (Pearson et al., 2002, Taveira et al., 2021, Radaelli et al., 2021).

A lower force generating capacity independent of a change in muscle size may be a consequence of a reduced ability to voluntarily recruit the muscle. Reduced voluntary activation has indeed been seen to contribute to the reduced force generating capacity in old age (Degens et al., 2009, McPhee et al., 2018) but it is controversial whether regular exercise improves the ability of voluntary activation (Degens et al., 2009). One could argue that patients will have a lower level of physical activity, but disuse does not appear to result in a reduced voluntary activation (De Boer et al., 2007) and even diseases may not be accompanied with a reduced voluntary activation, as seen for instance in cachectic rheumatoid arthritis patients (Matschke et al., 2010). Nevertheless, it is a distinct possibility, deserving further attention, that part of the loss of force generating capacity in our hepatobiliary cancer patients was attributable to a reduced voluntary activation. Another potential explanation for the reduction in force generating capacity without a change in muscle size might be IMAT accumulation (Delmonico et al., 2009), that in hepatobiliary surgery patients has been related with poor surgical outcomes (West et al., 2019b) (evaluated in chapter 5).

Longer periods of exercise training have been shown to reduce IMAT, that will ultimately improve muscle functionality (Ramírez-Vélez et al., 2021, Tuñón-Suárez et al., 2021). In addition, Given that neuromuscular joints seem to be stable during cachexia (Boehm et al., 2020), strategies that seek to enhance muscle strength by immediate neuromuscular adaptations, such as intermuscular or intramuscular coordination (Moritani, 1993) in patients waiting for abdominal surgery are expected to be beneficial to improve muscle function . In line with this hypothesis, it has been observed that gastro-oesophageal cancer surgery patients can improve knee extension force with a planned and tailored exercise program with a length ranging 11 to 19 weeks during neoadjuvant treatment (Christensen et al., 2018). Exercise programs could therefore be time and cost-effective to improve muscle function in patients waiting for abdominal surgery (Koizia et al., 2020, Rostron et al., 2021) with a potential to improve surgical outcomes. Therefore, the relationship of muscle function with surgical outcomes will be assessed in chapter 6.

While muscle tissue composition is an important factor to determine muscle function (Goodpaster et al., 2001), we could not assess changes in muscle tissue composition due to the impossibility of comparing echogenicity between different ultrasound machines used for patients, MAs and old healthy adults (Kim and Kim, 2021). However, the patients had a higher BMI than MAs and healthy adults, and it can therefore be expected that patients had higher IMAT accumulation that may negatively affect muscle function (Berry et al., 2019, Harris-Love et al., 2019, Degens, 2018). IMAT may be revealed by a lower muscle radio intensity attenuation (Goodpaster et al., 2000), something that has recently been included more often in preoperative assessment of the muscular system (Aleixo et al., 2020, Kroenke et al., 2018, Zhuang et al., 2019, West et al., 2019a), due to its association with poor surgical outcomes in patients waiting for major abdominal surgery (Aleixo et al., 2020, Kroenke et al., 2018, Zhuang et al., 2019, West et al., 2019a, van Dijk et al., 2017). Chapter 6 assess whether adding a measure of MQ to the preoperative assessment may further improve the risk stratification strategies currently used in clinical practice.

4.4.1. Study limitation

Measurements of VL-MT were not taken with the same ultrasound device and by the same assessor. Different studies have reported high reliability to measure dimensions of anatomical locations and segments between different US devices (Alfuraih et al., 2023, Bigler et al., 2022). It should be noted that absolute differences of VL-MT lie inside the 95% LOA reported for inter-rater reliability in chapter 3, therefore, the similarity in VL-MT between the three cohorts should be interpreted with caution.

Different load cells were used between populations, however, after posture standardization and appropriate calibration of the load cells, inter-load cell reliability is high in assessing knee extensor MVC (Nordin et al., 2020, Sung et al., 2019).

Finally, it is unlikely that the VL would be affected differently from the other quadriceps muscles by the disease the patients included in this study present with, as the effects of cachexia or muscle disuse are systemic and it is assumed that would affect all muscles similarly (Fearon et al., 2011). Future research should assess differences between populations in quadriceps specific tension (Reeves et al., 2004b) to more accurately understand the factors implicated in the reduced knee extension force observed in patients. Results of this study are exploratory aiming to create new hypotheses. Data from MAs and the healthy age-matched control was collected from previous datasets with the intention of including the biggest number of participants that matched the inclusion/exclusion criteria. Statistical power was not calculated as a result. Therefore, the findings of this studies should be interpreted with caution.

4.4.2. Conclusion

Maximal isometric knee extension force, and not muscle mass, was lower in patients compared to MAs and healthy old participants. The use of muscle mass alone seems to be limited to assess the muscle functionality in patients waiting for hepatobiliary surgery.

CHAPTER FIVE: VENTILATORY INEFFICIENCY TOGETHER WITH LOW PSOAS MUSCLE MASS INDEX CAN PREDICT PREMATURE MORTALITY AFTER LIVER RESECTION AND PANCREATICODUODENECTOMY

What it is known	What will be assessed
- MQ is reduced in patients waiting for hepatobiliary surgery compared to MAs and old healthy adults. Therefore, IMAT-CSA may aid to stratify the risk of liver resection and pancreaticoduodenectomy. - Abdominal muscle mass, abdominal muscle density and cardiopulmonary fitness of patients waiting for hepatobiliary surgery are related to surgical outcomes, independently.	- The relation between abdominal muscle mass, muscle density and the proportion of IMAT compared to abdominal muscle mass with cardiopulmonary fitness of patients waiting for liver and pancreaticoduodenectomy surgery. - Whether the combination of muscle and cardiopulmonary fitness derived parameters enhance liver and pancreaticoduodenectomy surgery prognosis compared to the use of muscle and cardiopulmonary fitness derived parameters independently.

5.1. INTRODUCTION

Low physical function leads to poor outcomes after major surgery (Wolters et al., 1996). The assessment of objectively measurable variables that informs the fitness of patients before major abdominal surgeries is important to inform clinicians of a patients' subsequent premature mortality risk but also for assessment of the impact of surgery on post-operative quality of life. Abdominal CT imaging has become a popular tool to predict surgical outcomes following major abdominal surgery, due to its capacity to assess myosteatosis (low muscle radiation attenuation) and sarcopenia (low SM mass) (Jones et al., 2017, Aleixo et al., 2020). This is an important pre-operative observation, as patients scheduled for major abdominal surgery who present with both conditions -sarcopenia and myosteatosis – show reduced long-term survival (Kroenke et al., 2018, Zhuang et al., 2019).

Patients scheduled for major surgery, in the presence of malignancy in the gastrointestinal system with the same SM, may show different BMI (Martin et al., 2013) suggesting higher or lower adipose tissue accumulation. Therefore, assessing muscle mass in relation to adipose tissue accumulation may better predict surgical outcomes than muscle mass independently. Another point to consider when using CT images as a risk stratification tool is its protocol standardization for RA comparison between participants (Amini et al., 2019, Kim and Kim, 2021). Variation between image acquisition protocols may produce variability in RA scores, leading to misinterpretation of results. Therefore, knowing that RA is associated with IMAT accumulation (Aubrey et al., 2014), a ratio IMAT/SM may be a stable parameter to assess muscle tissue composition, as in each patient each tissue controls for one another (Kim and Kim, 2021).

Another popular tool to assess the risk of major abdominal surgery is CPET (Moran et al., 2016b). In patients waiting for hepatobiliary and pancreatic surgery, a low AT and high VE/VCO_2 at AT were reported to have a negative association with poor short-term surgical outcomes (short-term survival, LOS and post-operative complications) and long-term survival (Ausania et al., 2012, Chandrabalan et al., 2013, Dunne et al., 2014, Junejo et al., 2012, Junejo et al., 2014).

The relationship between CT-derived parameters and CPET parameters has not yet been explored to a great extent. SM-RA has been positively associated with AT and VO_2 peak in patients waiting for hepatopancreatobiliary surgery (West et al., 2019b). However, the influence of the amount of IMAT infiltration in relation to muscle mass on cardiopulmonary fitness has not yet been evaluated. IMAT infiltration is related to mitochondrial disruption and therefore the ratio IMAT/SM could be better related with cardiopulmonary fitness. As discussed above, although CT- and CPET-derived parameters independently predict risks of abdominal surgery, the predictive value could be further improved when both measures are considered together. Therefore, the objectives of this study are to assess 1) the associations of CT-derived measures with CPET parameters and how this is modulated by adipose tissue accumulation; 2) the impact of CT and CPET parameters separately or 3) in combination on LOS, complications, and 1-year and 3-year mortality. It is hypothesized that IMAT/SM ratio will be associated with poor cardiopulmonary fitness CT-derived measures combined with CPET-derived measures will better predict surgical outcomes compared to their independent use.

5.2. METHODS

5.2.1. Study design

This was a retrospective pilot study approved by the NHS Northwest ethics committee and certified by the Manchester Metropolitan University ethics committee (Ref. number: 34601, date: 10/08/2021). CPET data and CT scans were obtained from the CPET NHS Manchester Foundation Trust research databases. Data from patients that underwent a pancreaticoduodenectomy or liver resection surgery due to cancer disease between 2009 and 2020 by the same surgeon (AKS) was consulted for analysis. To be included, the patients' dataset required a full outcome data set which included CT scans and CPET data within 3 months prior surgery. Patients undergoing neoadjuvant therapy, or with incomplete data set were excluded from analysis. (Figure 11). Patients scheduled for major abdominal surgery selected for CPET at Manchester University NHS Foundation Trust are ≥60 years or <60 years with a known cardio-respiratory disease.

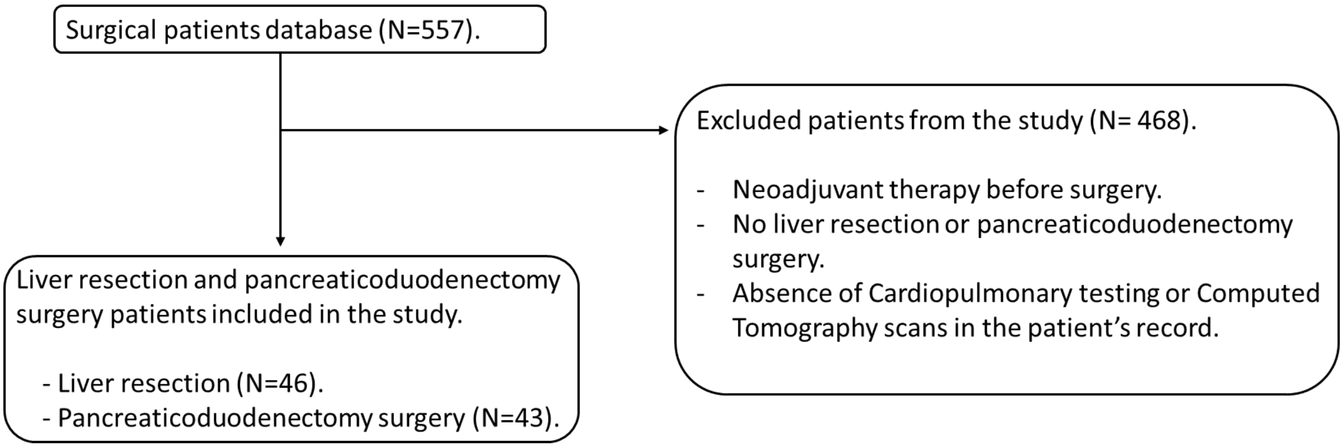


Figure 11. Flow chart of the patient's selection process.

5.2.2. Body composition analysis. Computed tomography imaging.

Abdominal CT images taken as close as possible to the date of surgery (mean days from CT scan to operation day (IQR): 35 (11-62) days) were segmented in an anonymised and blinded format by a trained researcher (PDO) using a semi-automated image-analysis system (3D slicer v. 4.11.20210226 for Microsoft Windows). Two images at L3-L4 (one with L3 totally visible and another one at the lowest level of L4 in which the iliac crest was not visible) were segmented to calculate muscle and adipose tissue CSAs using previously reported HU (West et al., 2019b). Thus, for each image the next segments were computed (Figure 12), and the mean value of the two obtained segments for each patient was used for further analysis:

- Psoas muscle CSA (P-CSA, -29 to 150 HU, in cm^2).
- Total abdominal muscle CSA (SM-CSA, -29 to 150 HU, in cm^2).
- Subcutaneous adipose tissue CSA (SAT-CSA, -190 to -30 HU, in cm^2).
- Intra-muscular adipose tissue CSA (IMAT-CSA, -190 to -30 HU, in cm^2).
- Visceral adipose tissue CSA (VAT-CSA, -150 to -50, in cm^2).

Mean HU of SM-CSA and P-CSA was taken as a measure of SM-RA and psoas radio attenuation (P-RA) that is associated with increased IMAT infiltration (Aubrey et al., 2014). SM-CSA and P-CSA were normalized to the height squared of the patient to obtain SM-index and P-index (P-index) (both in cm^2·m^{-2}). Lastly, three ratios were created to assess the relationship between muscle mass and adipose tissue accumulation: SM-CSA/SAT-CSA, SM-CSA/VAT-CSA and IMAT-CSA/SM-CSA. Indexes and ratios were used to assess associations between CT-derived measures and CPET parameters and the impact of CT-derived measures on surgical outcomes.

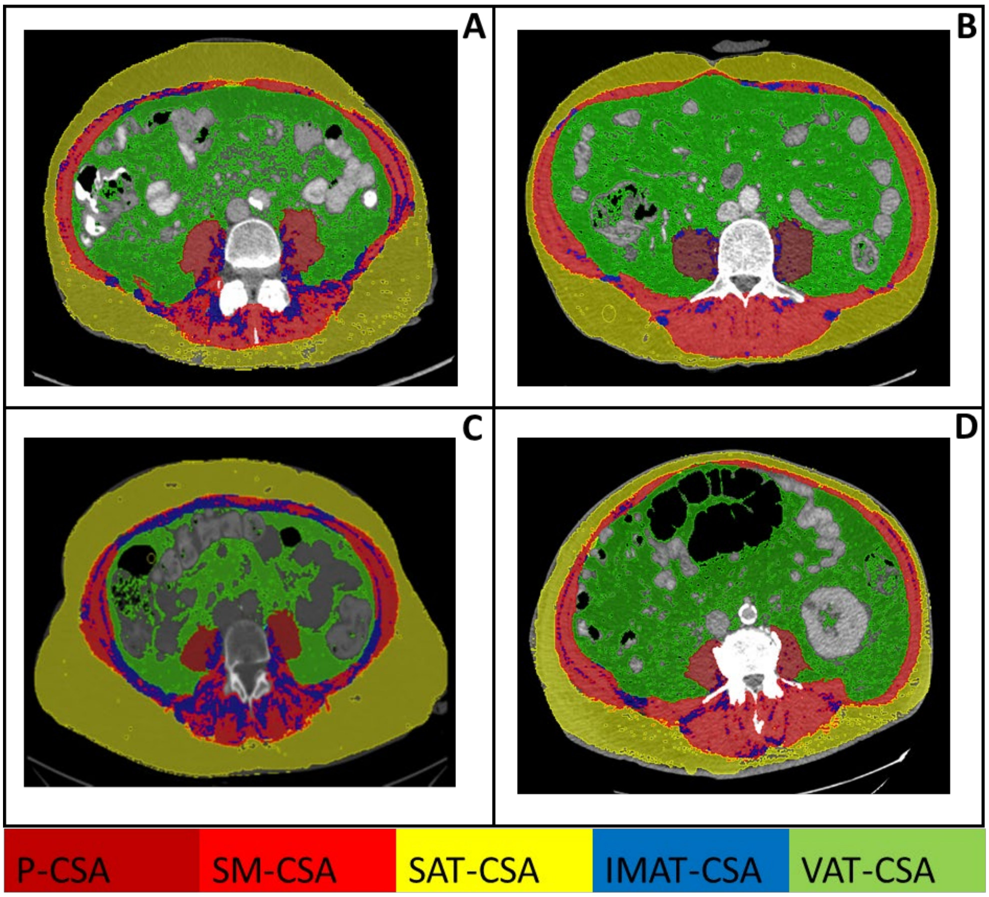


Figure 12. Skeletal muscle segmentation from computed tomography scan.

A. BMI: 22.2, IMAT-index/SM-index: 0.096; B. BMI: 22.1, IMAT-index/SM-index: 0.018; C. BMI: 29.7, IMAT-index/SM-index: 0.148: D. BMI: 30.2, IMAT-index/SM-index: 0.043.

SM-CSA: skeletal muscle cross-sectional area (-29 - 150 HU); P-CSA: psoas muscle cross-sectional area (-29 – 150 HU); SAT-CSA: subcutaneous adipose tissue cross-sectional area (-190 - -30 HU); IMAT-CSA: intramuscular adipose tissue cross-sectional area (-190 - -30 HU); VAT-CSA: visceral adipose tissue cross-sectional area (-150 - -50 HU). SM-CSA is the sum of P-CSA and the rest of muscle tissue area coloured in red.

5.2.3. Cardiopulmonary fitness. Cardiopulmonary exercise testing parameters.

Analysed variables from the patients CPET were searched for each included patient by an informatics specialised in Structured Query Language. Every patient performed the CPET using a cycle ergometer and gas exchange analysis system (Ultima™ CardiO2® MedGraphics (Medical Graphics, St Paul, MN, USA), which were linked with a BreezeSuite™ software package (Medical Graphics, St Paul, MN, USA) to collect breath by breath gas samples while patients performed a CPET (mean days from CPET to operation (IQR): 22 (14-47) days). CPET followed international and European standards (Guazzi et al., 2012b, Weissman et al., 2003). In brief, the protocol consisted of 3 min of unloaded cycling at 60 RPM followed by 6-10 min of ramped incremental cycling until volitional exhaustion and a warm down of 2-5 min. The ramp gradient was set at 10-20 $W \cdot min^{-1}$. The variation in the ramping gradient depended on an algorithm using the predicted freewheel VO_2, VO_2 peak, sex, height, and age. VO_2 peak (in $mL \cdot kg^{-1} \cdot min^{-1}$), VO_2 at AT (in $mL \cdot kg^{-1} \cdot min^{-1}$) and VE/VCO_2 slope were used for further analysis. VO_2 peak was the average VO_2 over the last 30 s of exercise before volitional exhaustion (Wasserman, 2012). AT was determined as the VO_2 ($L \cdot min^{-1}$) at the breakpoint in the VCO_2-VO_2 relationship (Weissman et al., 2003). The AT was manually interpreted by a qualified CPET physician/clinical scientist, registered with Perioperative Exercise Testing and Training Society (POETTS), using the modified V-slope method (Sue et al., 1988) supported by ventilatory equivalents for O_2 and CO_2 and end-tidal partial pressures of O_2 and CO_2 in accordance with ATS/ACCP guidelines (Weissman et al., 2003) for perioperative CPET. VE/VCO_2 slope was the ratio of VE by CO_2 production. The calculation used the data from the beginning of loaded exercise to peak effort (Guazzi et al., 2012a). CPET were supervised by a qualified specialist nurse and a clinical scientist or anaesthetist. VO_2 peak and AT was determined as described above by a CPET qualified clinical scientists or an anaesthetist for diagnostic purposes.

5.2.4. Surgical outcomes

LOS, critical care LOS, number of post-operative complications, and number of post-operative severe complications were recorded as short-term surgical outcomes. All complications during the inpatient stay were recorded. Post-operative complications were defined as adverse events after surgery scored as grade ≥I in the Clavien-Dindo scale, in the same way those complications scored as grade ≥III were considered severe post-operative complications (Clavien et al., 2009). Mortality was followed up to 3 years for every patient.

5.2.5. Statistical analysis

This is a pilot study and hence the analyses presented here are mainly descriptive. Any statistical test was for exploratory and hypothesis generation purposes only and should be interpreted with caution. Statistical analysis was performed with SPSS (IBM v.27.0). Normality of data was assessed using the Shapiro-Wilk test. Pearson or Spearman correlations, where appropriate, were used to assess correlations between CT indexes and ratios with CPET parameters. If more than one CT index or ratio was associated with the same CPET parameter, a simultaneous multivariate linear regression was performed adjusted to age and sex. Those independent variables with a P-value above 0.05 were discarded from the model (Tabachnick and Fidell, 2014). To assess if any CPET parameter or CT index or ratio had a significant association with short-term surgical outcomes, Pearson, Spearman, or univariate binary logistic analysis, where appropriate, was performed. If more than one CPET parameter, CT ratio or index was associated with the same short-term surgical outcome, a multiple linear regression or multiple binary logistic regression were performed adjusted to age and sex. Those independent variables with a P-value above 0.05 were discarded from the model. Similarly, 1-year and 3-year univariate Cox regression analysis was performed with the CPET parameters and CT indices and ratios to find independent associations with 1-year and 3-year mortality. If more than one CPET parameter or CT ratio or index was associated with 1-year or 3-year mortality a forward Wald Cox regression analysis was performed adjusted to age and sex. Those independent variables with a p-value above 0.05 were discarded from the model. CT and CPET parameters significantly associated with premature mortality were further explored creating categorical-dichotomous variables using the median value as cut-off (Altman and Bland, 1994). CT parameters cut-off was sex specific (Higashi et al., 2016, Kim and Kim, 2021). Hazard ratios of the created categorical-dichotomous variables were calculated using a univariate Cox regression analysis. Sensitivity and specificity of significant dichotomous variables was assessed.

5.3. RESULTS

All patients underwent a Liver Resection or Pancreaticoduodenectomy due to cancer. Patients' Clinical characteristics are reported in Table 3.

Table 3. Patient characteristics.

Liver resection patients and pancreaticoduodenectomy patients	
Patients' clinical characteristics	Value
Number of patients	89
Men	64%

Women	36%
Age (yrs)	70 (64-74)
BMI (kg·m^{-2})	25 (22-28)
VO_2 peak (mL·kg^{-1}·min^{-1})	16.5 (14.5-36.3)
AT (mL·kg^{-1}·min^{-1})	11.7±2.0
VE/VCO_2 slope (AU)	32.1 (27.2-36.3)
SAT-index (cm^2·m^{-2})	57.4 (40.7-82.9)
VAT-index (cm^2·m^{-2})	346 (169-572)
IMAT-index (cm^2·m^{-2})	5.4 (2.9-8.5)
SM-index (cm^2·m^{-2})	45.7±8.1
SM-RA (HU)	33.7±8.4
P-index (cm^2·m^{-2})	7.2±1.8
SM-CSA/SAT-CSA	0.79 (0.53-1.21)
SM-CSA/VAT-CSA	0.14 (0.09-0.24)
IMAT-CSA/SM-CSA	0.11 (0.06-0.19)
Relevant blood parameters	
Bilirubin (μmol·L^{-1})	10.0 (7.0-19.3)
Urea (mmol·L^{-1})	5.8±3.1
Albumin (g·L^{-1})	34.8±7.3
Creatinine (μmol·L^{-1})	79.4±27.0
Haemoglobin (g·L^{-1})	122.4±17.2
1-year mortality (No. patients died)	25 (28.1%)
3-year mortality (No. patients died)	43 (48.3%)
Post-operative complications (N_o events)	41 (46%)
Severe Post-operative complications (N_o events)	11 (12%)
LOS (days)	13 (8-20)
Critical care length (days)	4 (3-6)

AT: anaerobic threshold; BMI: body mass index; CSA: Cross-sectional area; IMAT: Intramuscular abdominal adipose tissue; LOS: Length of stay in hospital; P: total abdominal Psoas; RA: Muscle radiation attenuation; SAT: Subcutaneous abdominal adipose tissue; SM: Total abdominal skeletal muscle; VAT: Visceral abdominal adipose tissue; VE/VCO_2: Ventilatory equivalents of CO_2; VO_2 peak: oxygen uptake at peak.

Post operative complications were those complications considered as <3 in the Clavien-Dindo scale and severe post-operative complications were considered as >3 in the Clavien-Dindo scale (Clavien et al., 2009).

Data is presented as mean±standard deviation, median (IQR) or N (%)

5.3.1. Association between CT-derived measures and CPET measures.

Univariate regression analysis with cardiopulmonary fitness as dependent variables and CT-derived parameters as independent variables is reported in Table 4. There was a positive correlation between VO_2 peak with SM-CSA/VAT-CSA, SM-CSA/SAT-CSA, IMAT-CSA/SM-CSA, SM-RA, and P-index (All $p<0.05$). AT was positively correlated to IMAT-CSA/SM-CSA, SM-CSA/VAT-CSA, and SM-CSA/SAT-CSA (All $p<0.05$). Only P-RA was correlated to VE/VCO_2 slope ($p=0.042$). The multivariate regression model showed that only IMAT-CSA/SM-CSA and being male was associated with VO_2 peak and IMAT-CSA/SM-CSA was associated with AT (Table 5).

Table 4. Univariate regression model with cardiopulmonary fitness parameters as dependent variables and CT-derived parameters as independent variables.

Univariate regression model			
Dependent variable	Independent variable	R-value	P-value
VO_2 peak ($mL \cdot kg^{-1} \cdot min^{-1}$)	SM-CSA/VAT-CSA	0.215	0.048*
	SM-CSA/SAT-CSA	0.271	0.012*
	IMAT-CSA/SM-CSA	0.299	<0.001*
	SM-RA	0.257	0.019*
	P-index	0.251	0.020*
AT ($mL \cdot kg^{-1} \cdot min^{-1}$)	IMAT-CSA/SM-CSA	0.318	<0.001*
	SM-CSA/VAT-CSA	0.281	0.011*
	SM-CSA/SAT-CSA	0.261	0.018*
VE/VCO_2 slope	P-RA	0.223	0.042*

AT: Anaerobic threshold; IMAT-CSA: Intramuscular abdominal adipose tissue cross-sectional area; P-index: Psoas index; P-RA: Psoas radiation attenuation; SAT-CSA: Subcutaneous adipose tissue cross sectional area; SM-CSA: total abdominal skeletal *muscle cross-sectional area; SM-RA: Skeletal muscle radiation attenuation; VAT-CSA: Visceral adipose tissue; VE/VCO2 slope: ratio of minute ventilation (VE) by CO2 production; VO2 peak oxygen uptake at peak.*

Denotes significant association between variables.

Table 5. Multivariate linear regression analysis.

Multivariate regression model				
Dependent variable	Independent variable	Unstandardized Beta [95%CI]	R^2	p-value
VO_2 peak ($Ml \cdot kg^{-1} \cdot min^{-1}$)	IMAT-CSA/SM-CSA Sex (being male)	-10.793 [-19.352 to -0.013] -2.037 [-3.826 to -0.249]	0.093 0.147	0.014* 0.026*
AT ($ml \cdot kg^{-1} \cdot min^{-1}$)	IMAT-CSA/SM-CSA	-7.620 [-12.443 to -2.798]	0.110	<0.01*

AT: Anaerobic threshold; VO_2 peak oxygen uptake at peak; SM-CSA: total abdominal skeletal muscle cross-sectional area; IMAT-cs: Intramuscular abdominal adipose tissue cross-sectional area.

Sex was a dichotomous variable that uses 1 to determine that the patient is male and 2 to determine that the patient is female. to determined that the patient is not a male and 1 to determine that the patient is a male.

**Denotes significant association between variables.*

5.3.2. The association of CT-derived measures and CPET measures with surgical outcomes

VO_2 peak was the only parameter negatively correlated with LOS (p=0.017, R=-0.259). None of the CT indexes and ratios or CPET parameters were significantly associated with LOS in critical care, post-operative complications, post-operative severe complications.

Univariate Cox regression analysis showed that only P-index was negatively associated with 1-year mortality (p=0.012), and P-index, AT, VO_2 peak, and VE/VCO_2 slope (All p<0.05) were significantly associated with 3-year mortality. However, the multivariate Cox regression model showed that only high VE/VCO_2 slope and P-index were associated with 3-year mortality (p=0.041) (Table 6).

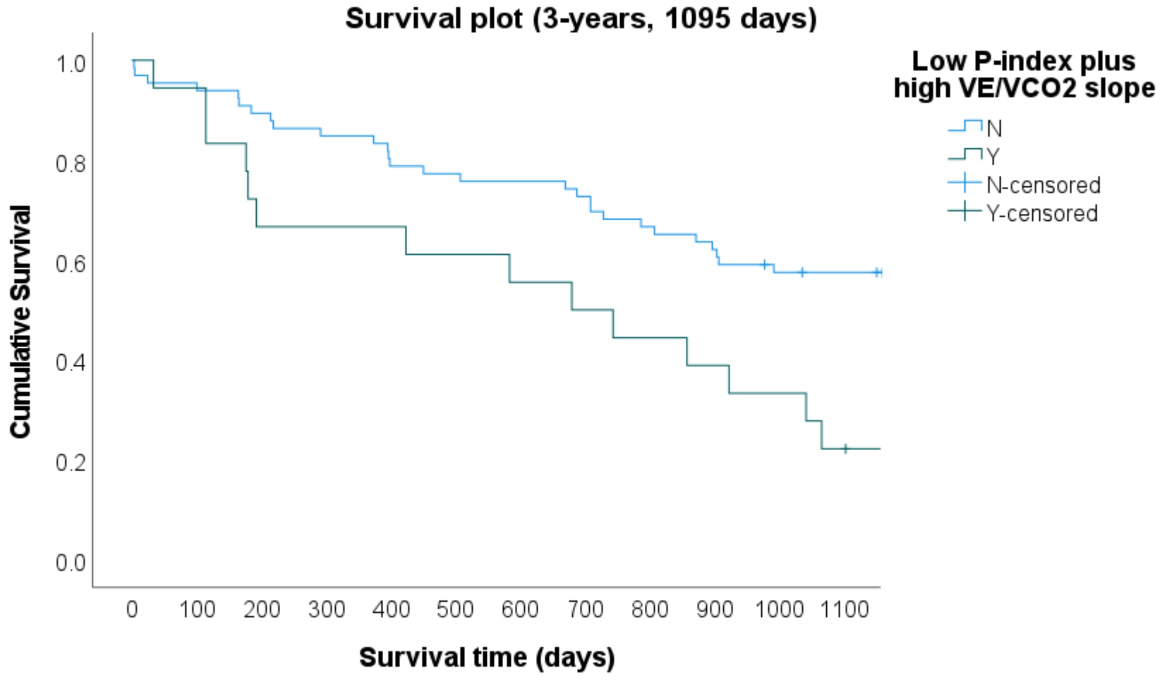
Table 6. Univariate and Multivariate Cox regression models. Cardiopulmonary fitness parameters and CT-derived parameters were used to predict 1-year and 3-year early mortality.

Dependent variable	Independent variable	HR [95% CI]	P-value
Univariate Cox regression model			
1-year early mortality	P-index	0.645 [0.460-0.907]	0.012*
3-year early mortality	P-index AT VO_2 peak VE/VCO_2 slope	0.830 [0.699-0.984] 0.822 [0.707-0.955] 0.910 [0.845-0.979] 1.041 [1.012-1.070]	0.035* 0.011* 0.012* 1.017*
Multivariate Cox regression model			
3-year early mortality	VE/VCO_2 slope P-index	1.041 [1.012-1.070] 0.830 [0.699-0.984]	0.041*

AT: Anaerobic threshold; P-index: Psoas index; VO_2 peak oxygen uptake at peak; VE/VCO_2 slope: ratio of minute ventilation by CO_2 production.

**Denotes significant association between variables.*

Thus, 3 categorical-dichotomous variables, based on the median values were created with two groups of patients in each: 1) patients with high (>7.5 $cm^2 \cdot m^{-2}$ for males and >5.9 $cm^2 \cdot m^{-2}$ for females) versus low P-index (<7.5 $cm^2 \cdot m^{-2}$ for males and <5.9 $cm^2 \cdot m^{-2}$ for females), 2) patients with high (>32.1) versus low VE/VCO_2 slope (<32.1), and 3) patients with high VE/VCO_2 slope and low P-index versus patients with low VE/VCO_2 slope and high P-index. No significant relationships were found between the created dichotomous variables and 1-year mortality (p>0.05). Only patients with both a low P-index and a high VE/VCO_2 were found to have higher risk of premature mortality 3-years after surgery (HR [95%CI]: 2.471 [1.292-4.723], p<0.01) (Figure 13). The sensitivity and specificity were 90.7% and 34.1%, respectively.



Number of patients at risk

	High VE/VCO$_2$ slope>32.1 and high P-index < 7.5 cm^2·m^{-2} (M) and 5.9 cm^2·m^{-2} (F)	Low VE/VCO$_2$ slope <32.1 and low P-index>7.5 cm^2·m^{-2} (M) and 5.9 cm^2·m^{-2} (F)
Baseline	18	66
1 year	12	56
2 years	9	45
3 years	4	38

Figure 13. 3-year Survival plot.

N: No; P-index: Psoas muscle index; VE/VCO$_2$ slope: slope of ventilatory equivalents of CO2; Y: Yes.

5.4. DISCUSSION

This data suggests that there is a negative association between IMAT-CSA/SM-CSA and the cardiopulmonary fitness of patients, but this ratio was not associated with any surgical outcome. P-index and VE/VCO$_2$ were positively and negatively associated, respectively, with 3-year mortality. When patients were divided into discrete groups, to explore which groups of patients may show different long-term survival, only those patients who presented low P-index and high VE/VCO$_2$ were at higher risk of dying within 3 years after surgery.

The individual power of CT-derived measures and CPET parameters to prognose surgical outcomes have been previously reported (Jones et al., 2017, Moran et al., 2016b), however what has been explored to a lesser extent is the relationship between cardiopulmonary fitness and muscle characteristics in major abdominal surgery patients. Recently, some authors have reported a negative relation between SM-RA with VO_2 peak and AT in patients waiting for hepatopancreatobiliary (West et al., 2019b) and colorectal surgery (Berkel et al., 2022b). In the present study, even though RA was independently associated with VO_2 peak and AT, it did not appear as a significant predictor in the multivariate regression model, only IMAT-CSA/SM-CSA appeared as significant predictor for VO_2 peak and AT in the multivariate regression model. This finding is to some extent in line with the studies mentioned previously, as SM-RA is an expression of an augmented IMAT infiltration (Goodpaster et al., 2000).

Myosteatosis, is a condition characterized by a reduced RA that leads to disruption of the oxidative phosphorylation causing a higher IMAT accumulation (Gumucio et al., 2019, Stretch et al., 2018, Goodpaster et al., 2000). This mechanism of mitochondrial disruption and IMAT infiltration is associated with insulin resistance (Miljkovic et al., 2013, Muoio, 2010) which is independently associated with low cardiopulmonary fitness (Jun et al., 2013). Even though we did not assess insulin resistance, previous studies have associated myosteatosis to insulin resistance (Correa-de-Araujo et al., 2017, Kim and Kim, 2021). This may well explain why the ratio of IMAT-CSA/SM-CSA was found to be associated with cardiopulmonary fitness outcomes. Additionally, another explanation as to why IMAT-CSA/SM-CSA and not SM-RA was found to be negatively associated with cardiopulmonary fitness in the multivariate regression model is the variability that SM-RA is seen between patients (Amini et al., 2019, Kim and Kim, 2021). IMAT-CSA/SM-CSA can be a stable measure for the quality of the muscle composition as IMAT and SM of an individual patient are pictured using the same CT image acquisition protocol and therefore, they control for one another to some extent. However, the ratio was not associated with any surgical outcome and VO_2 peak was weakly associated to LOS and as well as AT, even that both parameters were independently associated with 3-year mortality, they did not appear as significant independent variables in the multivariate model. While one may find such associations in a larger population, stratifying patients for risk of post-operative surgical outcomes based on IMAT-CSA/SM-CSA, AT or VO_2 peak does not seem adequate. As mentioned above, this data suggests that VO_2 peak weakly correlated with LOS, similar to previous findings that observed a moderate correlation between VO_2 peak and LOS (West et al., 2019b). However none of the CT-derived measures or other CPET parameters were associated with short-term surgical outcomes, in contrast to previous studies performed on the same clinical population (Ausania et al., 2012, Chandrabalan et al., 2013, Dunne et al., 2014, Junejo et al., 2012, Junejo et al., 2014). This lack of association with short term surgical outcomes, such as LOS, maybe due to the presence of other factors with a larger effect on post-operative morbidity, such as intra operative blood loss (Böttger and Junginger, 1999) or lower platelet count (Yang et al., 2011).

While this study suggests that CT-derived measures and cardiopulmonary fitness are not particularly powerful to predict short-term surgical outcomes, P-index and VE/VCO$_2$ slope were associated with 1- and 3-year mortality.

Clinicians and researchers have favoured the use of SM-index over P-index to assess muscle mass (Jones et al., 2017, Hajibandeh et al., 2019), P-index was included in this analysis due to its important involvement in locomotion, daily life activities (Andersson et al., 1997, Penning, 2002, Masuda et al., 2002) and association with cardiopulmonary fitness in the healthy population (Fitzpatrick et al., 2017). Interestingly, only the P-index and not SM-index was associated with 1-year and 3-year survival further supporting the applicability of P-index for risk stratification. This finding is similar to a previous observation found in patients undergoing pancreatectomy that presented with sarcopenia (defined as low P-index) (Okumura et al., 2015), but is in contrast to a previous study that reported higher efficiency of SM-index in predicting premature mortality in patients with liver cirrhosis undergoing surgery compared to P-index (Ebadi et al., 2018). It is difficult to determine if the lack of association of SM-index compared to P-index, in this study, is due to a closer relationship of P-index with the patient's physical activity patterns due to its close relation with locomotory activities. If so, P-index could be considered as a robust indicator of patients' physiological resilience, but its efficiency in determining this should be compared against cost-effective easy to perform and validated functional tests such as the sit-to-stand test, TUG to five times sit to stand test.

A 10-year longitudinal study has shown that changes in P-CSA are only associated with age and not to the amount of physical activity sustained (Murata et al., 2021), and a study assessing changes on anterior hip muscles after 8 weeks of bed rest did not find a significant change in P-CSA after the bed rest (Dilani Mendis et al., 2009). Here, P-index was not related with patients' cardiopulmonary fitness. Further research with a larger population is needed to ascertain whether the use of P-index demonstrates a robust long-term mortality prediction power compared to SM-index in patients waiting for liver or pancreaticoduodenectomy surgery. Moreover, whether the assessment of lower limb muscles, closely related to the amount of physical activity (Rostron et al., 2021), may even better predict long-term survival than P-index may be of interest.

Even though VE/VCO_2 slope and P-index were independently associated with 3-year mortality, when patients were divided into discrete groups to assess groups of patients with different risk of premature mortality, only those patients with the combination of low P-index and high VE/VCO_2 slope had a significantly risk of a higher 3-year mortality. Previous studies with patients scheduled for pancreatic surgery have reported an independent relationship of high VE/VCO_2 at AT and low P-index with higher rate of long-term mortality (Junejo et al., 2014, Okumura et al., 2015). In this study, we observed that both conditions had an additive effect on the risk of 3-year mortality, as those patients only presenting with one of the conditions (low P-index or high VE/VCO_2 slope) did not show a significant risk of 3-year mortality in contrast to those that presented with both conditions. The combination of low psoas index plus high VE/VCO_2 slope showed high sensitivity to identify patients under the risk of premature mortality within the first 3 years after surgery. These findings support the use of CT image analysis and CPET together to better stratify the risk of patients undergoing abdominal surgery. With CPET now well established as a tool to predict the risk of poor surgical outcomes (Benington et al., 2019, Hartley et al., 2012, Grant et al., 2015) and machine learning techniques able to automatically segment abdominal CT scans (Kim et al., 2020), the findings presented here may be tested with larger population to inform precise guidelines about the use of both techniques in conjunction with one another to evaluate physical function and to better stratify the risk of undergoing major abdominal surgery.

5.4.1 Strength and limitations

A unique strength of our analysis is that all patients were operated by one surgeon (AKS), reducing heterogeneity that may arise due to different in surgeon training and experience level (Bilimoria et al., 2009).

This is a single-centre retrospective study with a data collection time-window of 11 years, which is big enough to influence LOS, rate of complications and premature mortality, due to advances in surgical and recovery practices that enhance patient outcomes (Wyld et al., 2015). Furthermore, sample size was not calculated. Thus, results should be verified in a multi-centre prospective study that will control for co-founding variables and reduce the risk of selection bias.

VO_2 peak and not VO_2 max was used to assess patients' maximum aerobic capacity. VO_2 peak is dependent on the patient performing a maximal effort, and so may be affected by psychological factors. The use of VO_2 max is not viable in clinical settings, since reaching it is challenging for the patient, and in most of the cases the patients cease exercise in the CPET due to exhaustion or other reasons, such as chest or leg pain, use of beta-blocking drugs or premature termination by the supervising clinician, before reaching a plateau in the VO_2 consumption *vs* work curve. Even in healthy individuals only ~30% reach VO2 plateau at the end of the CPET (Sietsema et al., 2020). Therefore, despite the limitations of using VO_2 peak to determine a patients' maximum aerobic capacity, VO_2 peak provides objective evidence of a physiological endpoint and hence, its use in clinical settings (Sietsema et al., 2020).

HR CI upper and lower bound observed in the univariate and multivariate Cox regression analysis with P-index and VE/VCO_2 as continuous variables, respectively, were close to 1. Thus, due to the multiple univariate analysis performed in the study results should be interpreted with caution. Moreover, specificity to determine 3-years follow-up mortality in patients with low P-index and high VE/VCO_2 was low, showing a high rate of false negatives and suggesting that other patients' characteristics should be added to this model to better risk assess and triage patients. Prospective research with a larger sample size is needed to verify the results presented here and further understand the influence of muscle mass and cardiopulmonary fitness on premature mortality after liver or pancreaticoduodenectomy surgery.

5.4.2. Conclusion

This study showed that only the patients with a low P-index and high VE/VCO_2 slope were at higher risk of mortality within 3 years after surgery. This finding deserves further exploration with a larger data set, to confirm whether the combination of both conditions represent a higher risk of premature mortality than only one. In addition, the IMAT-CSA/SM-CSA ratio was the only CT derived measure associated with cardiopulmonary fitness.

CHAPTER SIX: CHANGES IN VASTUS LATERALIS SIZE AND ARCHITECTURE AFTER IN-HOSPITAL RECOVERY FROM HEPATOBILIARY SURGERY CANNOT PREDICT SHORT-TERM SURGICAL OUTCOMES AND 6-MONTHS MORTALITY

What it is known	What will be assessed
- P-index and VE/VCO_2 slope can predict 3-year mortality after hepatobiliary surgery. - In-hospital recovery reduces muscle size and power leading to a hospital acquired muscle weakness, that may negatively impact surgical outcomes. - IMAT-CSA/SM-CSA is related to VO_2 peak and AT but neither of them are related to surgical hepatobiliary surgery outcomes. - IMAT negatively impacts muscle strength and therefore reduces MQ. - Muscle speed of contraction is the main determinant of sport performance and physical functionality in MAs and old healthy adults, respectively.	- VL changes in muscle size and architecture and their relationship with 6-month survival after hepatobiliary surgery. - The relationship between VL MQ and cardiopulmonary fitness variables, and whether in combination, these factors are related to surgical outcomes. - The RFD during a knee extension contraction before surgery and to assess this measure as a marker of physiological resilience in hepatobiliary surgery patients and its relevance as a prognosticator of surgery risk.

6.1. INTRODUCTION

The negative impact of the age-related decline of muscle mass, muscle function and cardiopulmonary fitness on hepatobiliary surgical outcomes is widely reported (Aleixo et al., 2020, Jones et al., 2017, Junejo et al., 2014, Junejo et al., 2012). In line with previous observations, in chapter 5, the risk of premature mortality after pancreaticoduodenectomy and liver surgery was increased in patients with high VE/VCO_2 slope plus low P-index. Furthermore, results of chapter 4 indicated that patients scheduled for hepatobiliary surgery experienced a loss of muscle strength, but not of muscle mass compared to healthy adults and MAs. Therefore, the assessment of whether muscle mass and muscle strength are related to hepatobiliary surgical outcomes is warranted.

Several preoperative clinical studies define sarcopenia based on the independent assessment of muscle mass (Jones et al., 2017), whereas EWGSOP suggests the evaluation of muscle functionality to initially identify potential sarcopenic patients, followed by an assessment of muscle mass to confirm the presence of sarcopenia (Cruz-Jentoft et al., 2019). EWGSOP proposes the use of handgrip strength to determine the overall muscle function of an individual. However, knee extension force has been observed to be better related with some health characteristics, such as nutritional status and psychological factors, compared to handgrip strength (Yeung et al., 2018a). Moreover, different studies have reported a low to moderate correlation between handgrip strength and lower limb strength (Samuel and Rowe, 2012, Ostolin et al., 2021, Yeung et al., 2018b) and a cohort study showed a greater loss of lower limb strength compared to handgrip strength with age (Samuel et al., 2012). In addition, it is obvious that the lower limb function has more implications on locomotion and mobility (Sillanpää et al., 2014) than the upper limb function. Thus, the assessment of lower limb strength may be a more holistic measure in informing of the level of general muscle weakness in patients preparing for surgery compared with handgrip strength.

We found that lower limb function of MAs, expressed by take-off velocity in a counter movement jump was related with the age-related decline of indoor cycling performance (Ocana et al., 2021). In line with this finding, take-off velocity and lower limb power have been found to be related with 6 minutes-walk distance performance in older adults, over a mean age of 69 years old (Maden-Wilkinson et al., 2015, Sillanpää et al., 2014). The speed of muscle contraction of lower limb muscles therefore seems to be an important determinant of physical function and mobility. Thus, it may well represent the physiological resilience of patients, aiding in the prognosis of surgical outcomes. However, the association of pre-operative contraction speed and surgical outcomes has not yet been assessed in patients preparing for major abdominal surgery.

The age-related decline in muscle mass affects physical functionality considerably (Dos Santos et al., 2017) with the remaining muscle contractile capacity also impaired, further contributing to the age-related muscle weakness in older adults (Delmonico et al., 2009). This is demonstrated by a greater age-related decrease in knee extension torque compared to the age-related decrease of thigh CSA, which further contributes to an accelerated loss of MQ (the quotient between knee extension torque and thigh CSA) with age (Delmonico et al., 2009). Additionally, there is a progressive age-related infiltration of IMAT, which further contributes to a reduction of muscle strength and ultimately MQ (Goodpaster et al., 2001, Delmonico et al., 2009). It is not surprising then, to observe higher rates of premature mortality in older adults with lower MQ (Reinders et al., 2016). Even though the evidence points toward MQ presenting a robust marker of physiological resilience, capable of predicting premature mortality in older adults (Reinders et al., 2016), the capacity of MQ to prognose major abdominal surgical outcomes has not yet been assessed.

The most common way of assessing muscle preoperatively is through abdominal CT scans (Jones et al., 2017). However, this method does not allow the performance of bed-side measurements that can track the impact of in-hospital recovery in muscle mass and architecture. Ultrasound imaging may therefore present a valuable clinical tool in measuring patient muscle size and architecture throughout the peri-operative period (Turton et al., 2016). A meta-analysis assessing changes in leg muscle mass (all studies used Dual-energy X-ray absorptiometry except one that used bioimpedance analysis) and leg power, after bed rest in older adults, reported a significant reduction in leg muscle mass and leg power after 5-14 days of the bed rest (Di Girolamo et al., 2021). Additionally, pennation angle was reduced after 10 days of bed rest in intensive care (Turton et al., 2016). The in-hospital recovery-related muscle impairment may further increase muscle weakness on patients after surgery and negatively impact the prognosis of long-term surgical outcomes. Until now, there is no work assessing the associations of changes in lower limb muscle mass and architecture during in-hospital recovery with major abdominal surgical outcomes.

In chapter 5 there was a relationship between low levels of cardiopulmonary fitness with abdominal IMAT infiltration in relation to abdominal muscle mass. This observation suggests that patients with low cardiopulmonary fitness may also present with low MQ, due to the detrimental effects of IMAT infiltration on muscle force production (Goodpaster et al., 2001). Even though in chapter 5, relationships between IMAT/SM, VO_2 peak and AT with surgical outcomes were not observed, this may change when MQ is added into the model, as this is a more representative measure of the contractile capacities of the muscle tissue (Radaelli et al., 2021). The relationship between MQ and cardiopulmonary fitness, and MQ and surgical outcomes has not been explored in patients preparing for a major abdominal surgery.

Thus, the aim of this study is to assess the association of muscle mass, muscle density, percentage of change in VL muscle architecture and VL CSA between baseline and after in-hospital recovery, MQ, speed of muscle contraction and cardiopulmonary fitness with hepatobiliary surgical outcomes. Additionally, the relationship between VL-MQ with cardiopulmonary fitness will be examined.

6.2. METHODS

6.2.1. Study design

This is an observational prospective longitudinal study approved by the NHS North-West ethics committee and the Science and Engineering Research Ethics Committee at Manchester Metropolitan University. Patients scheduled for hepatobiliary surgery that did not have any muscular diseases or physical problems that would preclude the ability to perform a maximum knee extension and did not undergo neoadjuvant treatment or surgery in the preceding 6 weeks were recruited from the closest anaesthetic preoperative assessment clinic to the date of surgery at the MFT. Every patient meeting these characteristics between 19/05/2021 to 31/03/2022 that attended the pre-operative assessment clinic was invited for the study, aiming to recruit 60 patients. This cohort of patients is different to the one presented in chapter 5.

During the preoperative assessment clinic, anthropometric values, VL ultrasound images, maximum isometric knee extension contraction, and RFD were collected. Within the last three days of the in-hospital recovery, post-surgery, VL ultrasound images were collected again. When available, pre-operative CT scans (n=28) and CPET (n=15) were collected for analysis. Only in 13 patients was found the combination of CT scans and CPET data available. CT scans and CPET data was obtained from the CPET and CT NHS Manchester Foundation Trust research databases. CT scanning and CPET procedures were conducted by experienced clinical scientists during the pre-operative period as part of the routine pre-operative care. Surgical outcomes from patients were collected up to a follow-up of 6 months.

6.2.2. Vastus Lateralis ultrasound images

Vastus Lateralis ultrasound images

Extended field of view (EFOV) and conventional ultrasound images (Esaote, MyLab™Gamma portable ultrasound) using a 5cm linear array transducer (3.0 - 13.0 MHz, model: Esaote SL1543) were collected to assess VL size and architecture as explained in chapter 3 (Figure 8). In brief, conventional ultrasound images were taken at 50% of the femur length with the patient sitting with the knee and hip at 90° to assess VL-MT (in mm). Longitudinal EFOV ultrasound images collected the whole length of VL and were used to assess L_f (in mm) and pennation angle (in ^{0}). Transverse EFOV ultrasound images at 50% length of VL were collected to assess V-CSA (in mm^2). VL CSA was normalized to the height^2 (m^2) of the participants to obtain VL-CSA index for further analysis. The grey scale inside VL-CSA was quantified as a measure of VL muscle density (Kim and Kim, 2021). All ultrasound images were taken with the same contrast settings pre-operatively and at the end of the in-hospital recovery. Image analysis was performed with ImageJ v.1.8.0_172 for windows.

6.2.3. Maximum isometric voluntary contraction, rate of force development and muscle quality

MVC and RFD during a knee extension was collected with a custom-built dynamometry chair (Manchester Metropolitan University, Manchester) that was validated and used in a previous study with a similar population (McPhee et al., 2018). After explaining the force recording protocol, it was emphasised to the patient that they should contract the knee extensor muscles as fast and as hard as possible during the contractions that aim to record RFD. Patients performed 3 familiarisation contractions followed by 3 contractions to assess RFD and another 3 to assess MVC. Between each set and repetition of contractions there was a resting period of at least 3 minutes and 30 seconds, respectively. Force was measured by a load cell attached to the chair at one side and to the ankle to the patient at the other side.

Care was taken in this attachment, ensuring the load cell was perpendicular to the floor and in line with the force direction exerted by the patients. There was no compliance in the defined attachment method. Thus, the patients could only perform a knee extension from the initial position, preventing a knee flexion that would generate a countermovement and would overestimate RFD.

The force signal was collected at a rate of 1000 Hz with a 2-channel power lab (PL2062, ADinstruments) after calibration against a known weight before starting to record force data. Force data was processed with MATLAB (v. R2021a) to quantify maximum RFD (RFD_{max}, in $N\cdot s^{-1}$), time to maximum RFD (time RFD_{max}, in ms), and MVC percentage at 200ms ($\%MVC_{200}$, in %). Lab chart Pro (v. 8.19, ADinstruments) was used to quantify MVC. To quantify RFD-derived variables force data signal was not filtered. The start of the contraction was considered when the force signal increased by 3 standard deviations over the mean 5 seconds noise baseline value prior to contraction (Maffiuletti et al., 2016). The contraction with the highest RFD_{max} was selected for analysis. RFD_{max} was the maximum value of the derivative of force *vs* time, time RFD_{max} was the time from the start of the contraction to RFD_{max} and $\%MVC_{200}$ was the percentage of MVC at 200ms of contraction. The highest average force in a 0.5 seconds window during the contraction was selected as MVC (in N). The highest MVC of three maximum knee extensions was collected for further analysis. VL MQ_{ACSA} was the ratio between MVC and VL CSA (in $N\cdot mm^2$).

6.2.4. Pre-operative computed tomography scans and cardiopulmonary exercise testing

Preoperative abdominal CT images taken in the pre-operative period (mean [IQR]: 61 [42-79] days before surgery) and were analysed as explained in chapter 5. Thus, the following variables were quantified for analysis: total abdominal skeletal muscle index (SM-index), total abdominal IMAT-index, SM-RA, P-index psoas intramuscular adipose tissue index ($P\text{-}IMAT_{index}$) and P-RA and the ratios SM-IMAT/SM and P-IMAT/P.

The CPET protocol is explained in chapter 5. In brief, patients performed a maximal cycle-ergometer cardiopulmonary test after 3 min. unloading cycling. Patients performed CPET if they were >60 years or if they were <60 years and had a known cardiorespiratory disease). Peak oxygen uptake (VO_2 peak), VO_2 at AT and ventilatory equivalents of CO_2 slope (VE/VCO_2) were collected for analysis as explained in chapter 5

6.2.5. Surgical outcomes

LOS, LOS in critical care, in-hospital post-operative complications and 6-month survival was collected for analysis. This data was collected using MFT databases patients' administration systems and data warehouse in MFT. Post-operative complications were defined as adverse events after surgery scored as ≥I in the Clavien-Dindo scale, in the same way those complications scored ≥ grade III were considered severe post-operative complications (Clavien et al., 2009).

6.2.6. Statistical analysis

This is a pilot study and hence the analyses are mainly descriptive. Any statistical test was for exploratory and hypothesis generation purposes only and should be interpreted with caution. The sample size was assessed by referring to the CPET research database for referral for the surgical cohort of hepatobiliary patients undergoing liver resection for bowel cancer metastases with no chemotherapy or surgery in the preceding 6 weeks, this was more than 250 patients for 2019. Recruitment took into account some patients not wishing to take part and are considering the time within the educational programme and frequency of the scheduled CPET and subsequent patient visits. In addition, this surgical cohort was studied as this group of patients did not undergo any hospital referred pre-habilitation or re-habilitation programmes at the Manchester NHS Foundation Trust. Therefore, any changes recorded in muscle function or architecture are more likely to be reflective of the surgical patient pathway. Normality of data was assessed using the Shapiro-Wilk test. T-test and Mann-Whitney test, where appropriate, were used to assess differences in VL muscle architecture and VL CSA index between baseline and after in-hospital recovery. Spearman non-parametric test was performed to assess correlations between VL ultrasound derived measures, RFD derived measures, MVC, VL-MQ, percentage of change in VL muscle architecture and VL-CSA between baseline and after in-hospital recovery, CT-derived measures and cardiopulmonary fitness with LOS and LOS in critical care. Binary logistic regression was performed to assess relationships between VL ultrasound derived measures, RFD derived measures, MVC, VL-MQ, percentage of change in VL muscle architecture and VL-CSA between baseline and after in-hospital recovery, CT-derived measures and cardiopulmonary fitness with post-operative complications and severe post-operative complications. Lastly, Cox regression analysis was performed to assess relations between VL ultrasound derived measures, RFD derived measures, MVC, VL-MQ, percentage of change in VL muscle architecture and VL-CSA between baseline and after in-hospital recovery, CT-derived measures and cardiopulmonary fitness with 30-day, 90-day and 6-months mortality.

6.3. RESULTS

Baseline patient's characteristics are reported in Table 7 Overall, 58 patients joined the study at baseline but VL ultrasound images at follow-up were collected from 29 participants. The reasons from the loss of follow-up were withdrawal from the study due to adverse event after surgery during the in-hospital recovery or absence of discharge notification during unsocial hours due to changes in administrative organization due to the COVID-19 pandemic. Pre-operative CT scans were available from 27 patients and CPET data was available from 15 patients. In-hospital complications were recorded for 31 patients.

Table 7. Baseline patient characteristics

Parameter	Value	N (%)
No	-	58
Men (%)	-	45 (77.5)
Women (%)	-	13 (22.4)
Age (yrs)	69 (59-74)	58 (100)
Height (m)	1.71±0.08	58 (100)
Body mass (kg)	79.8±14.5	58 (100)
BMI (kg·m^{-2})	27.4±4.5	58 (100)
VL CSA (mm^{2})	1773 (1465-2010)	58 (100)
VL CSA index (mm·m^{-2})	598 (518-705)	58 (100)
VL grey scale (AU)	141±22	58 (100)
VL MT (mm)	19.1±4.6	58 (100)
VL L_f (mm)	107.7±18.8	58 (100)
VL pennation angle (°)	12.2±2.3	58 (100)
VL MQ_{ACSA} (N·mm^{2})	12.1 (10.8-13.7)	58 (100)
SM-index (cm·m^{-2})	37.1±29.4	28 (48.3)
P-index (cm·m^{-2})	5.1±3.6	28 (48.3)
SM-RA (HU)	33.3±5.9	28 (48.3)

P-RA (HU)	42.0±5.5	28 (48.3)
SM-IMAT/SM (AU)	0.11 (0.06-0.20)	28 (48.3)
P-IMAT/P (AU)	0.1 (0.06-0.19)	28 (48.3)
MVC (N)	313 (261-394)	58 (100)
RFD_{max} ($N \cdot s^{-1}$)	9516 (8263-12378)	58 (100)
Time RFD_{max} (ms)	52 (36-544)	58 (100)
$\%MVC_{200}$ (%)	80.2 (66.0-87.7)	58 (100)
VO_2 peak ($mL \cdot kg^{-1} \cdot min^{-1}$)	16.7±2.5	15 (25.9)
AT ($mL \cdot kg^{-1} \cdot min^{-1}$)	11.0±2.0	15 (25.9)
VE/VCO_2 slope (AU)	32.1±4.4	15 (25.9)
Bilirubin ($\mu mol \cdot L^{-1}$)	11 (8-18)	56 (96.6)
Urea ($\mu mol \cdot L^{-1}$)	5.3 (4.1-5.9)	56 (96.6)
Albumin ($g \cdot L^{-1}$)	38 (35-40)	56 (96.6)
Creatinine ($\mu mol \cdot L^{-1}$)	75 (59-89)	56 (96.6)
Haemoglobin ($\mu mol \cdot L^{-1}$)	134 (125-143)	56 (96.6)
6-months mortality (No. patients)	2	58 (100)
Post-operative complications (N_o events)	7	58 (100)
Severe Post-operative complications (N_o events)	1	58 (100)
LOS (days)	6 (5-9)	58 (100)
Critical care length of stay (days)	2 (1-4)	58 (100)

AT: lactate threshold; AU: arbitrary units; CSA: cross-sectional area; IMAT: intramuscular adipose tissue; MT: muscle thickness; L_f*: fascicle length;* MQ_{ACSA}*: cross-sectional area-based muscle quality using anatomical cross-sectional area; MVC: Maximum isometric voluntary contraction during a leg extension; P: psoas; RA: radiation attenuation; SM: skeletal muscle;* RFD_{max}*: maximum rate of force development; Time* RFD_{max}*: time to maximum rate of force development;* VE/VCO_2*: Ventilatory equivalents of carbon dioxide VL: Vastus Lateralis;* VO_2 *peak: peak volume of oxygen uptake* $\%MVC_{200}$*: percentage of MVC at 200ms.*

Data is presented as mean±SD or median (IQR).

6.3.1. Changes in Vastus Lateralis from preoperative assessment to end of in-hospital recovery

Due to loss at follow-up, 29 patients were included for analysis. Changes in VL muscle architecture, quality and CSA are reported in Table 8. Overall, MT ($p<0.001$), pennation angle ($p=0.005$) and VL CSA index ($p<0.001$) were significantly reduced by 2%, 10% and 8% after the in-hospital recovery, respectively (Figure 14). This was not the case for L_f and VL density ($p>0.05$).

Table 8. Vastus Lateralis muscle architecture and cross-sectional area at baseline and at follow-up

Parameter	Baseline	Follow-up	N at follow-up (%)
VL CSA (mm^2)	1773 (1465-2010)	1692 (1328-1963)*	29 (50.0)
VL CSA index ($mm \cdot m^{-2}$)	598 (518-705)	546 (467-621)*	29 (50.0)
VL grey scale (AU)	141±22	145±27	29 (50.0)
VL MT (mm)	19.1±4.6	18.8±4.3*	29 (50.0)
VL L_f (mm)	107.7±18.8	110.3±16.4	29 (50.0)
VL pennation angle (°)	12.2±2.3	11.0±2.2*	29 (50.0)

Data presented as mean±SD or median (IQR)

CSA: cross-sectional area; L_f: fascicle length; MT: muscle thickness; VL: Vastus Lateralis.

**Denotes statistically significant different between baseline and follow-up ($p<0.01$).*

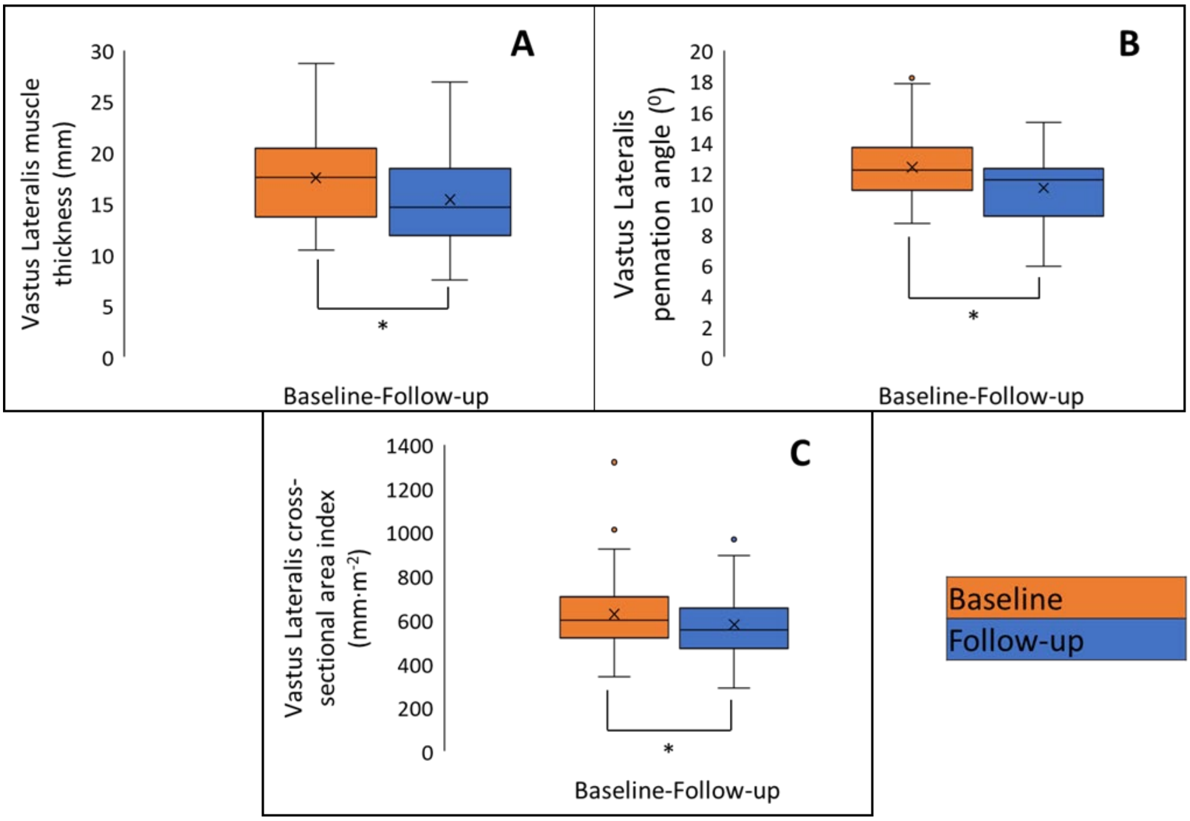


Figure 14. Differences in Vastus lateralis architecture and cross-sectional area index between baseline and after in-hospital recovery (follow-up) (N=29).

A: Differences between baseline and follow-up in Vastus Lateralis muscle thickness. B: Differences between baseline and follow-up in Vastus Lateralis pennation angle. C: Differences between baseline and follow-up in Vastus Lateralis cross-sectional area index.

**Denotes significant difference between baseline and follow-up timepoints (p<0.05).*

6.3.3. Correlations with surgical outcomes

Only AT was statistically significantly correlated with LOS in critical care (R=-0.658, p=0.014) (Figure 15). Only BMI was significantly positively associated with post-operative complications. One unit increase of BMI increased the odds of post-operative complications in 1.334 (Odds ratio (OR)=1.334, 95%CI=1.058-1.682; p=0.015). No analysis was performed for severe post-operative complications as only 1 severe post-operative complication was registered. After Cox regression analysis, no 30 and 90-day mortality analysis was performed because all patients survived the first 90 days after surgery. All patients survived within the group of patients from which cardiopulmonary fitness data was available and therefore associations between cardiopulmonary fitness and 6-months mortality were not assessed. None of the rest of the parameters were associated with 6-months mortality (p>0.05).

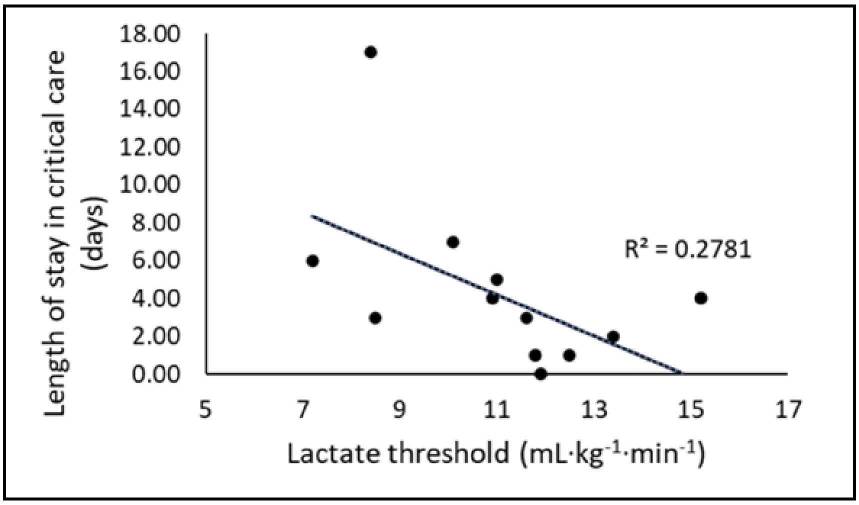


Figure 15. Significant correlation between Length of stay in critical care and anaerobic threshold (N=13).

6.4. DISCUSSION

Overall, VL-MT, VL pennation angle and VL-CSA index were significantly reduced after the in-hospital recovery period. However, the percentage change of these variables was not related to any surgical outcome. Only AT was moderately correlated with LOS at critical care.

There were no observed relationships between any muscle parameters with the surgical outcomes reported in this study. In chapter 5, P-index was correlated with 1-year and 3-year premature mortality. In this study, we lacked long-term follow-up survival data. Thus, we could not assess if the new muscle parameters included in this study followed a similar association with long-term follow-up premature mortality as seen in chapter 5. Therefore, it remains to be seen as to whether the muscle parameters analysed in this study may enhance the prognosis of long-term mortality compared to P-index.

In the present study, AT was negatively associated with LOS in critical care in line with a previous study (Junejo et al., 2012), although it should be noted that Junejo et al. (2012) only included liver resection patients, in this study liver resection and hepatopancreatobiliary surgery patients, both with cancer, are included. This association may be explained by the impairment of pulmonary function what leads into poor tissue oxygenation (Hedenstierna and Edmark, 2015). Thus, anaerobic pathways become more responsible for energy metabolism during exercise and homeostatic challenges (Bigatello and Pesenti, 2019). This anaerobic state is induced at the point of general anaesthesia and persists post-operatively, increasing the risk of longer LOS in critical care (Lawton et al., 2019a). Hence those patients with lower AT are potentially less able to cope with the physiological stress induced by the mechanisms of action of general anaesthesia.

The lack of association between CT, CPET and ultrasound-derived parameters might be due to the short follow-up period for mortality compared to other studies, which have found a relationship between AT, VO_2 peak and SM-RA with 1-year mortality (West et al., 2019b) in hepatopancreatobiliary surgery patients and 4-years mortality (Junejo et al., 2012) in pancreaticoduodenectomy surgery patients. The lack of association of any fitness and muscle parameters, included in this study, with 6-months premature mortality reinforce the limitation of the findings found chapter 5. Despite a statistical association with P-index and VE/VCO_2 was found with 3-year mortality, the 95% CI effect size of these associations was close to 1. Further studies with larger sample size and preventing the loss of follow-up are needed to verify the results reported in chapter 5.

VL-MT, VL pennation angle and VL-CSA index were significantly reduced after the in-hospital recovery, in line with a previous study assessing changes in muscle architecture after a period of intensive care (Turton et al., 2016). While the bed rest derived from the in-hospital recovery reduces sarcomeres in parallel, sarcomeres in series are seemingly unaffected, as shown by an unchanged L_f. As a consequence of the muscle fibre atrophy the fascicle pennation angle decreases and hence the fascicles of the muscle become better aligned with the line of pull that, all else staying the same, results in an improved, rather than reduced tendon force during the VL contraction (Degens et al., 2009). This advantage is, however, negligible in comparison to the impact of the reduction in VL size and despite the mechanical advantage gained by the VL fascicles, it is likely that patients suffered a loss of force generating capacity, even independent of any changes in MQ, as muscle size is the main determinant of muscle force generating capacity (Reggiani and Schiaffino, 2020). However, MVC was not collected after in-hospital recovery because most patients did not feel comfortable to perform the test, thus this assumption remained to be confirmed..

A previous meta-analysis reported a reduction of muscle strength after 5-14 days of bed rest in an older population (Di Girolamo et al., 2021). Despite the observation that the in-hospital recovery reduces VL muscle mass and alters architecture, the percentage of these changes were not correlated with the total LOS or the LOS in critical care. This shows a variation in the effect of LOS on VL mass as shown by Di Girolamo et al. (2021), who observed that low knee leg extension strength and not low leg muscle mass was significantly associated with the amount of bed rest days (Di Girolamo et al., 2021). This suggests that MQ may be the muscle derived parameter most affected after a period of physical inactivity. This lack of association between LOS and percentage of change in muscle derived parameters shows a between patient variation on the physiological adaptations to muscle disuse, which complicates the prognosis of muscle loss and impairments on pennation angle prior to surgery. This interpretation should be taken with caution as other intra-operative factors and physiological characteristics of patients may influence LOS, as mentioned in chapter 5 (Böttger and Junginger, 1999, Yang et al., 2011). In any case, this does not seem to be an immediate question to solve as these changes were not related with any of the surgical outcomes reported here. However, a re-evaluation of these data when 1-year and 3-year survival rate is available is necessary, in view of the findings of chapter 5 where it was shown that muscle-derived parameters seem to influence long-term mortality. New studies should focus on evaluating whether these changes may affect the quality of life of patients, considering factors beyond the lack of association with higher risk of premature mortality.

Future studies should also explore if muscle architecture and mass recover to baseline values after hospital discharge. It has been observed that intensive care unit acquired weakness

(ICUAW) may remain for up to 24 months after hospital discharge in critically ill patients (Jolley et al., 2016). This could be the case for hepatobiliary surgery patients, which would explain why muscle and cardiopulmonary fitness parameters only show an effect on longer-term survival (chapter 5). Those patients with a preoperative low muscle mass, low muscle function and low cardiopulmonary fitness are more susceptible of increasing their weakness if they do not reduce their sedentary time, and at the same time, weak patients show a reduced physical activity profile (Kehler and Theou, 2019). Therefore, pre-operative muscle weakness that is worsened during the in-hospital recovery, may further impair patients, in turn increasing sedentary time post-operatively, further exaggerating the condition and negatively impacting on long-term survival (Hermans et al., 2014, Ekram et al., 2021) as shown in chapter 5.

6.4.1. Limitations

There is significant loss of follow-up data that may have affected the results found in this study. This was due to some patients not willing to take part in the follow-up measures and changes in data collection in human studies due to the Covid-19 pandemic. Furthermore, confidence intervals from baseline and post-baseline overlapped. However, the changes observed in VL-MT, VL pennation angle and VL-CSA index are in line with previous bed-rest studies in old people (Di Girolamo et al., 2021) and bed-rest in critical care (Turton et al., 2016), suggesting that the loss data could show similar results. Similarly, cardiopulmonary fitness data was available from only 15 patients what compromises the negatively association between AT and LOS in critical care. Despite that previous studies have found associations of LOS with AT (Chandrabalan et al., 2013, Junejo et al., 2012), the findings of this study should be interpreted carefully due to the low sample size and lack of association between AT and LOS and LOS in critical care in chapter 5.

Significant changes after in-hospital recovery in VL-MT, VL-CSA and VL pennation angle are inside the error observed for intra-raterreliability reported in chapter 3 therefore caution should be taken when interpreting these results as the observed changes may be an error in the measurement. This error may be further aggravated due to the presence of thick thigh SAT (echo-waves could therefore not effectively travel to the deeper parts of the muscle) (Varanoske et al., 2021), and the higher brightness of ultrasound images (likely due to higher IMAT infiltration) compared to those of the participants of chapter 3, it cannot be ruled out that the intra-rater error in this study could be higher than reported, despite the learning effect of the operator (PDO). Therefore, more evidence is needed to confirm that VL size and VL pennation angle is reduced after in-hospital recovery in hepatobiliary surgery patients.

Lack of association of muscle parameters with 6-months follow-up mortality should also be interpreted carefully as only two events were registered. Thus, it is possible that this study lacks statistical power to assess whether the lack of association was not found by chance. Re-analysis with a longer follow up or future studies with larger sample size are needed to better understand the influence of lower limb muscle mass, architecture and strength, and its changes during in-hospital recovery on patient's survival rate.

The measure of MQ implemented in this study is limited and overestimates the real specific force (Reeves et al., 2004b) of the VL as: 1) As shown in chapter 3 the approach used to outline the VL overestimates VL-ACSA. 2) MVC was normalized to VL ignoring the contribution of the other quadriceps muscles on knee extension force. However, chapter 3 showed that VL-MQ_{ACSA} had a high correlation with quadriceps $MQ_{ACSA,}$ indicating that VL- MQ_{ACSA} is representative for the quadriceps MQ_{ACSA}. Measuring the CSA of all quadriceps muscles would not be viable for clinical application due to the limited time to collect data during the pre-surgery anaesthetic consultation; 2) MVC was normalized to the VL ACSA (Delmonico et al., 2009, Goodpaster et al., 2001) and not the PCSA (Reeves et al., 2004b, McPhee et al., 2018). This decision was taken because PCSA measures show higher variability than ACSA (Erskine et al., 2009) as PCSA is a compound measure. Further building upon this variation is the higher intrinsic variation of ultrasound images (chapter 3) and the difficulty on some occasions to adequately measure L_f and pennation angle in this population. Some patients presented thick thigh SAT which increased the brightness of the muscle tissue and reduced the contrast with the perimysium required to identify fascicles (Varanoske et al., 2021). Thus, it was considered that measures of VL-ACSA and VL-MQ_{ACSA} could better identify changes during the in-hospital recovery, even though the measure does result in an overestimated specific force of the VL. The intention of including a measure of MQ in this chapter was not so much to obtain an accurate measure of specific force but rather to obtain a measure that is less variable, easier to obtain and potentially allowing detection of changes over time in muscle size and specific tension than a more comprehensive method that gives a truer estimate of specific tension.

6.4.2. Conclusions

VL-MT, VL pennation angle and VL-CSA index are statistically significantly reduced after in-hospital recovery in hepatobiliary surgery patients. Only AT was negatively associated with LOS in critical care. The lack of associations of the percentage of change of muscle size and architecture with LOS, LOS in critical care, post-operative complications, and 6 months survival, highlights the challenges in prognosing short-term surgical outcomes based on muscle size and architecture impairments provoked by the bed rest during in-hospital recovery. Future studies should therefore examine alternative methods of prognostic assessment, as it remains to be seen as to whether longer term survival outcomes are influenced by these factors.

CHAPTER SEVEN: EFFICACY OF SUPERVISED EXERCISE PREHABILITATION PROGRAMS TO IMPROVE MAJOR ABDOMINAL SURGERY OUTCOMES: A SYSTEMATIC REVIEW AND META-ANALYSIS

What it is known	What will be assessed
- Patients with low P-index and high VE/VCO_2 slope have 2.5 higher risk of mortality within the three first years of hepatobiliary or liver resection surgery. - VO_2 peak and AT are negatively related to LOS and LOS in critical care respectively. - Exercise can improve muscle size, muscle function and cardiopulmonary fitness in an old population independently of the moment in life when a regime of physical activity is started.	- The efficacy of supervised exercise prehabilitation programs to enhance physical functionality and cardiopulmonary fitness. - Whether supervised exercise prehabilitation programs have a positive impact on surgical outcomes and recovery of physical function after surgery.

7.1. INTRODUCTION

Most patients facing major abdominal surgery are over 60 years old (Jones et al., 2017), an age when cardiorespiratory fitness and muscle function has already started to decline, even in highly active people (Bagley et al., 2019, Ocana et al., 2021). The negative impact of poor cardiorespiratory fitness (Hennis et al., 2011, Kaibori et al., 2013, Moran et al., 2016a, West et al., 2016) and muscle weakness (Aleixo et al., 2020, Jones et al., 2017) on surgical outcomes after abdominal surgeries is widely reported. Exercise programs that enhance cardiorespiratory fitness and muscle health may be effective “prehabilitation” strategies for abdominal surgeries. The big challenge of exercise prehabilitation programs, particularly in oncology surgery, is the short time interval available to improve patient fitness. The length of prehabilitation programs is commonly 4-6 weeks for major abdominal surgeries (Carli et al., 2020, Barakat et al., 2016), a period that may be insufficient to promote significant cardiopulmonary and muscular adaptations (Hickson et al., 1977, Hughes et al., 2018, Macpherson et al., 2011), and hence, limiting their potential clinical benefit. Some studies report that exercise prehabilitation programs for major surgery resulted in a reduced LOS (Bousquet-Dion et al., 2018, Morkane et al., 2020) and incidence of post-operative complications (Soares et al., 2013, Barakat et al., 2016), while others report no significant effects on LOS (Barberan-Garcia et al., 2017) and incidence of post-operative complication (Bousquet-Dion et al., 2018). These conflicting findings may be due to different factors related to prehabilitation program planning and training principles.

The optimal package of components for a prehabilitation intervention remains unclear. A previous systematic review was unable to detect differences on outcomes of physical function, hospital LOS and post-operative pulmonary complications between multimodal programs (including exercise alongside nutritional and psychological support) and unimodal exercise programs delivered prior to major abdominal surgery for cancer (Waterland et al., 2021). Others have highlighted sufficient clinical trial data to support exercise training as being safe and efficacious component of prehabilitation (Hijazi et al., 2017, Lambert et al., 2021, Thomas et al., 2019, Waterland et al., 2021). However, to facilitate the translation of this evidence into clinical practice, clinicians must know sufficient details about the effects of exercise components. A published guideline of pre-operative exercise training for patients awaiting major non-cardiac surgery recommended exercise to be delivered under supervision

(Tew et al., 2018). However, the magnitude of effects of prehabilitation programs containing supervised exercise on outcomes following all types of major abdominal surgery remains unclear. This is important for optimising the outcomes of prehabilitation programs in clinical practice, and for providing estimates of effect that newer self-managed (unsupervised) or remote exercise programs (that are increasing in popularity) can be compared against. Previous reviews of prehabilitation for abdominal cancer surgery have either not attempted to perform a meta-analysis or have performed analyses irrespective of exercise supervision (Waterland et al., 2021, Thomas et al., 2019, Hijazi et al., 2017). Therefore, the aim of this meta-analysis is to evaluate the efficacy of supervised exercise prehabilitation programs to enhance physical functionality before surgery and improve surgical outcomes. Furthermore, we aimed to understand whether efficacy of supervised exercise prehabilitation programs was influenced by type of surgery and exercise delivery (e.g., frequency of sessions).

7.2. METHODS

The methods for this review were pre-specified and registered in PROSPERO (Centre for Reviews and Dissemination international database of prospectively registered systematic reviews, CRD42020180693, 18-05-2020). Ethical approval was given by the Manchester Metropolitan University ethics committee (24-04-2020). This review is reported in accordance with PRISMA.

7.2.1. Search strategy

The search strategy was built in consultation with an academic librarian at Manchester Metropolitan University. Following the development of a search strategy according to the PICO framework, the following databases and trial registers were searched for relevant studies: PubMed Central (PMC), the online counterpart to the Medical Literature Analysis and Retrieval System (MEDLINE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Allied and Complementary Medicine Database (AMED), Cochrane Central Register of Controlled Trials CENTRAL, Physiotherapy Evidence database (PeDro), ClinicalTrials.gov (www.clinicaltrials.gov) and WHO International Clinical Trials Registry Platform (www.who.int/ictrp). The search was conducted in January 2022. See Appendix1 for further details of search strategies. In addition, citations in selected studies were checked for further references.

7.2.2. Eligibility criteria

Studies were included in the systematic review if they met the following inclusion criteria:

Population: Adults (>18 years) that had abdominal surgery. Abdominal surgery was defined as surgery involving a cut in the abdominal cavity (Jones et al., 2017). Selection of articles was not limited by choice of surgical technique. This included but was not limited to patients undergoing gastrointestinal, hepatobiliary, pancreatic, endocrine, urological, gynaecological, vascular and abdominal transplantation surgery for elective indications.

Intervention: The exercise prehabilitation program included at least one supervised exercise session per week. Supervised exercise was controlled by a physician or health professional and had to be explicitly mentioned in the study report for inclusion. All included exercise interventions had a duration of ≥ 3 weeks. Sensitivity analyses were performed where studies reporting a mix of durations contributed data towards meta-analyses (excluding studies where not all participants received ≥ 3 weeks). The supervised exercise prehabilitation program should involve planned, structured and repetitive bodily movement to improve or maintain one or more components of physical fitness (Caspersen et al., 1985). Programs involving only respiratory training or physiotherapy that did not involve any type of exercise based on Caspersen, et al. (1985) definition were excluded to avoid high heterogeneity between interventions.

Comparator: Adults (>18 years) that underwent an abdominal surgery and followed usual care (UC) pathway. Patients in this group did not complete any supervised exercise program during the prehabilitation stage, but could be involved in other type of interventions, such as nutritional or psychological support.

Outcomes: At least one of the following outcomes was reported in the study: i) post-operative mortality, ii) total number of post-operative complications iii) severe post-operative complications defined as a) those requiring reoperation or b) ≥ grade 3 in the Clavien-Dindo scale (Barakat et al., 2016, Bousquet-Dion et al., 2018), iv) LOS, v) any functional test, including but not limited to 6MWD, Timed-up-and-Go (TUG), VO_2 peak (measured by gas exchange analysis), and O_2 uptake at AT, or any strength measurement pre and post the exercise prehabilitation program.

Study design: Randomised controlled trials (RCTs).

7.2.3. Data extraction

Two researchers (Pablo Duro-Ocana [PDO] and Fabio Zambolin [FZ]) screened the titles and abstracts of all search results according to review eligibility criteria. The full text of records after title and abstract screening were obtained and screened independently by two researchers (PDO and FZ). In case of a discrepancy in decision to include a study, a third researcher was consulted (Liam Bagley [LB]).

For all eligible studies, data was extracted by one researcher (PDO) and cross-checked by another (FZ). Extracted data included: authors and year of publication, participant characteristics (age, body mass index (BMI), type of surgery, involvement in neoadjuvant treatment), characteristics of the prehabilitation program (program length, frequency and duration of the supervised sessions, type and intensity of exercises, progression of the exercise program and any other type of support apart from the supervised exercise sessions) and outcome measures. The time points of interest were ‘baseline (before surgery), pre-surgery (the end of UC or prehabilitation just before surgery), and post-surgery.

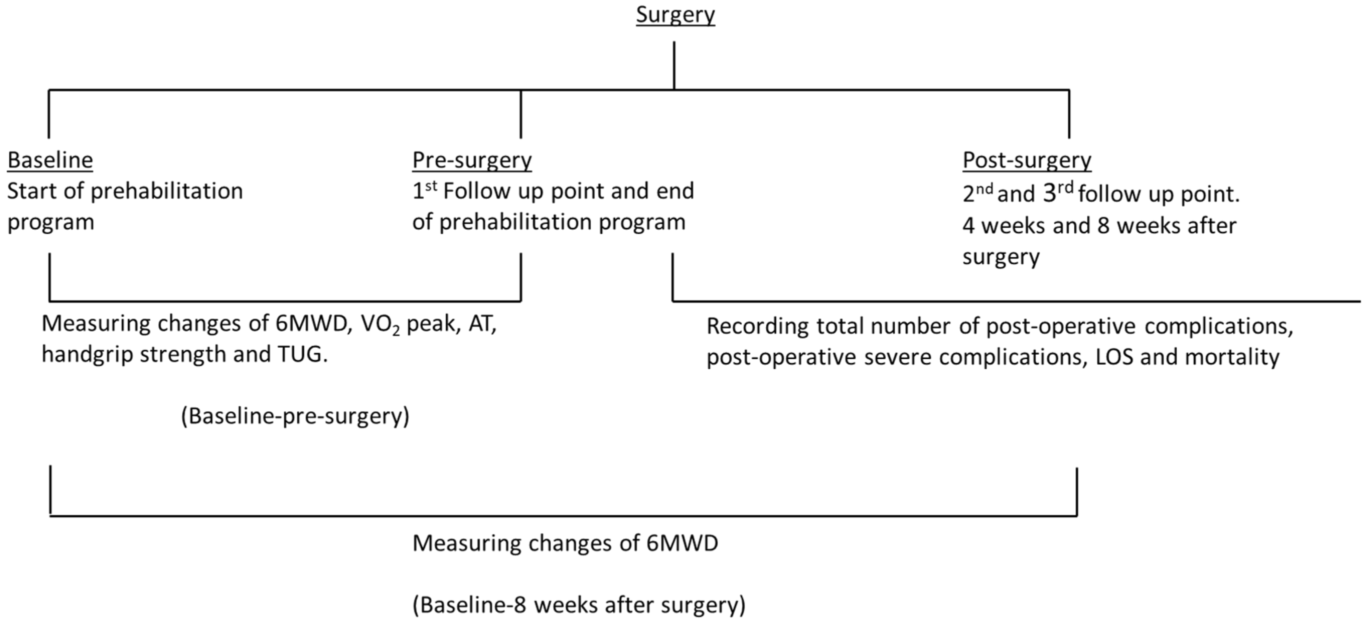


Figure 16. Data Extraction Timepoints.

AT: Anaerobic threshold; LOS: length of stay in hospital; TUG: Timed up and go; 6MWD: 6MWD.

7.2.4. Data synthesis

Study, patients and prehabilitation program characteristics (Table 9), and risk of bias are summarized narratively. Continuous outcomes and dichotomous outcomes are summarized narratively, as mean difference of changes between baseline and follow-up time points, and 95% confidence interval (CI) risk ratios (RR) and 95% CI. In one case (Blackwell et al., 2020), estimates of the effect of this study were extracted from previous meta-analysis (Waterland et al., 2021) and a sensitivity analysis with this data was performed to evaluate if it significantly changed the outcome.

7.2.5. Risk of bias assessment

Two researchers (PDO and FZ) independently assessed the risk of bias of each included article for meta-analysis using the tool in the Cochrane handbook for RCTs (Higgins et al., 2008) used in the RevManager software (v.5.3). In case of discrepancy between the researchers in any of the domains assessing a given article, a third researcher (LB) was consulted. The domains assessed are given in appendix 22. Blinding of the patients was not taken into consideration because it is impossible to blind an exercise session. Each domain was allocated either low, unclear or high risk of bias, following the recommendations of the Cochrane handbook (Higgins et al., 2008).

7.2.6. Heterogeneity

Heterogeneity was assessed with the statistic I^2 and describes the percentage of variability due to other sources than sampling error (Higgins et al., 2008). More than 40% represents moderate heterogeneity (Higgins et al., 2008). In that case, a subgroup analysis was performed to analyse sources of the heterogeneity between studies.

7.2.7. Statistical analysis

All data analysis was performed using RevMan 5.4 (Review Manager Version 5.4, The Cochrane Collaboration, 2020). To analyse differences between groups in premature mortality, total number of post-operative complications and number of severe post-operative complications, a meta-analysis for dichotomous data using the Mantel-Haenszel method with a random effects model was performed. A meta-analysis for continuous data using the inverse variance method with random effects model was performed for LOS. A meta-analysis for continuous data using the inverse variance method with random effects model was performed for 6MWD, handgrip strength of the right hand, TUG and VO_2 peak using the mean changes and SD of changes between baseline and after completing the prehabilitation (before surgery) and between baseline and 4-8 weeks after surgery (if reported). To control for baseline physical activity levels in participants of individual studies, mean changes and SD of changes instead of absolute values at a certain follow-up time point was used to compared between groups. It was necessary to estimate the mean changes and SD of changes of 6MWD (Wallen et al., 2019, Steffens et al., 2021b, Carli et al., 2020, Soares et al., 2013, Fulop et al., 2021), handgrip strength of the right hand (Wallen et al., 2019), TUG (Dronkers et al., 2010), five times sit to stand (Steffens et al., 2021b) and VO_2 peak (Banerjee et al., 2018, Barakat et al., 2016, Wallen et al., 2019, Tew et al., 2017, Loughney et al., 2021) of some studies as they were not reported. The estimation was performed using Cochrane handbook guidelines (Higgins et al., 2008). To do so, a calculated correlation coefficient from other studies in this meta-analysis was used (Bousquet-Dion et al., 2018, Kim et al., 2009, Northgraves et al., 2019) to estimate SD of changes where this was not reported, and authors could not be reached. Meta-analysis for continuous data using the inverse variance method with random effects model was performed for AT using the follow-up values (i.e., post-intervention, before surgery). In the case a study reported median and interquartile range (IQR) or 95% CI instead of mean and SD, mean and SD were estimated following methods reported previously (Wan et al., 2014, Higgins et al., 2008). Data was presented as RR or mean difference of changes between baseline and follow-up time points (before surgery and 4-8 weeks after surgery) and 95% CI.

7.3. RESULTS

7.3.1. Study characteristics

A total of 10,539 records were identified in the initial search. After using the criteria indicated in the PRISMA flow diagram (Figure 17), 17 studies were included in the meta-analysis.

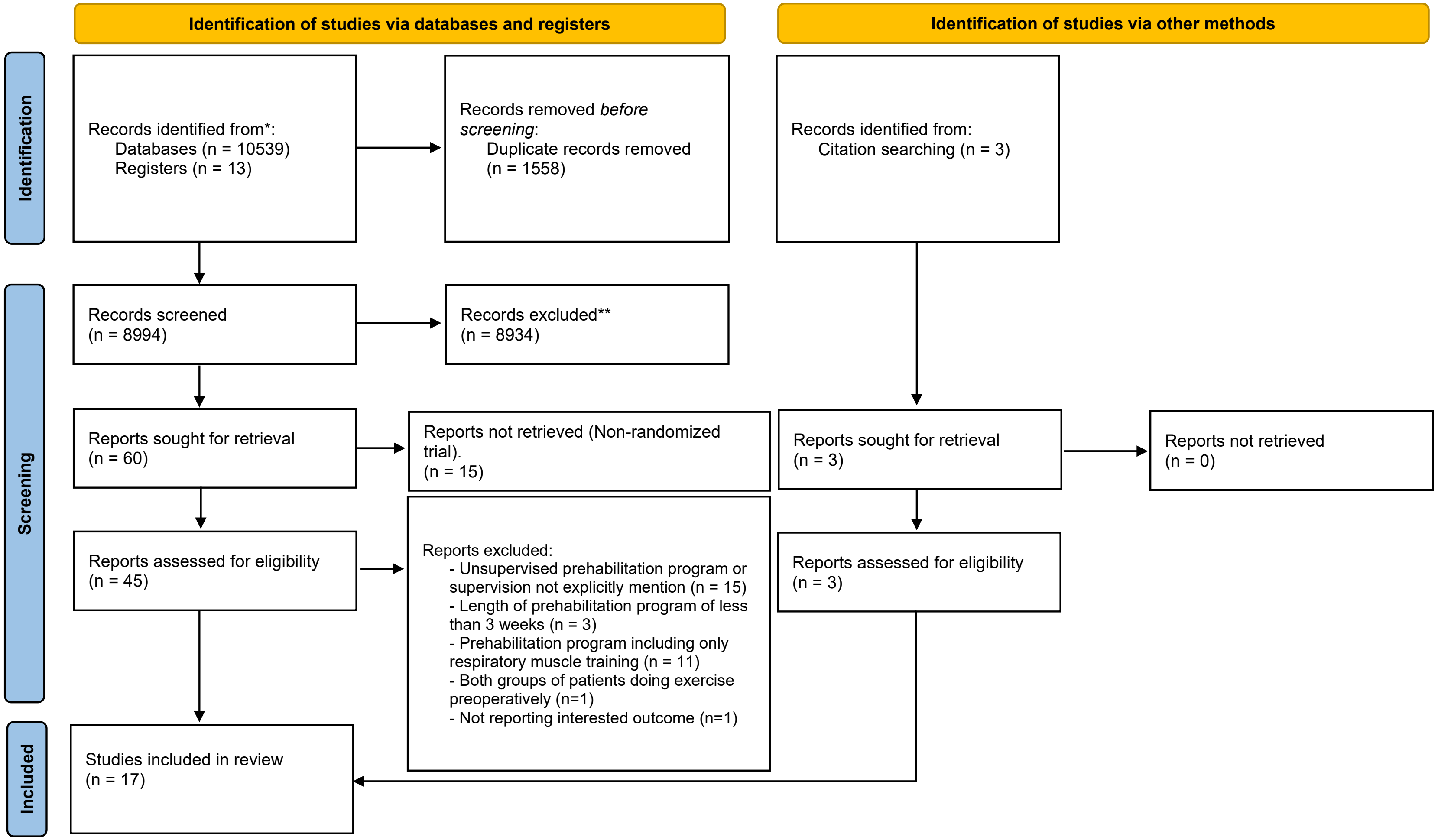


Figure 17. PRISMA 2020 flow diagram.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

For more information, visit: http://www.prisma-statement.org/

7.3.2. Characteristics of the patients

A total of 1,034 patients were included in these studies, of which 524 patients completed prehabilitation and 510 UC. The minimum mean age of the patients across studies was 49 years and the maximum was 82 years. The majority of patients underwent colorectal surgery (Berkel et al., 2022a, Bousquet-Dion et al., 2018, Carli et al., 2020, Dronkers et al., 2010, Dunne et al., 2016, Fulop et al., 2021, Kim et al., 2009, Northgraves et al., 2019, Loughney et al., 2021). One study included only patients with frailty as defined by the Fried Frailty Index (Carli et al., 2020). Another study included only patients considered at high risk of adverse events (age>70 years, and/or *'American society of anaesthesiology stage'* III/IV) (Barberan-Garcia et al., 2017).

7.3.3. Characteristics of the prehabilitation program

Nine studies had a prehabilitation program length of 3-4 weeks (Blackwell et al., 2020, Bousquet-Dion et al., 2018, Carli et al., 2020, Dunne et al., 2016, Kim et al., 2009, Tew et al., 2017, Berkel et al., 2022a, Northgraves et al., 2019, Wallen et al., 2019), three studies had a length of 3-6 weeks (Banerjee et al., 2018, Barakat et al., 2016, Barberan-Garcia et al., 2019), one study a length of 9 weeks (Loughney et al., 2021), and three studies had a prehabilitation length of 2-6 weeks(Dronkers et al., 2010, Soares et al., 2013, Steffens et al., 2021b). A sensitivity analysis was performed to assess how removal of the data from these 3 studies affected the outcome (Forest plot of these sensitivity analysis is reported in supplementary material). In one study, the prehabilitation until a liver transplantation was 4 weeks for some patients and up to 8 weeks for other patients due to longer preoperative period (Wallen et al., 2019).

Eight studies (Wallen et al., 2019, Barakat et al., 2016, Bousquet-Dion et al., 2018, Carli et al., 2020, Dronkers et al., 2010, Northgraves et al., 2019, Berkel et al., 2022a, Steffens et al., 2021b) included both resistance and endurance training as part of the prehabilitation program. The resistance training included exercises of upper and lower limbs, and functional exercises. Eight studies only included endurance training, six in the form of HIIT (Banerjee et al., 2018, Barberan-Garcia et al., 2017, Blackwell et al., 2020, Dunne et al., 2016, Tew et al., 2017, Loughney et al., 2021) and two in the form of continuous endurance training (Kim et al., 2009, Fulop et al., 2021). One study included continuous endurance training and global body mobilisation (Soares et al., 2013). Fifteen studies reported a progressive and tailored exercise program according to the aerobic and/or muscle capacity of patients (Steffens et al., 2021b, Berkel et al., 2022a, Fulop et al., 2021, Loughney et al., 2021, Blackwell et al., 2020, Bousquet-Dion et al., 2018, Carli et al., 2020, Northgraves et al., 2019, Banerjee et al., 2018, Barberan-Garcia et al., 2017, Tew et al., 2017, Dunne et al., 2016, Soares et al., 2013, Dronkers et al., 2010, Kim et al., 2009). One of these studies only reported tailored exercise and not progressive (Dunne et al., 2016). Another three studies included respiratory muscle training as part of the exercise prehabilitation program (Dronkers et al., 2010, Soares et al., 2013, Fulop et al., 2021).

All prehabilitation programs involved supervised and unsupervised exercise sessions except five that only included supervised exercise sessions (Banerjee et al., 2018, Barakat et al., 2016, Blackwell et al., 2020, Tew et al., 2017, Loughney et al., 2021). In eleven studies, patients were encouraged to complete an exercise program at home (Berkel et al., 2022a, Fulop et al., 2021, Steffens et al., 2021b, Wallen et al., 2019, Kim et al., 2009, Dunne et al., 2016, Bousquet-Dion et al., 2018, Carli et al., 2020) or to increase daily physical activity with walking or cycling (Barberan-Garcia et al., 2017, Dronkers et al., 2010, Soares et al., 2013). Two studies encouraged patients in the Usual care group to do exercise at home during the pre-operative period (Dronkers et al., 2010, Dunne et al., 2016). In two studies, the UC and prehabilitation patients followed a post-surgery exercise program with a length of 7 days (Soares et al., 2013) and 8 weeks (Bousquet-Dion et al., 2018). In another study, only UC patients followed a 4-week post-surgery exercise program (Carli et al., 2020).

7.3.4. Risk of bias

All but six studies (Dronkers et al., 2010, Berkel et al., 2022a, Steffens et al., 2021b, Blackwell et al., 2020, Carli et al., 2020, Banerjee et al., 2018) did not report whether the outcome assessors or statisticians were blinded, and one explicitly mentioned that data collectors were aware of group allocation (Soares et al., 2013) (See supplementary document 2 for further information on risk of bias assessment).

Some studies experienced loss of follow-up data (Berkel et al., 2022a, Barakat et al., 2016, Blackwell et al., 2020, Bousquet-Dion et al., 2018, Carli et al., 2020, Tew et al., 2017, Soares et al., 2013). In some cases, data of surgical outcomes were reported, but physical function, aerobic capacity and muscular strength data was missing. The Forest plots are accompanied by a risk of bias assessment for each outcome.

Table 9. Characteristics of included studies

First author	Prehabilitation group characteristics/Exercise apart of supervised prehabilitation program	Usual care group characteristics/additional non-supervised exercise apart of usual care	Surgery	Neoadjuvant therapy	Length of supervised prehabilitation program	Type of supervised prehabilitation program
Berkel 2022	N=28; Age: 74±7 yrs; BMI: 29.8±4.1 kg·m^{-2}. Moderate homebased exercise.	N=29; Age: 73±6 yrs; BMI: 30.5±4.9 kg·m^{-2}. No exercise suggested	Colorectal cancer.	Y	3 weeks	*Frequency of supervised sessions:* 3/week. *Session length:* 60 min. *Type:* Moderate to high intensity interval training on cycle ergometer. Peripheral resistance training *Intensity:* 120% of the work rate achieved at the ventilatory anaerobic threshold was alternated with active recovery at 50% of the work rate achieved at the ventilatory anaerobic threshold. Resistance training was performed at 70%82% of baseline 1 maximum repetition (RM). *Progression:* In the first week, exercise lasted 120 seconds and recovery lasted 180 seconds, which progressed to 140 and 160 seconds, respectively, in the second week, and 160 and 140 seconds in the third week. Resistance training progressed from 70% to 82% from the first to the third week *Additional support:* Not reported.
Fulop 2021	N=77; Age: 70(60-75) yrs; BMI: 27.9±5.6 kg·m^{-2}. Repeating the in-hospital exercise at home.	N=72; Age: 70(64-75) yrs; BMI: 27.9±5.3 kg·m^{-2}. No exercise suggested.	Colorectal surgery.	N	3-6 weeks	*Frequency of supervised sessions:* 1/week. *Session length:* 40-45 min. *Type:* Aerobic training and breathing exercises.

						Intensity: moderate aerobic exercise. *Progression:* training intensity was weekly increased according to patient's ability. *Additional support*: Nutritional supplementation if needed and psychological support.
Steffens 2021	N=11; Age: 62(48-72) yrs; BMI: 29.6 kg·m^{-2} (imputed from reported height and weight so variation was not possible to calculate). Home-based functional exercise and encourage to walk at least 30 min. daily	N=11; Age: 66(46-70) yrs; BMI: 26.97 kg·m^{-2} (imputed from reported height and weight so variation was not possible to calculate). No exercise suggested.	Pelvic exenteration.	N	2-6 weeks	*Frequency of supervised sessions:* 1/week. *Session length:* 60 min. *Type:* Aerobic, breathing and muscle strength exercise. *Intensity:* Aerobic exercise at 12-14 RPE and strength training at 40%-60% RM *Progression*: Increasing the number of intervals or adding further load to the flywheel. *Additional support:* Not reported
Loughney 2021	N=17; Age: 64±14 yrs; BMI: 26.0±4.0 kg·m^{-2}. No more exercise suggested.	N=16; Age: 57±10 yrs; BMI: 27.0±3.0 kg·m^{-2}. No exercise suggested.	Rectal cancer patients.	Y	9 weeks	*Frequency of supervised sessions:* 3/week. *Session length:* 40 min. *Type:* HIIT on cycle ergometer. *Intensity:* 80 % of the O_2 uptake at ventilatory anaerobic threshold and power output half-way between ventilatory anaerobic threshold and VO_2 peak.

						Progression: Increasing the time of HIIT training from 30 min. to 40 min. *Additional support:* Not reported.
Blackwell 2020	N=19; Age: 71±2 yrs; BMI: not reported. No more exercise.	N=21; Age: 72±4 yrs; BMI not reported. No exercise suggested	Urological cancer.	N	4 weeks	*Frequency of supervised sessions:* 3-4/week. *Session length:* ~30 min. *Type:* HIIT on cycle ergometer. *Intensity:* 100-115% of maximal load reached during initial CPET *Progression:* Increased in wattage at mid-way point of training. *Additional support:* Not reported.
Carli 2020	N=55; Age: 78 (72-82) yrs; BMI 24.9 (23-30.1) $kg\cdot m^{-2}$ Frail patients/ Patients were encouraged to follow a homebased training program during the prehabilitation period.	N=55; Age: 82(75-84) yrs; BMI 26.4 (23.8-30.6) $kg\cdot m^{-2}$. Frail patients/ Patients were included in a 4-week rehabilitation program.	Non-metastatic colorectal cancer.	N	4 weeks.	*Frequency of supervised sessions:* 1/week. *Session length:* 60 min. *Type:* aerobic exercise and resistance exercises with elastic band. *Intensity:* Moderate aerobic exercise. Elastic band resistance training. *Progression:* Increased intensity in resistance exercise when patients reported 12 in Borg scale. *Additional support:* Nutritional and psychological support.

Wallen 2019	N=10; Age: 49 (40-60) yrs; BMI: not reported/Patients were encouraged to replicate the supervised program at home	N=11; Age: 49 (40-60) yrs; BMI: not reported/ No exercise suggested	Liver transplantation.	N	4 weeks (4 patients completed exercise for 8 weeks).	*Frequency of supervised sessions:* 2/week. *Session length:* Not reported. *Type:* Stationary walking or cycling and circuit-based resistance exercise. *Intensity:* Not reported. Progression: Not reported *Additional support:* Not reported.
Northgraves 2019	N=11; Age: 64.1±10.5 yrs; BMI: 30.3±4.3 kg·m^{-2}. No more exercise suggested	N=11; Age: Age 63.5±12.5 yrs; BMI: 27.8±5.7 kg·m^{-2}. No exercise suggested.	Elective cancer colorectal surgery.	Y 3 patients in UC. 4 in prehab.	22±7.5 days.	*Frequency of supervised sessions:* 3/week. *Session length:* 60 min. *Type:* Functional exercise training, including aerobic (cycle ergometer) and resistance exercises. *Intensity:* Aerobic exercise at 40-60% of heart rate reserve or 11-13 reported Borg-scale Progression: every 2-3 sessions increasing the repetitions/duration, adding resistance or increasing changing to an exercise that requires a more difficult technique. Aerobic exercise was increased 2-5 min. each session until a maximum of 25 min. *Additional support:* Not reported.
Banerjee 2018	N=30; Age: 71.6±6.8 yrs; BMI: 27.1±4.2 kg·m^{-2}. No more exercise	N=30; Age: 72.5±8.4 yrs; BMI: 26.9±4.5 kg·m^{-2}. No exercise suggested.	Bladder cancer surgery. Eligibility not limited by	Y 5 patients in UC and 10 patients in prehab.	3-6 weeks	*Frequency of supervised sessions:* 2/week. *Session length:* 60 min. *Type:* HIIT on cycle ergometer.

			chose of surgical technique.			*Intensity:* 13-15 RPE equating to 70-85% of maximum heart rate. Progression: gradually added more load to maintain the target RPE. *Additional support:* Not reported.
Bousquet-Dion 2018	N=41; Age 74 (67.5-78) yrs; BMI: BMI 27.5±4.1 kg·m^{-2}. Patients were encouraged to follow a homebased training program during the prehabilitation and post-surgery period.	N=39; Age 71 (54.5-74.5) yrs; BMI 28.6±4.5 kg·m^{-2}. Patients were included in an 8-week home-based rehabilitation program.	Colon or rectal cancer resection.	N	4 weeks.	*Frequency of supervised sessions:* 1/week. *Session length:* 60 min. *Type:* aerobic exercise and resistance exercises with elastic band. *Intensity:* Moderate aerobic exercise and perceived mild exertion in resistance exercise: 12 in Borg scale. *Progression:* Increased intensity in resistance exercise to maintain 12 in Borg scale. *Additional support:* Nutritional and psychological support.
Barberan-Garcia 2017	N=62; Age: 71±11 yrs; BMI: 21±7 k kg·m^{-2} Patients were encouraged to increase the number of steps taken per day.	N=63; Age: 71±10 yrs; BMI: 22±7 kg·m^{-2}. Physical activity recommendation.	Elective major abdominal surgery.	N	6 weeks.	*Frequency of supervised sessions:* 2/week. *Session length:* ~50 min. *Type:* HIIT exercise on cycle ergometer. *Intensity:* 70%-40% of peak work rate. *Progression:* After second week, every week, intensity increased 5% of peak work rate until a maximum of 85%-50% of peak work rate.

						Additional support: Psychological support.
Tew 2017	N=27; Age 74.6±5.5 yrs, BMI: 26.5±4.1 kg·m^{-2}. No more exercise.	N=26; age 74.9±6.4 yrs, BMI:26.8±3.4 kg·m^{-2}. No exercise suggested.	Open or endovascular repair of an infrarenal AAA.	N	4 weeks	*Frequency of supervised sessions:* 3/week. *Session length:* ~50 min. *Type:* HIIT on cycle ergometer. *Intensity:* alternating intervals of 5-7 of 10 perceived exertion in Borg scale. *Progression:* Maintaining 5-7 of 10 perceived exertion in Borg scale. *Additional support:* Not reported.
Barakat 2016	N=62; Age: 73.8±6.5 yrs; BMI: 26.7±3.5 kg·m^{-2}. No more exercise.	N=62; Age: 72.9±7.9 yrs; BMI: 27.4 ±4.2 kg·m^{-2}. No exercise suggested.	Open or endovascular AAA repair.	N	6 weeks.	*Frequency of supervised sessions:* 3/week. *Session length:* 60 min. *Type:* bodyweight exercises and moderate aerobic training. *Intensity:* Not reported. *Progression:* Not reported *Additional support:* Not reported
Dunne 2016	N=20; Age: 61 (56-66) yrs; BMI: 29.7±4.2 kg·m^{-2}. Patients were encouraged to follow clinical advice on home exercise before surgery.	N=18; Age: 62(53-72) yrs; BMI: 29.3±4.2 kg·m^{-2}. Patients were encouraged to follow clinical advice on home exercise before surgery.	Colorectal liver metastasis resection.	11 in prehab and 7 in UC	4 weeks	*Frequency of supervised sessions:* 3/week. *Session length:* 30 min. plus warm-up and cool down. *Type:* HIIT on cycle ergometer.

						Intensity: Alternating moderate (less than 60 % of VO_2 peak) exercise and vigorous exercise (more than 90 per cent VO_2 peak). *Progression:* Not reported. *Additional support:* Not reported.
Soares 2013	N=18; Age: 58.5 (51.3–63.5) yrs; BMI: 23.6 (19.7–25.9) $kg \cdot m^{-2}$. Patients were encouraged to perform inspiratory muscle training and follow a walking program at home 4 times a week that was part of the rehabilitation program. Patients were included in a 7-day rehabilitation program.	N=19; Age 55.0 (49.3–64.3) yrs; BMI: 24.2 (21.3–28.4) $kg \cdot m^{-2}$. Patients were included in a 7-day rehabilitation program.	Elective open abdominal surgery (defined as opening of the peritoneal cavity).	N	2-3 weeks.	*Frequency of supervised sessions:* 2/week. *Session length:* 50 min. *Type:* stretching exercises, global body mobilization, deep breathing, respiratory muscle training and walking. *Intensity:* 20% of maximal inspiratory pressure. Walking never exceeded 15 on Borg scale. *Progression:* Every week the load in respiratory training was increased 2 cmH_2O. *Additional support:* Not reported.
Dronkers 2010	N=22; Age: 71.1±6.3 yrs; BMI 26.6±3.6 $kg \cdot m^{-2}$. Patients were encouraged to follow an inspiratory training program and walk or cycle daily for 30 min at home.	N= 20; Age: 68.8±6.4 yrs; BMI 25.7±3.1 $kg \cdot m^{-2}$. Patients were advised to follow a home-based training program.	elective colon surgery.	N	2-4 weeks. Depending on waiting time to surgery.	*Frequency of supervised sessions:* 2/week. *Session length:* 60 min. *Type:* Lower limb extensions, inspiratory muscle training, aerobic training and functional activities. *Intensity:* lower limb extensions performed with an intensity of 60-80% maximum repetition, inspiratory muscle training at 10-60% of maximal inspiratory pressure and aerobic exercise at 55-75% of maximum heart rate or 11-13 of Borg scale.

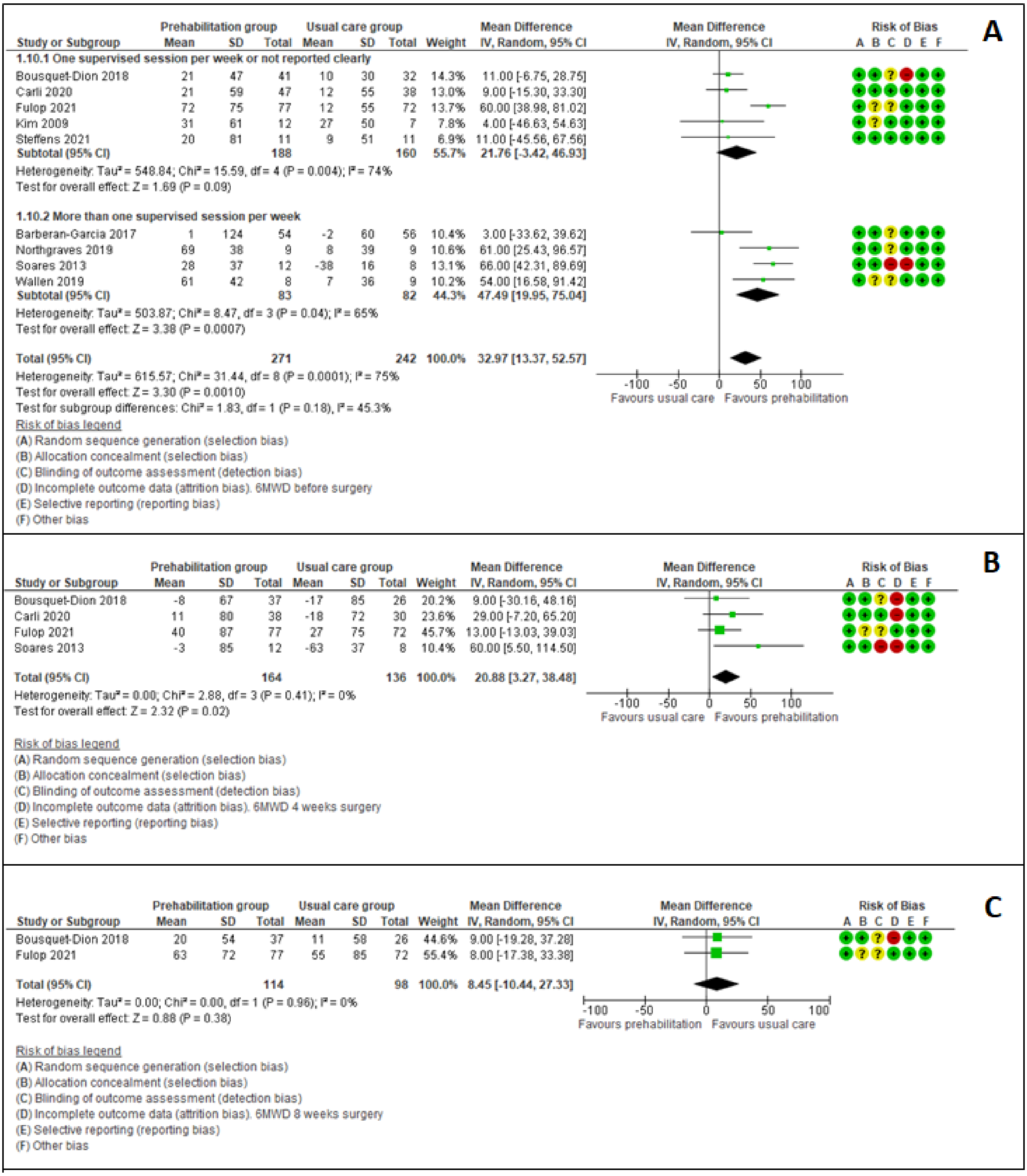
						Progression: Increased 10% of maximal inspiratory pressure if reported Borg scale was less than 13. *Additional support:* Not reported.
Kim 2009	N= 14; Age: 55±15 yrs; BMI: 26.6±5.9 kg·m^{-2}. The program was completed at home. Physiotherapist visited patients to make sure that patients were correctly completing and recording the exercise program.	N= 7; Age: 65±9 yrs; BMI: 25.3±2.7 kg·m^{-2}. No exercise suggested.	Colorectal surgery.	N	3.8±1.2 weeks.	*Frequency of supervised sessions:* ~1/week. *Session length:* 20-30 min. *Type:* Aerobic exercise on cycle-ergometer. *Intensity:* 40-65% of maximum heart rate or 11-16 of Borg scale. *Progression:* Increasing volume from 20 to 30 min, intensity from 40-65% of maximum heart rate or 11 to 16 of Borg scale along the prehabilitation program. *Additional support:* Not reported.

Data is presented as mean±SD or median (IQR).

AAA: Abdominal aortic aneurysm; BMI: Body mass index; Y: Yes; N: No; Yrs: years.

7.3.5. Physical function and strength changes

The most prevalent measure of physical function was the 6MWD (N=9). The change in 6MWD in the prehabilitation group was +33 m (95%CI: 13, 53 m; P: 0.001; I^2: 75%) compared to the change in the UC group before surgery (Figure 18A) (Barberan-Garcia et al., 2017, Bousquet-Dion et al., 2018, Carli et al., 2020, Kim et al., 2009, Northgraves et al., 2019, Soares et al., 2013, Wallen et al., 2019, Steffens et al., 2021b, Fulop et al., 2021). There was, however, substantial heterogeneity between the studies. The change in 6MWD in the prehabilitation programmes with one supervised session per week did not differ statistically significantly from the change in the UC group (mean differences of changes (baseline-pre-surgery between prehabilitation group and UC group: 22m, 95%CI: [-3, 47]; P: 0.09; I^2: 74%) (Bousquet-Dion et al., 2018, Carli et al., 2020, Kim et al., 2009, Fulop et al., 2021, Steffens et al., 2021b), while programmes with more than one session per week resulted in a change in 6MWD in the prehabilitation group of +47m (95%CI: 20, 75; P<0.001; I^2: 65%) compared to the change in the UC group (Figure 18A) (Barberan-Garcia et al., 2017, Northgraves et al., 2019, Soares et al., 2013, Wallen et al., 2019). Substantial heterogeneity remained in both subgroups. At 4 weeks after surgery, the change in 6MWD in the prehabilitation group was +21m (95%CI: 3, 38; P:0.02; I^2: 0%) compared to the UC group, from baseline (Figure 18B) (Soares et al., 2013, Bousquet-Dion et al., 2018, Carli et al., 2020, Fulop et al., 2021). In contrast, at 8 weeks after surgery, the prehabilitation group and UC group had a similar change in 6MWD, from baseline (mean differences of changes (baseline-8-weeks post-surgery) between prehabilitation group and UC group: 8m, 95%CI: [-10, 27]; P: 0.38; I^2: 0%) (Figure 18C)(Bousquet-Dion et al., 2018, Fulop et al., 2021).



A

	Prehabilitation group			Usual care group				Mean Difference	Risk of Bias					
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**A**	**B**	**C**	**D**	**E**	**F**
1.10.1 One supervised session per week or not reported clearly														
Bousquet-Dion 2018	21	47	41	10	30	32	14.3%	11.00 [-6.75, 28.75]	+	+	?	-	+	+
Carli 2020	21	59	47	12	55	38	13.0%	9.00 [-15.30, 33.30]	+	+	+	+	+	+
Fulop 2021	72	75	77	12	55	72	13.7%	60.00 [38.98, 81.02]	+	?	?	+	+	+
Kim 2009	31	61	12	27	50	7	7.8%	4.00 [-46.63, 54.63]	+	?	+	+	+	+
Steffens 2021	20	81	11	9	51	11	6.9%	11.00 [-45.56, 67.56]	+	+	+	+	+	+
Subtotal (95% CI)			**188**			**160**	**55.7%**	**21.76 [-3.42, 46.93]**						
Heterogeneity: Tau² = 548.84; Chi² = 15.59, df = 4 (P = 0.004); I² = 74%														
Test for overall effect: Z = 1.69 (P = 0.09)														
1.10.2 More than one supervised session per week														
Barberan-Garcia 2017	1	124	54	-2	60	56	10.4%	3.00 [-33.62, 39.62]	+	+	?	+	+	+
Northgraves 2019	69	38	9	8	39	9	10.6%	61.00 [25.43, 96.57]	+	+	?	+	+	+
Soares 2013	28	37	12	-38	16	8	13.1%	66.00 [42.31, 89.69]	+	+	-	-	+	+
Wallen 2019	61	42	8	7	36	9	10.2%	54.00 [16.58, 91.42]	+	?	?	+	+	+
Subtotal (95% CI)			**83**			**82**	**44.3%**	**47.49 [19.95, 75.04]**						
Heterogeneity: Tau² = 503.87; Chi² = 8.47, df = 3 (P = 0.04); I² = 65%														
Test for overall effect: Z = 3.38 (P = 0.0007)														
Total (95% CI)			**271**			**242**	**100.0%**	**32.97 [13.37, 52.57]**						
Heterogeneity: Tau² = 615.57; Chi² = 31.44, df = 8 (P = 0.0001); I² = 75%														
Test for overall effect: Z = 3.30 (P = 0.0010)														
Test for subgroup differences: Chi² = 1.83, df = 1 (P = 0.18), I² = 45.3%														

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias). 6MWD before surgery
(E) Selective reporting (reporting bias)
(F) Other bias

B

	Prehabilitation group			Usual care group				Mean Difference	Risk of Bias					
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**A**	**B**	**C**	**D**	**E**	**F**
Bousquet-Dion 2018	-8	67	37	-17	85	26	20.2%	9.00 [-30.16, 48.16]	+	+	?	-	+	+
Carli 2020	11	80	38	-18	72	30	23.6%	29.00 [-7.20, 65.20]	+	+	+	-	+	+
Fulop 2021	40	87	77	27	75	72	45.7%	13.00 [-13.03, 39.03]	+	?	?	+	+	+
Soares 2013	-3	85	12	-63	37	8	10.4%	60.00 [5.50, 114.50]	+	+	-	-	+	+
Total (95% CI)			**164**			**136**	**100.0%**	**20.88 [3.27, 38.48]**						
Heterogeneity: Tau² = 0.00; Chi² = 2.88, df = 3 (P = 0.41); I² = 0%														
Test for overall effect: Z = 2.32 (P = 0.02)														

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias). 6MWD 4 weeks surgery
(E) Selective reporting (reporting bias)
(F) Other bias

C

	Prehabilitation group			Usual care group				Mean Difference	Risk of Bias					
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**A**	**B**	**C**	**D**	**E**	**F**
Bousquet-Dion 2018	20	54	37	11	58	26	44.6%	9.00 [-19.28, 37.28]	+	+	?	-	+	+
Fulop 2021	63	72	77	55	85	72	55.4%	8.00 [-17.38, 33.38]	+	?	?	+	+	+
Total (95% CI)			**114**			**98**	**100.0%**	**8.45 [-10.44, 27.33]**						
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%														
Test for overall effect: Z = 0.88 (P = 0.38)														

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias). 6MWD 8 weeks surgery
(E) Selective reporting (reporting bias)
(F) Other bias

Figure 18. 6 minutes walk distance forest plots.
A: Forest plot comparing changes in 6-minute walking distance between prehabilitation group and usual care group. Mean changes between baseline and after completing the prehabilitation program (pre-surgery). B: Forest plot comparing changes in 6-minute walking distance between prehabilitation group and usual care group. Mean changes between baseline and after completing the prehabilitation program (4 weeks post-surgery). C: Forest plot comparing changes in 6-minute walking distance between prehabilitation group and usual care group. Mean changes between baseline and after completing the prehabilitation program (8 weeks post-surgery).
Risk of bias assessment symbols: + = low risk of bias, - = high risk of bias and ? = unclear risk of bias.

Data is presented as mean [CI].

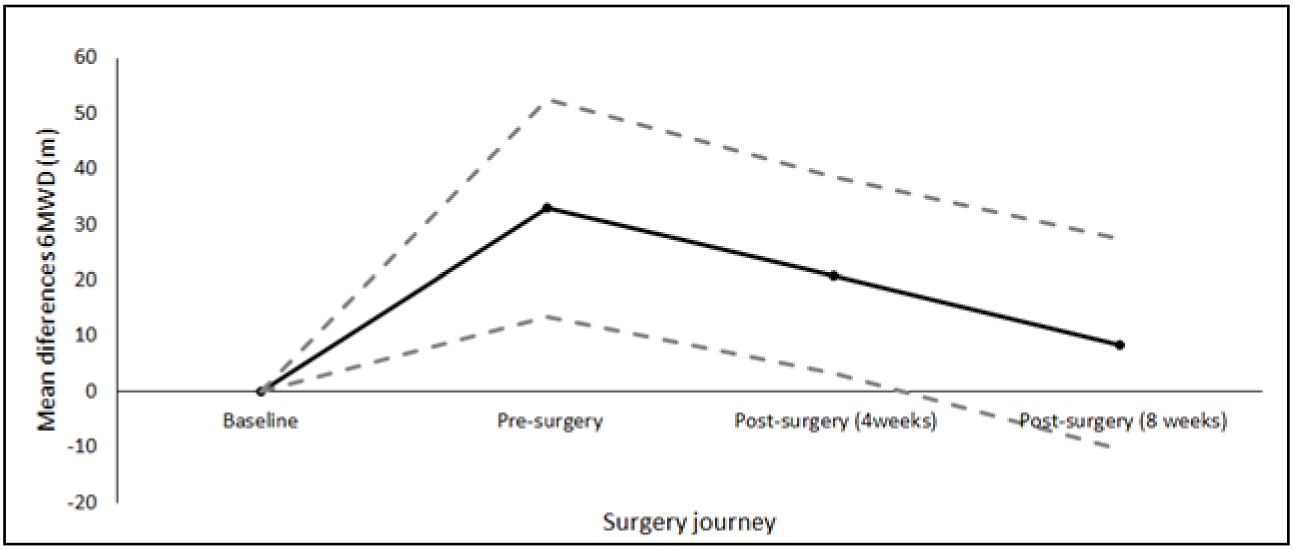
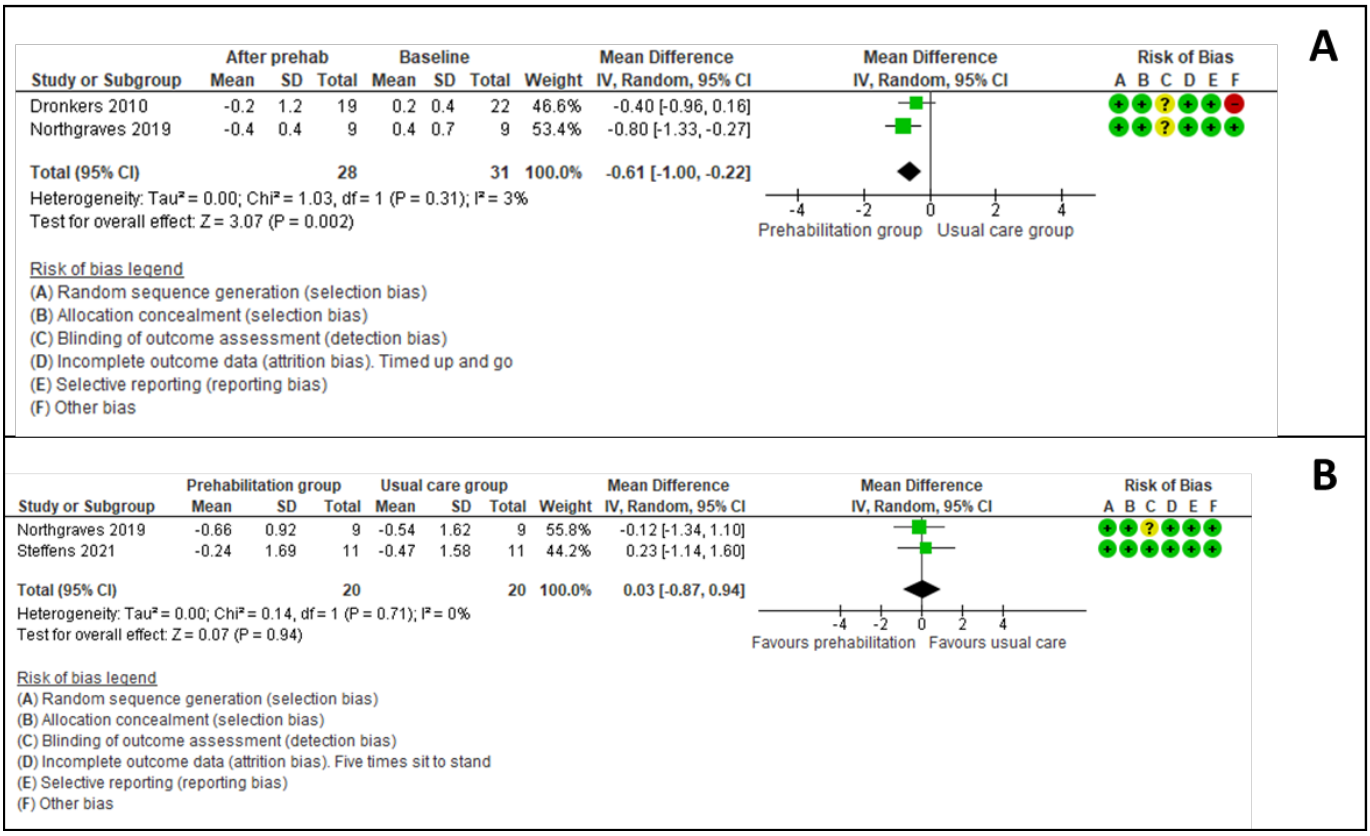


Figure 19: Line graph of the mean differences in changes in 6MWD between prehabilitation group and usual care group through the surgery journey.
Solid line represents the mean differences in 6MWD between prehabilitation group and usual care group and the dashed line represents the 95% confidence interval of the mean differences in 6MWD between prehabilitation group and usual care group.

While the change in TUG in the prehabilitation group was -0.6 s (95%CI: [-1, -0.2]; P<0.01; I^2: 3%) compared to that seen in UC group before surgery (Dronkers et al., 2010, Northgraves et al., 2019) the changes in ‘five times sit to stand test’ did not differ significantly between groups (Mean differences of changes (baseline-pre-surgery) between prehabilitation group and UC group: 0.03 s, 95% CI: [-0.87, 0.94]; P: 0.71; I^2: 0%) (Figure 20A and Figure 20B). Chair rise test was only reported in one study, and it was not significantly improved by prehabilitation before surgery (Dronkers et al., 2010).



Study or Subgroup	After prehab Mean	After prehab SD	After prehab Total	Baseline Mean	Baseline SD	Baseline Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Dronkers 2010	-0.2	1.2	19	0.2	0.4	22	46.6%	-0.40 [-0.96, 0.16]	+	+	?	+	+	-
Northgraves 2019	-0.4	0.4	9	0.4	0.7	9	53.4%	-0.80 [-1.33, -0.27]	+	+	?	+	+	+
Total (95% CI)			**28**			**31**	**100.0%**	**-0.61 [-1.00, -0.22]**						

Heterogeneity: Tau² = 0.00; Chi² = 1.03, df = 1 (P = 0.31); I² = 3%
Test for overall effect: Z = 3.07 (P = 0.002)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias). Timed up and go
(E) Selective reporting (reporting bias)
(F) Other bias

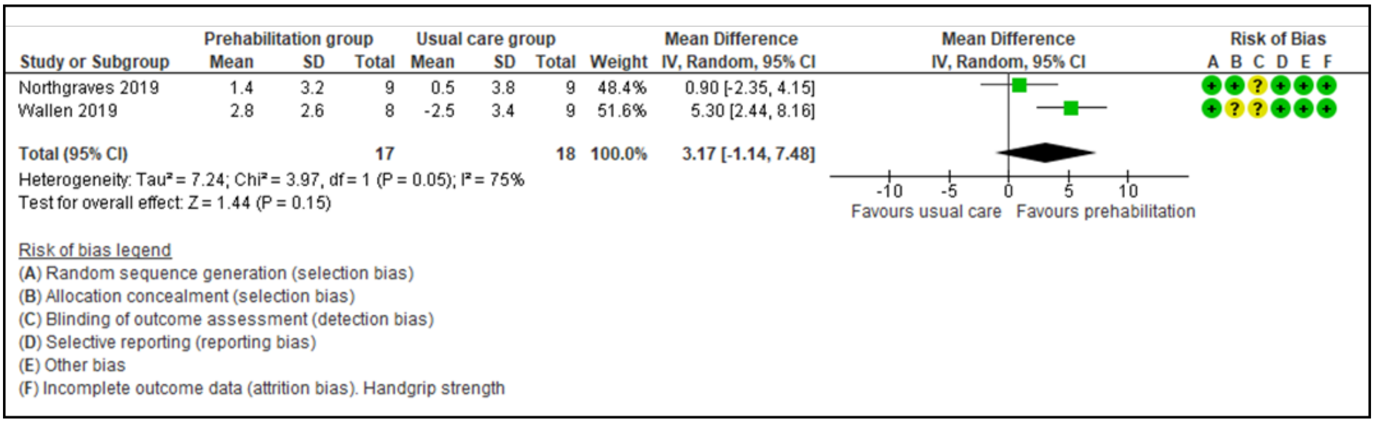
Study or Subgroup	Prehabilitation group Mean	Prehabilitation group SD	Prehabilitation group Total	Usual care group Mean	Usual care group SD	Usual care group Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Northgraves 2019	-0.66	0.92	9	-0.54	1.62	9	55.8%	-0.12 [-1.34, 1.10]	+	+	?	+	+	+
Steffens 2021	-0.24	1.69	11	-0.47	1.58	11	44.2%	0.23 [-1.14, 1.60]	+	+	+	+	+	+
Total (95% CI)			**20**			**20**	**100.0%**	**0.03 [-0.87, 0.94]**						

Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.94)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias). Five times sit to stand
(E) Selective reporting (reporting bias)
(F) Other bias

Figure 20. Timed up and go and five times sit to stand forest plots.
A: Mean differences of timed up and go changes (Baseline-Pre-surgery) between prehabilitation and usual care group. B: Mean differences of five times sit and go (Baseline-Pre-surgery) between prehabilitation and usual care group. Risk of bias assessment symbols: + = low risk of bias, - = high risk of bias and ? = unclear risk of bias.
Data is presented as mean [CI].

No significant differences were observed in the change of handgrip strength between groups before surgery (mean differences of changes (baseline-pre-surgery) between prehabilitation group and UC group: 3.2 kg, 95%CI: [-1.1, 7.5]; P:0.15; I^2:75%) (Wallen et al., 2019, Northgraves et al., 2019) (Figure 21).



	Prehabilitation group			Usual care group				Mean Difference	Risk of Bias					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	A	B	C	D	E	F
Northgraves 2019	1.4	3.2	9	0.5	3.8	9	48.4%	0.90 [-2.35, 4.15]	+	+	?	+	+	+
Wallen 2019	2.8	2.6	8	-2.5	3.4	9	51.6%	5.30 [2.44, 8.16]	+	?	?	+	+	+
Total (95% CI)			**17**			**18**	**100.0%**	**3.17 [-1.14, 7.48]**						

Heterogeneity: Tau² = 7.24; Chi² = 3.97, df = 1 (P = 0.05); I² = 75%
Test for overall effect: Z = 1.44 (P = 0.15)

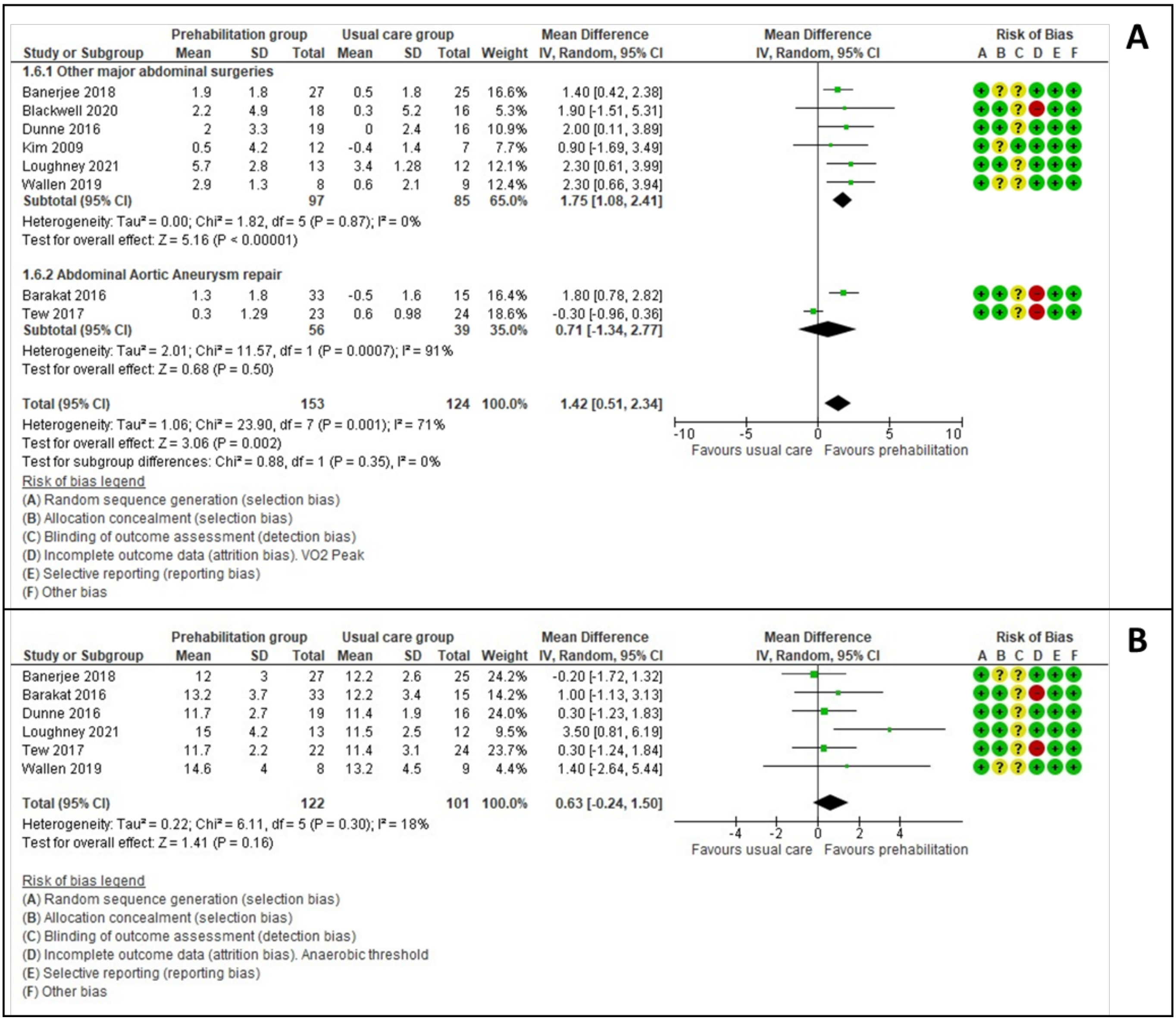
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Selective reporting (reporting bias)
(E) Other bias
(F) Incomplete outcome data (attrition bias). Handgrip strength

Figure 21. Forest plot of mean differences of handgrip strength changes (Baseline-Pre-surgery) between prehabilitation and usual care group.
= high risk of bias and ? = unclear risk of bias.
Data is presented as mean [CI].

7.3.6. Cardiopulmonary changes

One study was excluded from the meta-analysis because the VO_2 peak was calculated indirectly using the physical work capacity at a heart rate of 170 beats test (PW_{170} test) (Dronkers et al., 2010). In the remaining studies, the change in VO_2 peak in the prehabilitation group was +1.42 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$ (95%CI: 0.51, 2.34; P: 0.002; I^2: 0%) above the UC group (Figure 22A) (Barakat et al., 2016, Dunne et al., 2016, Kim et al., 2009, Tew et al., 2017, Wallen et al., 2019, Banerjee et al., 2018, Loughney et al., 2021, Blackwell et al., 2020). There was, however, substantial heterogeneity. As all studies, except one, delivered more than one supervised session per week in their prehabilitation programs, other pre-specified factors (apart from supervised training frequency) were considered to resolve the substantial heterogeneity. A subgroup analysis by the surgery type was performed. In subgroup analysis, VO_2 peak change of the prehabilitation group was not significantly different from that achieved by the UC group in patients preparing for an Abdominal aortic aneurysm (AAA) repair (mean differences of changes (baseline-pre-surgery) between the prehabilitation group and UC group: 0.71 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$, 95%CI: [-1.34, 2.77]; P: 0.5; I^2: 91%) but it was significantly different in patients preparing for other types of abdominal surgeries (mean differences of changes (baseline-pre-surgery) between prehabilitation group and UC group: 1.75 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$; 95%CI: [1.08, 2.41]; P<0.001; I^2: 0%) (Figure 22A) (Barakat et al., 2016, Tew et al., 2017). The two studies included in this subgroup were assessing as having high risk of bias due to the loss of follow-up data. Data from Blackwell et al. (2020) was retrieved from previous meta-analysis (Waterland et al., 2021). Including the data from this study (Figure 23) did not significantly change the outcomes reported above (Mean differences of changes (baseline-pre-surgery) between prehabilitation and UC: 1.40 ml·kg^{-1}·min^{-1}, 95%CI: [0.44, 2.36]; P<0.01; I^2:75%).

The change in AT between baseline and pre-surgery was not significantly different between groups (mean differences of changes (baseline-pre-surgery) between prehabilitation group and UC group: 0.63 ml·kg^{-1}·min^{-1}, 95%CI: [-0.24, 1.50]; P: 0.16; I^2: 18%) (Figure 22B) (Barakat et al., 2016, Dunne et al., 2016, Tew et al., 2017, Wallen et al., 2019, Banerjee et al., 2018, Loughney et al., 2021)



	Prehabilitation group			Usual care group				Mean Difference	Risk of Bias					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	A	B	C	D	E	F
1.6.1 Other major abdominal surgeries														
Banerjee 2018	1.9	1.8	27	0.5	1.8	25	16.6%	1.40 [0.42, 2.38]	+	?	?	+	+	+
Blackwell 2020	2.2	4.9	18	0.3	5.2	16	5.3%	1.90 [-1.51, 5.31]	+	+	?	−	+	+
Dunne 2016	2	3.3	19	0	2.4	16	10.9%	2.00 [0.11, 3.89]	+	+	?	+	+	+
Kim 2009	0.5	4.2	12	-0.4	1.4	7	7.7%	0.90 [-1.69, 3.49]	+	?	+	+	+	+
Loughney 2021	5.7	2.8	13	3.4	1.28	12	12.1%	2.30 [0.61, 3.99]	+	+	?	+	+	+
Wallen 2019	2.9	1.3	8	0.6	2.1	9	12.4%	2.30 [0.66, 3.94]	+	?	?	+	+	+
Subtotal (95% CI)			**97**			**85**	**65.0%**	**1.75 [1.08, 2.41]**						
Heterogeneity: Tau² = 0.00; Chi² = 1.82, df = 5 (P = 0.87); I² = 0%														
Test for overall effect: Z = 5.16 (P < 0.00001)														
1.6.2 Abdominal Aortic Aneurysm repair														
Barakat 2016	1.3	1.8	33	-0.5	1.6	15	16.4%	1.80 [0.78, 2.82]	+	+	?	−	+	+
Tew 2017	0.3	1.29	23	0.6	0.98	24	18.6%	-0.30 [-0.96, 0.36]	+	+	?	−	+	+
Subtotal (95% CI)			**56**			**39**	**35.0%**	**0.71 [-1.34, 2.77]**						
Heterogeneity: Tau² = 2.01; Chi² = 11.57, df = 1 (P = 0.0007); I² = 91%														
Test for overall effect: Z = 0.68 (P = 0.50)														
Total (95% CI)			**153**			**124**	**100.0%**	**1.42 [0.51, 2.34]**						
Heterogeneity: Tau² = 1.06; Chi² = 23.90, df = 7 (P = 0.001); I² = 71%														
Test for overall effect: Z = 3.06 (P = 0.002)														
Test for subgroup differences: Chi² = 0.88, df = 1 (P = 0.35), I² = 0%														

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias). VO2 Peak
(E) Selective reporting (reporting bias)
(F) Other bias

	Prehabilitation group			Usual care group				Mean Difference	Risk of Bias					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	A	B	C	D	E	F
Banerjee 2018	12	3	27	12.2	2.6	25	24.2%	-0.20 [-1.72, 1.32]	+	?	?	+	+	+
Barakat 2016	13.2	3.7	33	12.2	3.4	15	14.2%	1.00 [-1.13, 3.13]	+	+	?	−	+	+
Dunne 2016	11.7	2.7	19	11.4	1.9	16	24.0%	0.30 [-1.23, 1.83]	+	+	?	+	+	+
Loughney 2021	15	4.2	13	11.5	2.5	12	9.5%	3.50 [0.81, 6.19]	+	+	?	+	+	+
Tew 2017	11.7	2.2	22	11.4	3.1	24	23.7%	0.30 [-1.24, 1.84]	+	+	?	−	+	+
Wallen 2019	14.6	4	8	13.2	4.5	9	4.4%	1.40 [-2.64, 5.44]	+	?	?	+	+	+
Total (95% CI)			**122**			**101**	**100.0%**	**0.63 [-0.24, 1.50]**						
Heterogeneity: Tau² = 0.22; Chi² = 6.11, df = 5 (P = 0.30); I² = 18%														
Test for overall effect: Z = 1.41 (P = 0.16)														

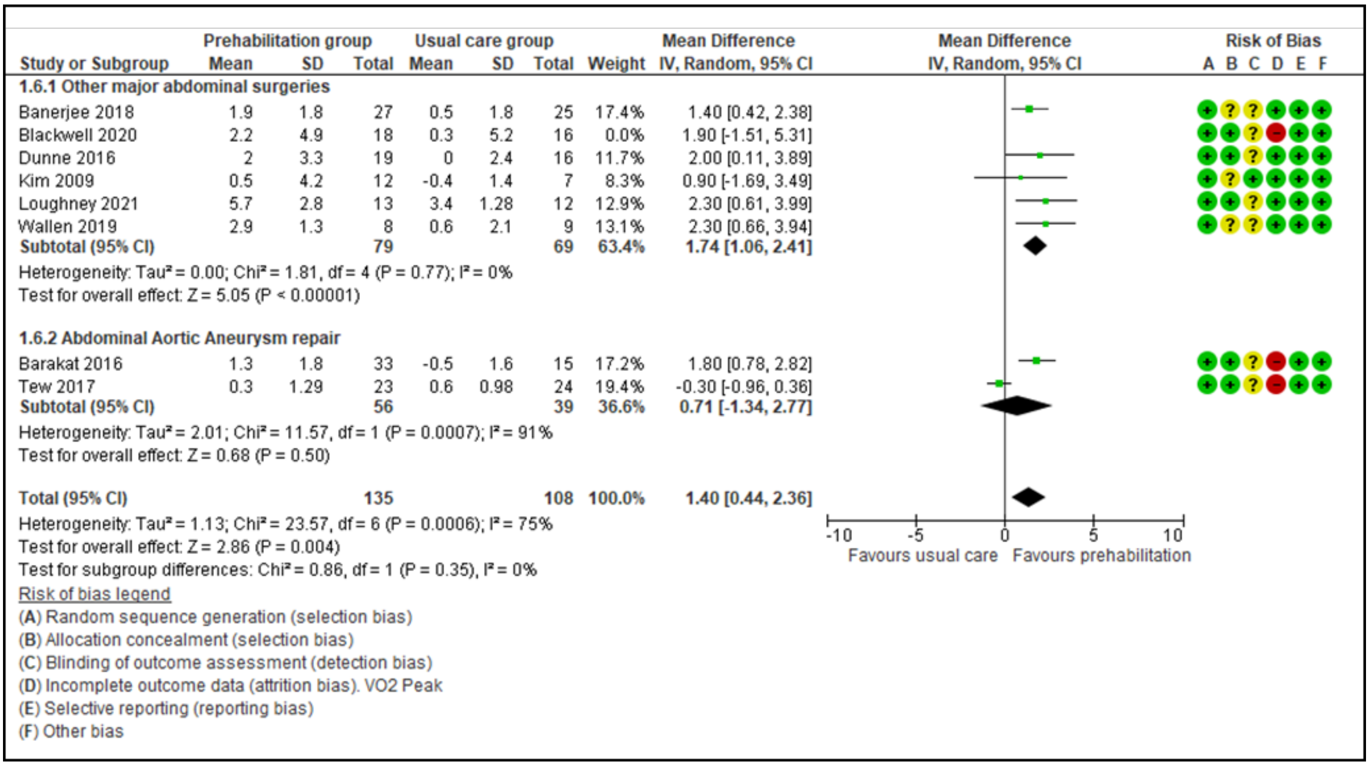
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias). Anaerobic threshold
(E) Selective reporting (reporting bias)
(F) Other bias

Figure 22. Cardiorespiratory capacity forest plots.

A: Forest plot comparing changes in VO$_2$ *peak (ml·kg*$^{-1}$*·min*$^{-1}$*) between prehabilitation group and usual care group. Mean changes between baseline and after completing the prehabilitation program (pre-surgery). B: Forest plot comparing changes* *in anaerobic threshold (ml·kg^{-1}·min^{-1}) between prehabilitation group and usual care group. Follow-up values after completing the prehabilitation program (pre-surgery).*

Risk of bias assessment symbols: + = low risk of bias, - = high risk of bias and ? = unclear risk of bias.

Data is presented as mean [CI].



	Prehabilitation group			Usual care group				Mean Difference	Risk of Bias					
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**A**	**B**	**C**	**D**	**E**	**F**
1.6.1 Other major abdominal surgeries														
Banerjee 2018	1.9	1.8	27	0.5	1.8	25	17.4%	1.40 [0.42, 2.38]	+	?	?	+	+	+
Blackwell 2020	2.2	4.9	18	0.3	5.2	16	0.0%	1.90 [-1.51, 5.31]	+	+	?	−	+	+
Dunne 2016	2	3.3	19	0	2.4	16	11.7%	2.00 [0.11, 3.89]	+	+	?	+	+	+
Kim 2009	0.5	4.2	12	-0.4	1.4	7	8.3%	0.90 [-1.69, 3.49]	+	?	+	+	+	+
Loughney 2021	5.7	2.8	13	3.4	1.28	12	12.9%	2.30 [0.61, 3.99]	+	+	?	+	+	+
Wallen 2019	2.9	1.3	8	0.6	2.1	9	13.1%	2.30 [0.66, 3.94]	+	?	?	+	+	+
Subtotal (95% CI)			**79**			**69**	**63.4%**	**1.74 [1.06, 2.41]**						
Heterogeneity: Tau² = 0.00; Chi² = 1.81, df = 4 (P = 0.77); I² = 0%														
Test for overall effect: Z = 5.05 (P < 0.00001)														
1.6.2 Abdominal Aortic Aneurysm repair														
Barakat 2016	1.3	1.8	33	-0.5	1.6	15	17.2%	1.80 [0.78, 2.82]	+	+	?	−	+	+
Tew 2017	0.3	1.29	23	0.6	0.98	24	19.4%	-0.30 [-0.96, 0.36]	+	+	?	−	+	+
Subtotal (95% CI)			**56**			**39**	**36.6%**	**0.71 [-1.34, 2.77]**						
Heterogeneity: Tau² = 2.01; Chi² = 11.57, df = 1 (P = 0.0007); I² = 91%														
Test for overall effect: Z = 0.68 (P = 0.50)														
Total (95% CI)			**135**			**108**	**100.0%**	**1.40 [0.44, 2.36]**						
Heterogeneity: Tau² = 1.13; Chi² = 23.57, df = 6 (P = 0.0006); I² = 75%														
Test for overall effect: Z = 2.86 (P = 0.004)														
Test for subgroup differences: Chi² = 0.86, df = 1 (P = 0.35), I² = 0%														

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias). VO2 Peak
(E) Selective reporting (reporting bias)
(F) Other bias

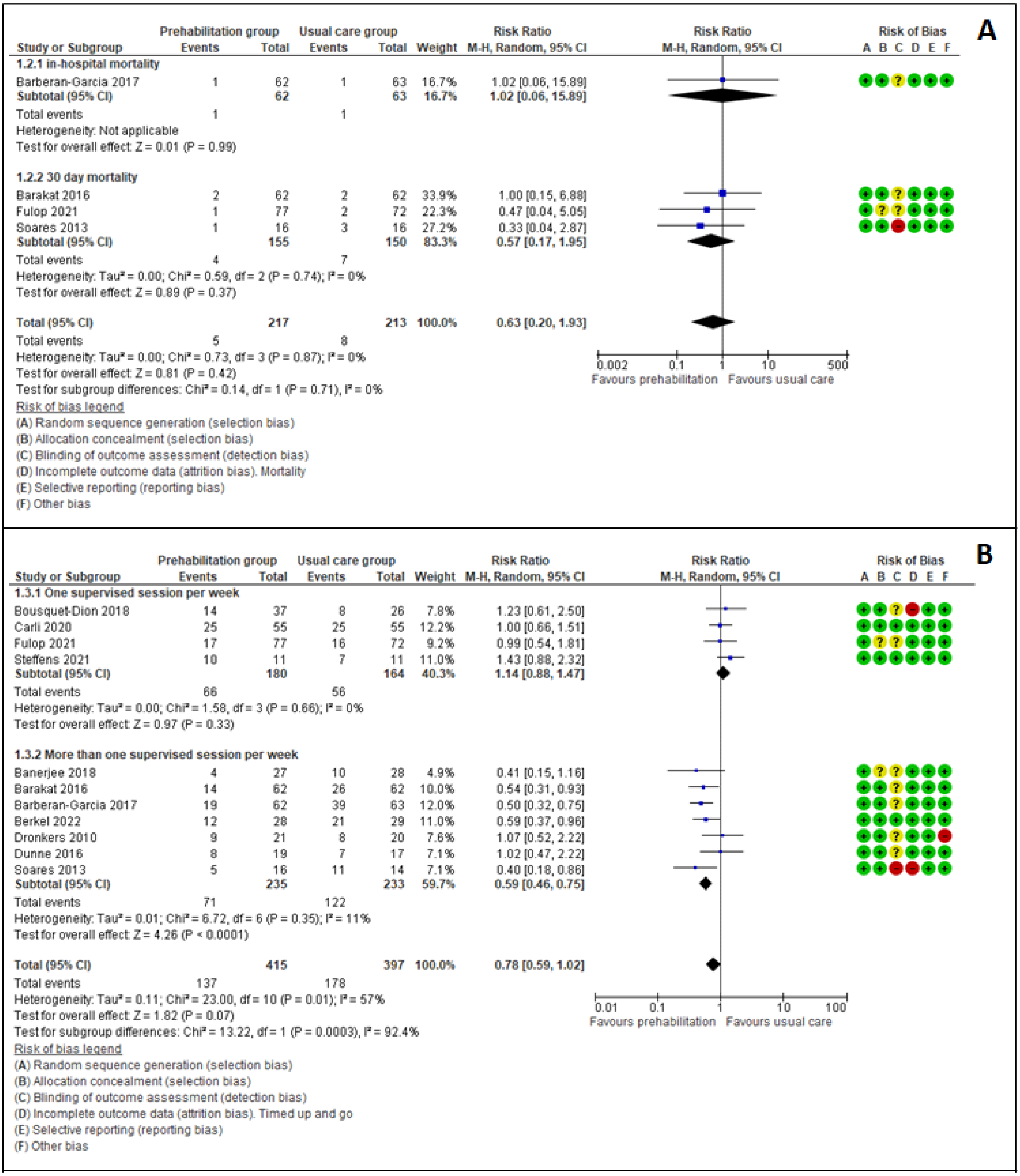
Figure 23. Forest plot of mean differences of VO_2 peak changes (Baseline-Pre-surgery) between prehabilitation group and usual care group without Blackwell et al. (2020).

7.3.7. Surgical outcomes

Meta-analyses were only performed with four studies for in-hospital and 30-day mortality (Barberan-Garcia et al., 2017, Barakat et al., 2016, Soares et al., 2013, Fulop et al., 2021). Overall, premature mortality risk was not statistically significantly reduced in patients that followed a prehabilitation program compared to patients that followed UC (RR [95%CI]: 0.63 [0.20, 1.93]; P: 0.42; I^2:0%) (Figure 24A). One study, including liver transplantation patients, reported no mortality in any group 90 days after surgery (Wallen et al., 2019).

The incidence of post-operative complications - incidents that prevented a participant from a normal recovery after surgery - was not significantly less in the prehabilitation group compared to the UC group (RR [95%CI]: 0.78 [0.59, 1.02]; P: 0.07; I^2:57%) (Berkel et al., 2022a, Barakat et al., 2016, Barberan-Garcia et al., 2017, Bousquet-Dion et al., 2018, Carli et al., 2020, Dronkers et al., 2010, Dunne et al., 2016, Fulop et al., 2021, Steffens et al., 2021b, Soares et al., 2013). Sub-group analysis revealed that only in studies including a minimum of 2 supervised sessions per week was a reduction in the total number of post-operative complications was observed (RR [95%CI]: 0.59 [0.46, 0.75]; P<0.001; I^2:11%, Figure 24B).

Severe post-operative complications were defined as those requiring further surgical interventions (Barakat et al., 2016, Barberan-Garcia et al., 2017, Soares et al., 2013, Berkel et al., 2022a) or complications assessed as ≥III by the Clavien-Dindo scale (Banerjee et al., 2018, Bousquet-Dion et al., 2018, Carli et al., 2020, Dunne et al., 2016, Fulop et al., 2021). The incidence of severe post-operative complications was not significantly different between groups (RR: 0.98, 95%CI: [0.63, 1.53]; P: 0.79; I^2: 0%, Figure 25).



A

Study or Subgroup	Prehabilitation group Events	Total	Usual care group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
1.2.1 in-hospital mortality												
Barberan-Garcia 2017	1	62	1	63	16.7%	1.02 [0.06, 15.89]	+	+	?	+	+	+
Subtotal (95% CI)		**62**		**63**	**16.7%**	**1.02 [0.06, 15.89]**						
Total events	1		1									
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.01 (P = 0.99)												
1.2.2 30 day mortality												
Barakat 2016	2	62	2	62	33.9%	1.00 [0.15, 6.88]	+	+	?	+	+	+
Fulop 2021	1	77	2	72	22.3%	0.47 [0.04, 5.05]	+	?	?	+	+	+
Soares 2013	1	16	3	16	27.2%	0.33 [0.04, 2.87]	+	+	-	+	+	+
Subtotal (95% CI)		**155**		**150**	**83.3%**	**0.57 [0.17, 1.95]**						
Total events	4		7									
Heterogeneity: Tau² = 0.00; Chi² = 0.59, df = 2 (P = 0.74); I² = 0%												
Test for overall effect: Z = 0.89 (P = 0.37)												
Total (95% CI)		**217**		**213**	**100.0%**	**0.63 [0.20, 1.93]**						
Total events	5		8									
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 3 (P = 0.87); I² = 0%												
Test for overall effect: Z = 0.81 (P = 0.42)												
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² = 0%												

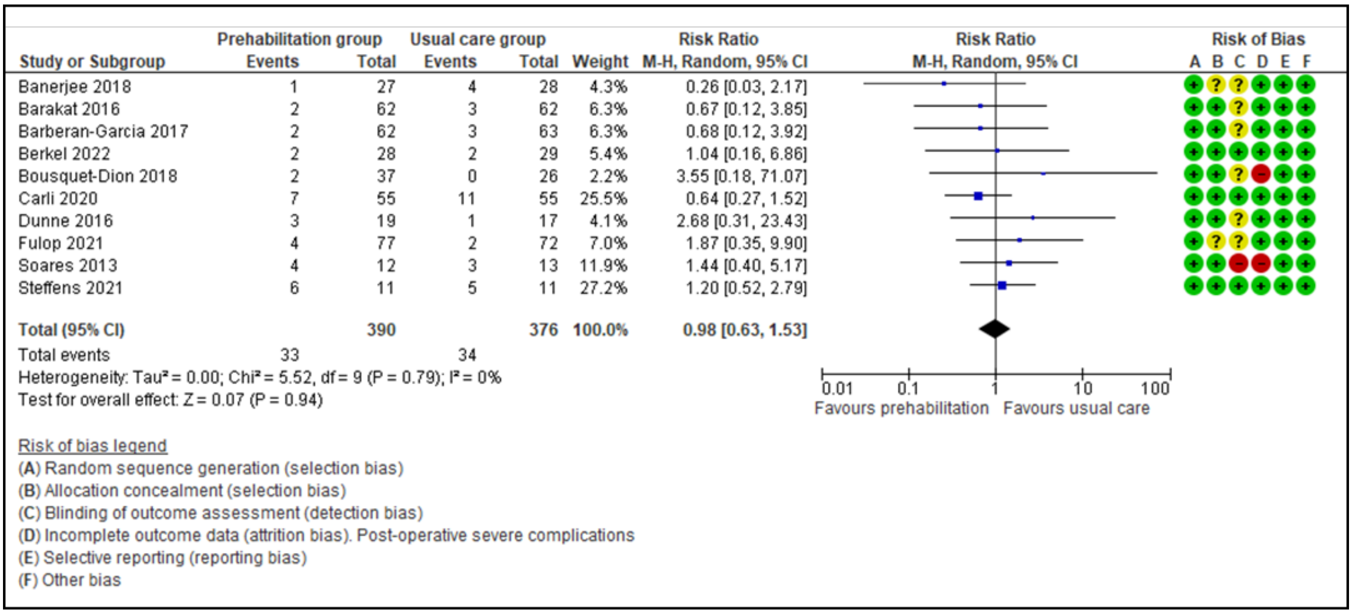
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias). Mortality
(E) Selective reporting (reporting bias)
(F) Other bias

B

Study or Subgroup	Prehabilitation group Events	Total	Usual care group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
1.3.1 One supervised session per week												
Bousquet-Dion 2018	14	37	8	26	7.8%	1.23 [0.61, 2.50]	+	+	?	-	+	+
Carli 2020	25	55	25	55	12.2%	1.00 [0.66, 1.51]	+	+	+	+	+	+
Fulop 2021	17	77	16	72	9.2%	0.99 [0.54, 1.81]	+	?	?	+	+	+
Steffens 2021	10	11	7	11	11.0%	1.43 [0.88, 2.32]	+	+	+	+	+	+
Subtotal (95% CI)		**180**		**164**	**40.3%**	**1.14 [0.88, 1.47]**						
Total events	66		56									
Heterogeneity: Tau² = 0.00; Chi² = 1.58, df = 3 (P = 0.66); I² = 0%												
Test for overall effect: Z = 0.97 (P = 0.33)												
1.3.2 More than one supervised session per week												
Banerjee 2018	4	27	10	28	4.9%	0.41 [0.15, 1.16]	+	?	?	+	+	+
Barakat 2016	14	62	26	62	10.0%	0.54 [0.31, 0.93]	+	+	?	+	+	+
Barberan-Garcia 2017	19	62	39	63	12.0%	0.50 [0.32, 0.75]	+	+	?	+	+	+
Berkel 2022	12	28	21	29	11.0%	0.59 [0.37, 0.96]	+	+	+	+	+	+
Dronkers 2010	9	21	8	20	7.6%	1.07 [0.52, 2.22]	+	+	?	+	+	-
Dunne 2016	8	19	7	17	7.1%	1.02 [0.47, 2.22]	+	+	?	+	+	+
Soares 2013	5	16	11	14	7.1%	0.40 [0.18, 0.86]	+	+	-	-	+	+
Subtotal (95% CI)		**235**		**233**	**59.7%**	**0.59 [0.46, 0.75]**						
Total events	71		122									
Heterogeneity: Tau² = 0.01; Chi² = 6.72, df = 6 (P = 0.35); I² = 11%												
Test for overall effect: Z = 4.26 (P < 0.0001)												
Total (95% CI)		**415**		**397**	**100.0%**	**0.78 [0.59, 1.02]**						
Total events	137		178									
Heterogeneity: Tau² = 0.11; Chi² = 23.00, df = 10 (P = 0.01); I² = 57%												
Test for overall effect: Z = 1.82 (P = 0.07)												
Test for subgroup differences: Chi² = 13.22, df = 1 (P = 0.0003), I² = 92.4%												

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias). Timed up and go
(E) Selective reporting (reporting bias)
(F) Other bias

Figure 24. Surgical outcomes forest plots.
A: Forest plot comparing the risk of mortality (RR) between prehabilitation group and usual care group. B: Forest plot comparing risk of post-operative complications (RR) between prehabilitation group and usual care group.
Risk of bias assessment symbols: + = low risk of bias, - = high risk of bias and ? = unclear risk of bias.
Data is presented as risk ratios [95% CI] and mean [95% CI].



Study or Subgroup	Prehabilitation group Events	Prehabilitation group Total	Usual care group Events	Usual care group Total	Weight	Risk Ratio M-H, Random, 95% CI	A	B	C	D	E	F
Banerjee 2018	1	27	4	28	4.3%	0.26 [0.03, 2.17]	+	?	?	+	+	+
Barakat 2016	2	62	3	62	6.3%	0.67 [0.12, 3.85]	+	+	?	+	+	+
Barberan-Garcia 2017	2	62	3	63	6.3%	0.68 [0.12, 3.92]	+	+	?	+	+	+
Berkel 2022	2	28	2	29	5.4%	1.04 [0.16, 6.86]	+	+	+	+	+	+
Bousquet-Dion 2018	2	37	0	26	2.2%	3.55 [0.18, 71.07]	+	+	?	-	+	+
Carli 2020	7	55	11	55	25.5%	0.64 [0.27, 1.52]	+	+	+	+	+	+
Dunne 2016	3	19	1	17	4.1%	2.68 [0.31, 23.43]	+	+	?	+	+	+
Fulop 2021	4	77	2	72	7.0%	1.87 [0.35, 9.90]	+	?	?	+	+	+
Soares 2013	4	12	3	13	11.9%	1.44 [0.40, 5.17]	+	+	-	-	+	+
Steffens 2021	6	11	5	11	27.2%	1.20 [0.52, 2.79]	+	+	+	+	+	+
Total (95% CI)		**390**		**376**	**100.0%**	**0.98 [0.63, 1.53]**						
Total events	33		34									

Heterogeneity: Tau² = 0.00; Chi² = 5.52, df = 9 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.94)

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of outcome assessment (detection bias)
(**D**) Incomplete outcome data (attrition bias). Post-operative severe complications
(**E**) Selective reporting (reporting bias)
(**F**) Other bias

Figure 25. Forest plot of the risk of severe post-operative complications between prehabilitation group and usual care group. Risk of bias assessment symbols: + = low risk of bias, - = high risk of bias and ? = unclear risk of bias.
Data is presented as risk ratios [95% CI] and mean [95% CI].

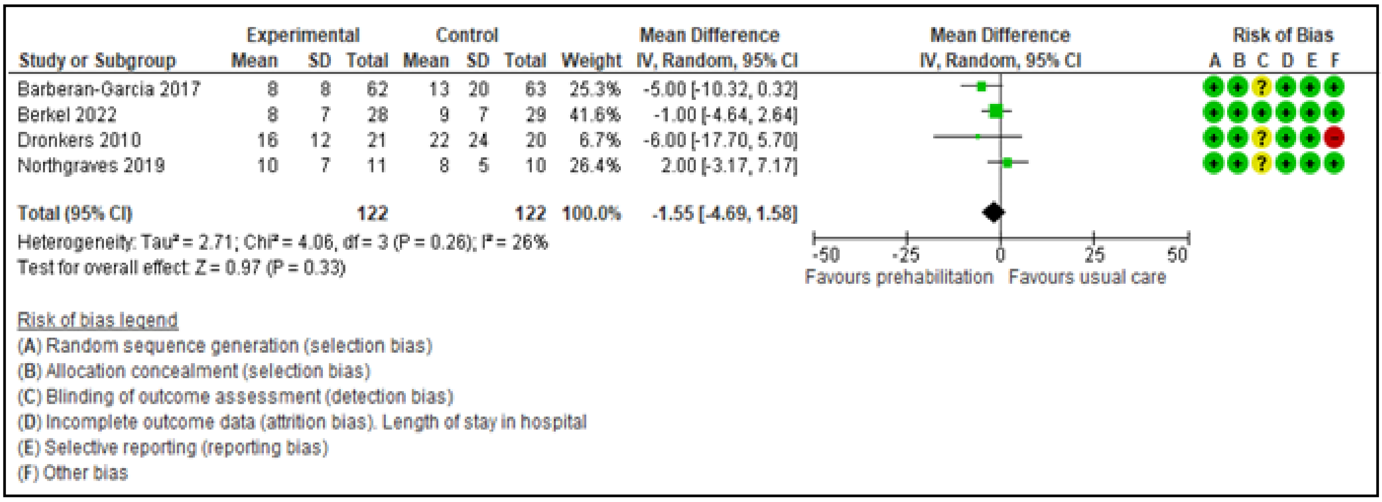
The LOS is reported in Table 10. All studies, except five (Loughney et al., 2021, Blackwell et al., 2020, Wallen et al., 2019, Tew et al., 2017, Kim et al., 2009), reported LOS. Studies that reported median and IQR were excluded from the analysis as it is probable that the data was not normally distributed and therefore the estimation of mean and SD could not be accurately determined. LOS was not significantly reduced in the prehabilitation group compared to the UC group (mean differences of changes (baseline-pre-surgery) between the prehabilitation group and UC group: -1.55 days, 95%CI: [-4.69, 1.58]; P: 0.33; I^2: 26%) (Figure 26).

Table 10. Length of stay in hospital.

	Prehab	Usual care
Berkel 2022	8.4±7.4	9.1±7.0
Fulop 2021	8 (7-10)	8 (7-9)
Steffens 2021	36 (15.0-52.0)	29.0 (15.0-53.0)
Carli 2020	4.0 (3.0-8.0)	5.0 (3.0-9.0)
Northgraves 2019	10.0±7.0	8.0±5.0
Banerjee 2018	7 [4-78]	7 [5-107]
Bousquet-Dion 2018*	3.0 (3.0-5.5)	3.0 (2.0-4.0)
Barberan-Garcia 2017	8.0±8.0	13.0±20.0

Barakat 2016*	7.0 (5.0-9.0)	8.0 (6.0-12.3)
Dunne 2016	5 (4-6)	5 (4.5-7)
Soares 2013	8.5 (4.8–12.3)	8.5 (6.5–17.3)
Dronkers 2010	16.2±11.5	21.6±23.7

*Data presented as median (IQR), median [range] or mean±SD. *denotes significant difference between groups.*



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Barberan-Garcia 2017	8	8	62	13	20	63	25.3%	-5.00 [-10.32, 0.32]	+	+	?	+	+	+
Berkel 2022	8	7	28	9	7	29	41.6%	-1.00 [-4.64, 2.64]	+	+	+	+	+	+
Dronkers 2010	16	12	21	22	24	20	6.7%	-6.00 [-17.70, 5.70]	+	+	?	+	+	-
Northgraves 2019	10	7	11	8	5	10	26.4%	2.00 [-3.17, 7.17]	+	+	?	+	+	+
Total (95% CI)			**122**			**122**	**100.0%**	**-1.55 [-4.69, 1.58]**						

Heterogeneity: Tau² = 2.71; Chi² = 4.06, df = 3 (P = 0.26); I² = 26%
Test for overall effect: Z = 0.97 (P = 0.33)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias): Length of stay in hospital
(E) Selective reporting (reporting bias)
(F) Other bias

Figure 26. Forest plot comparing the length of stay in hospital between prehabilitation group and usual care group.
Risk of bias assessment symbols: + = low risk of bias, - = high risk of bias and ? = unclear risk of bias.
Data is presented as risk ratios [95% CI] and mean [95% CI].

7.4. DISCUSSION

The key findings of this review are that supervised prehabilitation programs favour improvements in 6MWD and VO_2 peak but did not have any positive effect on surgical outcomes. However, after subgroup analysis it was found that those prehabilitation programs with more than one supervised session per week reduced the risk of post-operative complications.

7. 4.1. Physical function and strength changes

There was a greater improvement in the 6MWD in the prehabilitation group compared to the UC group before surgery. This is in support of findings from non-RCTs (Barakat et al., 2014, Christensen et al., 2018, Morkane et al., 2020, van Rooijen et al., 2019b) and previous meta-analysis (Waterland et al., 2021) but disagrees with another two meta-analysis (Lambert et al., 2021, Hughes et al., 2019). It should be noted, however, that some studies included for these meta-analyses (Lambert et al., 2021, Hughes et al., 2019) did not include any supervised session in the prehabilitation program. This highlights the importance of including supervised exercise sessions to provide an effective exercise stimulus that enhances the functional capacity of patients before surgery (Tew et al., 2018, Vemulapalli et al., 2015). Our pre-specified sub-group analysis indicate that the effect of prehabilitation program is likely modulated by the frequency of supervised sessions. We showed that the effect of prehabilitation programs is stronger with more than 1 supervised session per week, even when patients reported high compliance with unsupervised exercise in the subgroup of studies with one supervised session per week (Carli et al., 2020, Kim et al., 2009). However, this should be interpreted with caution. Firstly, differences in the subgroup are exploratory in nature. Secondly, while our sub-group analysis that included studies with only 1 supervised session per week reduced the heterogeneity between studies, there was still substantial heterogeneity in both groups. The heterogeneity in the subgroup of more than one supervised session per week could be caused by one study only including endurance training and high-risk patients (Barberan-Garcia et al., 2017). The heterogeneity in the subgroup of one supervised session per week was largely attributable also to one study (Fulop et al., 2021). The lack of a statistically significant clinical effect of the planned unsupervised exercise may be due to a lower exercise quality, resulting in lower intensity during the unsupervised sessions, leading to a lower training stimulus (Lacroix et al., 2017a). Supervised sessions could well provide an extra motivation to improve quality of exercise and thus, optimise the training stimulus.

6MWD is better preserved in the prehabilitation group compared to those who underwent UC, even if both groups participated in a post-surgery exercise rehabilitation (Bousquet-Dion et al., 2018, Soares et al., 2013). In fact, if only the UC group and not the prehabilitation group received post-surgical exercise rehabilitation, the recovery was still better in the prehabilitation group than the UC group (Carli et al., 2020). However, these results should be interpreted with caution as the lower bound of the CI in the 6MWD analysis 4 weeks after surgery is 3 m. which is below the minimally clinical important difference (MCID) (>20 m) (Carli et al., 2020, Bohannon and Crouch, 2017). Three of the four studies in the analysis included only one supervised session per week in the prehabilitation program. More research is needed to ascertain if prehabilitation programs aid in accelerating physical function recovery after surgery as well as determining the optimum supervised training frequency. At 8 weeks after surgery both groups had similar 6MWD performance.

Handgrip strength and five times sit to stand did not show a significant improvement before surgery in prehabilitation group in contrast to an improvement in TUG (Dronkers et al., 2010, Northgraves et al., 2019). The discrepancy between prehabilitation-induced improvements in handgrip and lower limb strength is most likely since exercise programmes are particularly focussed on improving lower leg, rather than handgrip strength. It should be noted that there were only few studies that measured handgrip strength, TUG and five-times-sit-to-stand with a low number of participants and therefore effects of prehabilitation programs in muscle mass and function remains unclear.

7.4.2. Cardiopulmonary changes

In contrast to a previous meta-analysis (Waterland et al., 2021) where no change in VO_2 peak was found, here we observed that VO_2 peak was significantly improved in the prehabilitation group compared to UC group before surgery. This discrepancy may be due to the improvement in the statistical power when 5 more studies were included in the present meta-analysis. When we analysed the benefits of prehabilitation programmes for the pre-surgery VO_2 peak in patients with AAA (Barakat et al., 2016, Tew et al., 2017), the analysis showed no difference between groups and opposing outcome was found between the two studies. In addition, these studies have some risk of bias due to loss of follow-up data. Therefore, this finding should be interpreted carefully. The cause of the large heterogeneity cannot be ascribed to the diameter of the aneurysm as both studies included patients with similar aneurysm size (≈6 cm diameter). Nevertheless, this is worthwhile exploring further in future studies, as it has been reported that VO_2 peak and AT were significantly improved after prehabilitation in patients with an AAA ≤5 cm diameter (Kothmann et al., 2009a, Myers et al., 2014, Tew et al., 2012). The length of the program may be another factor to consider, as those studies that found significant positive adaptations in VO_2 peak and AT in AAA patients were those with exercise programs of more than 4 weeks (Kothmann et al., 2009a, Myers et al., 2014, Tew et al., 2012).

As in previous meta-analysis (Waterland et al., 2021), we did not observe a significant improvement in the AT after prehabilitation compared to UC. The AT is considered an important predictor of in-hospital morbidity (West et al., 2016, Wilson et al., 2010), and determining if prehabilitation programs can enhance this cardiopulmonary parameter is important. AT analysis was performed with follow-up values due to the lack of data to estimate SD of changes. The lower bound of the CI is -0.24 mL·kg^{-1}·min^{-1}, which may account for the small baseline differences between groups, to the disadvantage of prehabilitation group (Barakat et al., 2016, Dunne et al., 2016, Wallen et al., 2019), and the small variability that AT estimation may have (Kothmann et al., 2009b). Thus, even though data points to the inability of prehabilitation programs to improve AT, more research in this area is needed.

7.4.3. Surgical outcomes

Poor physical condition may be a risk factor for 30-day mortality after abdominal surgeries, but most likely other factors, unmodifiable by exercise (cirrhosis, diabetes, disseminated cancer, type of surgery, etc.) are probably more important contributors to the 30-day mortality. Our analysis on premature mortality is in line with others (Lambert et al., 2021, Waterland et al., 2021) and showed no difference in 30-day and in-hospital mortality rate between groups. This lack of statistically significant effect on 30-day mortality may be caused by the low incidence of 30-day mortality in both groups. While increasing the number of patients in studies may allow for better detection of any effect of prehabilitation, the available evidence to data does not favour an effect of prehabilitation.

Here we found no significant reduction in the incidence of all kinds of post-operative complications. Previous meta-analyses, however, did report a significant reduction in the rate of complications in the prehabilitation group compared to UC group (Heger et al., 2020, Hughes et al., 2019, Moran et al., 2016a), but another one, that included a larger number of studies (both supervised and unsupervised prehabilitation), found no such improvement after prehabilitation (Waterland et al., 2021). The lack of impact of prehabilitation programs on the rate of post-operative complications, in this study and Waterland et al. (2021), may be due to the lack of effect of prehabilitation programs with less than two supervised sessions per week. A further sub-analysis revealed that those studies with more than one supervised training session per week showed reduced incidence of post-operative complications. The heterogeneity between studies was resolved in the group of more than one supervised session per week, the upper 95% CI bound indicated that prehabilitation programs may reduce the risk of post-operative complications a by a minimum of 25% compared to UC. Even though the meta-analysis of post-operative complications included a large number of patients (N=812), it is important to confirm these results with more evidence.

In the past, the use of LOS was reported as a conflicting surgical outcome due to the influence of non-clinical factors to its variation (Brasel et al., 2007). However, nowadays LOS is seen as an outcome measure of good care (Walters et al., 2016). In fact, other reviews in the topic have included LOS as a surgical outcome to evaluate the effectiveness of prehabilitation programs (Heger et al., 2020, Hughes et al., 2019, Moran et al., 2016a). Therefore, we decided to include LOS as an outcome to assess the efficacy of supervised prehabilitation programs. LOS was not significantly reduced in the prehabilitation group compared to the UC group as seen in other meta-analyses (Heger et al., 2020, Hughes et al., 2019, Moran et al., 2016a). This is not unequivocal however, as another meta-analysis reported significantly shorter LOS in the prehabilitation group compared to the UC group (Waterland et al., 2021, Lambert et al., 2021). Most studies reported IQR instead of SD and a contacted author indicated the possibility that LOS is usually not normally distributed, making comparisons between studies somewhat difficult. It, therefore, remains to be seen how effective a large-scale supervised prehabilitation program is to reduce the LOS.

7.4.4. Implications for practice and research

It has been suggested that a change of 1 MET (3.5 $ml \cdot kg^{-1} \cdot min^{-1}$) in VO_2 peak is the MCID in different clinical settings (Myers et al., 2002). Although the mean change in VO_2 peak as a result of prehabilitation programs was above that achieved by UC, it was not above the MCID nor was the upper bound of the CI. More evidence is required to ascertain whether prehabilitation programs have a positive significant impact on the cardiopulmonary fitness of patients preparing for a major abdominal surgery.

The mean changes of 6MWD after the prehabilitation program was +33 m. in the prehabilitation group, above the MCID (>20M) (Bohannon and Crouch, 2017, Carli et al., 2020). Nevertheless, the imprecision of this estimate of effect on 6MWD, however, means further trials of supervised prehabilitation programs are necessary to increase certainty in the evidence. Based on the current available evidence, the 95% CI around the best estimate of effect includes a change in 6MWD that would not be considered clinically meaningful.

Studies here included continuous or HIIT training, with both types of exercise promoting positive adaptations during prehabilitation. Recently, it was reported that HIIT resulted in a larger increase in AT 2 months after surgery (Minnella et al., 2020). This suggests that different types and intensities of exercise have different effects on the cardiopulmonary capacity of the patients. Such evidence, alongside that synthesised in the current review calls for head-to-head trials of prehabilitation programs that differ by supervision, intensity, type and duration of exercise to better understand the optimal exercise prescription within prehabilitation programs.

7.4.5. Applications and Limitations.

Similar to previous reviews in this area (Waterland et al., 2021) we had to estimate the SD of changes for some studies. This approach and all calculations were performed in accordance with Cochrane guidance and best practice (Higgins et al., 2008). Nevertheless, it is important to acknowledge that our estimates of effect on 6MWD, handgrip strength of the right hand, TUG and five times sit to stand and VO2 peak included such imputations for missing data. AT meta-analysis was performed with follow-up values, due to a lack of reporting of the SD of changes in the literature. Even though all efforts were made to reduce heterogeneity between studies, including only RCTs with at least one supervised training session per week, there are still sources of heterogeneity that require acknowledgement. Three studies included a multimodal prehabilitation program (inclusion of nutritional and psychological support (Coca-Martinez et al., 2020, van Rooijen et al., 2019a) with only one supervised session per week (Fulop et al., 2021, Bousquet-Dion et al., 2018, Carli et al., 2020). High heterogeneity was also found in meta-analysis of post-operative complications, but in this case was reduced when subgroup of analysis depending on the number of supervised sessions per week was performed by patients. The data presented here, showed that higher frequency of supervised exercise training sessions per week seems to be more effective to improve physical function and reduce the rate of post-operative complications than the planification of multimodal prehabilitation programs. It should be noted that subgroup analysis grouping studies in those with only 1 supervised session per week and those with more than one supervised session per week was a *post hoc* decision. However, in the published protocol (CRD42020180693), subgroup analysis assessing the number of supervised sessions per week was considered. Following this exploratory finding, further studies exploring the effect of the frequency of supervised sessions per week as a specific objective are needed to verify the results presented here.

Blinding of outcome assessor was not generally reported in the included studies. Future studies should ensure outcome assessment are blind to reduce bias during the analysis process. Loss of follow-up data was also seen in some studies. This was due to different reasons; appearance of adverse events that prevented patients to perform exercise programs (Bousquet-Dion et al., 2018, Dunne et al., 2016, Tew et al., 2017), rescheduling or not performing surgery (Wallen et al., 2019, Carli et al., 2020, Soares et al., 2013, Tew et al., 2017), mortality during the trial (Carli et al., 2020, Soares et al., 2013) and withdrawal from the trial (Soares et al., 2013, Bousquet-Dion et al., 2018, Wallen et al., 2019, Dunne et al., 2016, Barakat et al., 2016). It may be reasonable to suggest that psychological support may motivate patients to remain in the exercise program which could prevent patients from withdrawing the trial. However, this is difficult to know as one of the studies included psychological support (Bousquet-Dion et al., 2018) experienced loss of follow up data due to trial withdrawal.

There may be a risk of selective reporting as the history of changes on the protocol of the study was not inspected in detail and some studies did not have the history of changes publicly available. Only English language studies were considered for the search, therefore relevant articles may have been excluded from this search.

7.4.6. Conclusions

Exercise prehabilitation programs improved 6MWD and VO_2 peak before surgery in patients following the prehabilitation program compared to those that followed usual care. Moreover, patients in the prehabilitation program showed a greater improvement in 6MWD respective to baseline at 4 weeks post-surgery compared to those patients that followed usual care. These improvements in physical function were accompanied with a reduction in the risk of post-operative complications only when prehabilitation programs included more than one supervised exercise sessions per week.

CHAPTER EIGHT: GENERAL DISCUSSION

8.1. MAIN FINDINGS AND IMPLICATIONS

The aim of this thesis was to assess the effectiveness of existing and novel perioperative patient's fitness evaluation in the prognosis of adverse outcome following liver resection and hepatobiliary surgery and to review the efficacy of pre-operative supervised exercise programs to enhance patients' fitness and to ameliorate adverse major abdominal surgical outcomes. The results reported in this thesis address this aim and present a number of clinical and research implications, as well as recommendations for practice and/or future research requirements in order to implement into clinical practice.

8.1.1. Muscle quality and not muscle size is different in patients waiting for hepatobiliary surgery compared to master athletes and old healthy adults

In chapter 4 patients waiting for hepatobiliary surgery presented with a lower knee extension force and similar VL-MT when compared with MAs and old healthy adults. These differences may be due to a reduced voluntary activation (Manini et al., 2013, Tieland et al., 2018) and/or a higher IMAT in the patients' cohort (Goodpaster et al., 2001) that combined, may negatively affect muscle force production.

In the current literature, research and clinicians are focused on stratifying the risk of abdominal surgery assessing muscle size and muscle density (Aleixo et al., 2020, Jones et al., 2017). In chapter 6, a relationship between preoperative VL-MQ and surgical outcomes was not confirmed due to long-term survival data being unavailable (1-year survival and 3-year survival). Even though MQ shows promise as a marker of muscle weakness in hepatobiliary surgery patients, from the data presented in chapter 4, it cannot yet be recommended for use as a preoperative measure to stratify the risk of undergoing hepatobiliary surgery as chapter 6 did not observe any relationship between VL MQ and any surgical outcome. However, a re-analysis of the data when 1-year and 3-year survival data is available would be of interest to ascertain whether VL MQ is related to long-term survival.

8.1.2. Patient's muscle characteristics and cardiopulmonary fitness as predictors for hepatobiliary surgery risk stratification

In chapter 6 and 7, the effectiveness of evaluating pre-operative muscle characteristics and cardiopulmonary fitness to assess the risk of undergoing hepatobiliary surgery was examined.

VO_2 peak and AT were weakly to moderately correlated with LOS and LOS in critical care, respectively. P-index was negatively correlated to 1-year and 3-year mortality and VE/VCO_2 was positively related to 3-year mortality, all independently. When long-term survival analysis was performed, combining P-index and VE/VCO2 in a dichotomous variable, only those patients with low P-index and high VE/VCO_2 were at higher risk of 3-year mortality. Against the initial hypothesis, the reduction in VL-MT, VL-CSA and VL pennation angle during the in-hospital recovery were not related to surgical outcomes. The findings of this thesis suggest that combining measures of preoperative muscle and cardiopulmonary fitness aid to prognose long-term surgical outcomes.

8.1.3. Preoperative exercise training is effective to enhance physical function and VO_2 peak but did not reduce post-operative complications

Meta-analysis performed in chapter 7 showed that 4-6 weeks of supervised preoperative exercise enhance 6MWD, TUG and VO_2 peak pre-operatively. Subgroup analysis showed that those patients that performed at least 2 supervised sessions per week significantly improved 6MWD before surgery compared to those that only performed 1 supervised exercise session per week. Additionally, patients that underwent the preoperative exercise program showed greater 6MWD than patients that underwent usual care pathway 4 weeks after surgery. Despite this pre-operative physical function and cardiopulmonary fitness and rate of post-operative complications were not reduced in the prehabilitation group. However, subgroup analysis suggests that the rate of post-operative complications was reduced in those patients that performed at least 2 supervised exercise sessions per week compared to those that only performed 1 supervised session per week. Evidence presented in chapter 7 suggests that exercise prehabilitation programs should offer at least two supervised exercise sessions per week to maximize exercise stimulus and promote physiological adaptations that may help to reduce the risk of poor surgical outcomes.

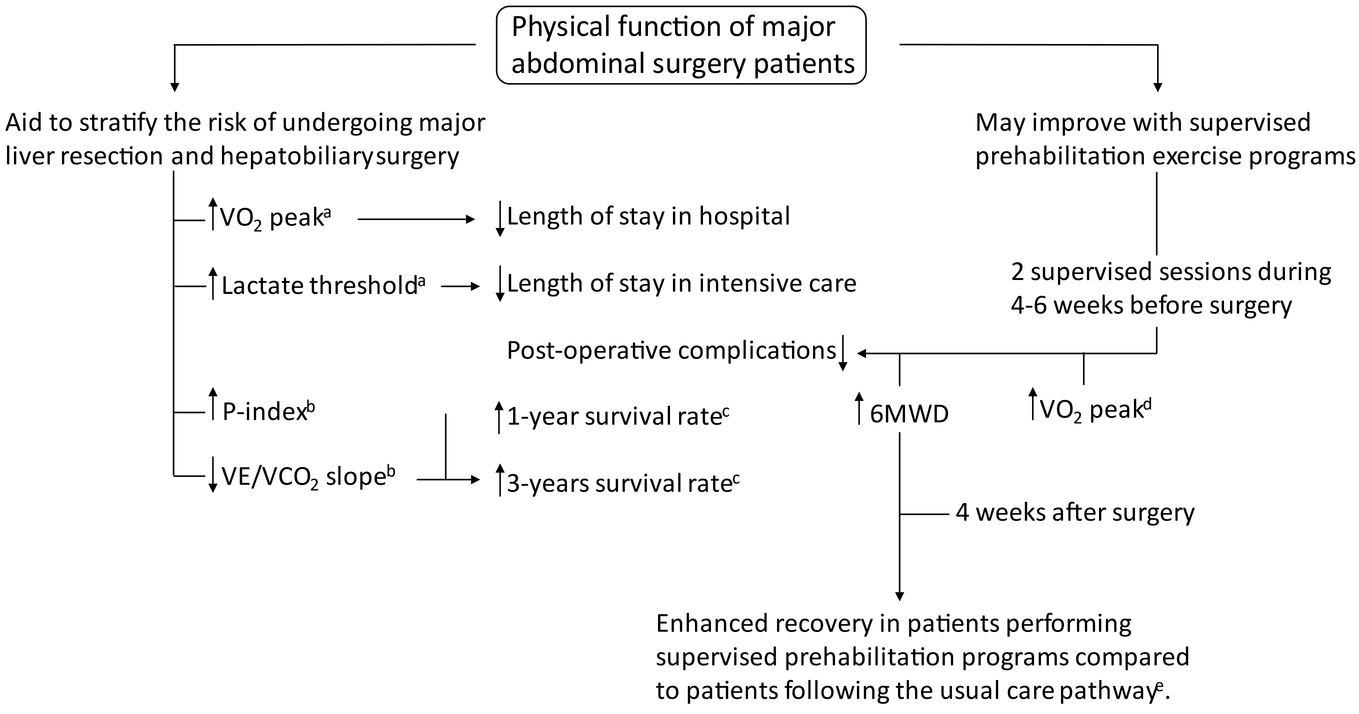


Figure 27. Diagram of the main findings of the thesis.

P-index: psoas muscle index; VE/VCO2 slope: ratio of minute ventilation by CO_2 production; VO2 peak: peak volume of oxygen consumption; 6MWD; 6 minutes walk distance.

Relations presented in this figure should not be interpreted as a direct cause of the interaction between variables. As presented along the previous chapters there are limitations that affect the relation between these variables which may alter the direct relation presented here. This figure should be interpreted as a general summary of the results obtained during the elaboration of this thesis.

[a] *Weak and limited negative relation*

[b] *Patients with a psoas index greater than 7.5 $cm^2 \cdot m^{-2}$ for males and 5.9 $cm^2 \cdot m^{-2}$ for females and a VE/VCO_2 below 32.1 has ~2.5 more times of surviving 3 years after a hepatobiliary surgery.*

[c] *Upper bound of 95%CI close to 1 almost not statistically significant finding.*

[d] *Mean improvement after prehabilitation below the MCID.*

[e] ***L**ower bound of 95%CI below the MCID*

8.2. PRE-OPERATIVE RISK ASSESSMENT BASED ON MUSCLE CHARACTERISTICS AND CARDIOPULMONARY FITNESS

Chapter 5 and chapter 6 were designed with the intention of assessing pre-existing and novel muscle and cardiopulmonary fitness parameters that aid in the stratification of risk of undergoing major abdominal surgery. Pre-existing parameters consist of the assessment of SM-index, P-index, SM-RA and P-RA at the level of L3-L4 (Aleixo et al., 2020, Jones et al., 2017), and VO_2 peak, AT and VE/VCO_2 (Moran et al., 2016b, Junejo et al., 2014). P-Index was found to be related with 1-year and 3-year premature mortality, in line with a previous study

(Okumura et al., 2015). However, in contrast to previous findings, SM-index (van Dijk et al., 2017) and SM-RA (van Dijk et al., 2017, West et al., 2019b) were not related to any surgical outcome. A possible explanation for this, is that the psoas is a muscle involved in locomotory and daily living activities (Andersson et al., 1997, Penning, 2002, Masuda et al., 2002), and thus, it may well represent the physiological resilience of patients. Following this hypothesis in chapter 6, 4 parameters representing the muscle characteristics of the lower leg were included to assess patient's their capacity to predict surgical outcomes: preoperative VL-MT, VL-CSA, VL-MQ and VL density. None of these parameters were found to be related to any surgical outcome, perhaps due to the brevity of survival data, following patients for up to only 6-months after surgery. When the relationship between cardiopulmonary fitness with surgical outcomes was assessed, VO_2 peak, AT and VE/VCO_2, positively (VO_2 peak and AT) and negatively (VE/VCO_2) showed a relationship with 3-year survival rate, independently. These results suggest that muscle and cardiopulmonary fitness derived parameters may only prognose long-term surgical outcomes, in line with other studies with the same clinical population (Junejo et al., 2014, Okumura et al., 2015). This may be explained due to an acquired muscle weakness after in-hospital recovery, as seen in chapter 6, and other studies (Hermans et al., 2014, Vanhorebeek et al., 2020). Additionally, in the long-term, a lack of persistent physical activity (Kehler and Theou, 2019) may negatively impact the survival rate of patients. This is shown to some extent in Figure 18 in chapter 7, where patients involved in a prehabilitation exercise program and patients following the usual care pathway demonstrate a similar 6MWD 8 weeks after surgery, even though patients that performed prehabilitation programs had a greater 6MWD 4 weeks after surgery compared to those following UC. Nevertheless, this still requires further assessment, as in chapter 6, accelerated muscle changes during in-hospital recovery were not related to 6-months survival.

8.2.1. Future directions and clinical implications

The findings of this thesis suggest that preoperative muscle derived parameters from CT scans and cardiopulmonary fitness may be used in combination to better prognose the risk of long-term mortality after liver resection and pancreaticoduodenectomy. Cardiopulmonary fitness of patients has been assessed for long-time in healthcare settings around the world. Most of those patients undergoing these preoperative assessments also have an associated pre-operative abdominal CT scan, that can be automatically analysed with the recent developed machine learning techniques (Kim et al., 2020). Longitudinal patient datasets offer the possibility of performing a large-scale retrospective study that may further support the results presented in chapter 5 and may refine the preoperative risk assessment before major abdominal surgery based on these measures. In addition, patients having a post-operative CT image may be used to evaluate changes in muscle mass after surgery and determine the factors which determine whether a patient is able to recover baseline muscle mass and density values, or otherwise as mentioned surgery permanently impairs muscle mass and function, thus increasing muscle weakness and long-term mortality postoperatively.

Longitudinal follow-up and analysis of data presented in chapter 6 when 1 and 3-year survival data is available is also required to ascertain if muscle changes derived from the in-hospital recovery negatively impact the long-term survival rate of patients. If this is the case, the assessment of changes in VL-MT and CSA after in-hospital recovery may be used to prognose long-term outcomes and prescribe preventative measures, such as supervised physical activity to avoid disease and age acquired muscle weakness to potentially reduce the risk of mortality within the first years postoperatively.

8.3. PREHABILITATION PROGRAMS TO ENHANCE MAJOR ABDOMINAL SURGICAL OUTCOMES

At least 2 supervised exercise sessions per week during 4-6 weeks of preoperative exercise before a major abdominal surgery is capable of improving physical functionality, and VO_2 peak but did not reduce the rate of post-operative complications. The rate of post-operative complications was observed to be reduced in the subgroup of patients that performed at least 2 supervised preoperative exercise sessions per week. It should be noted that improvement on VO_2 peak was not over the MCID and therefore its influence on the reduction of post-operative complications in the subgroup of patients remains unclear.

Even though these results are not conclusive the development and investment of supervised prehabilitation programs, such as those currently performed in care settings across the NHS on a large scale (Moore et al., 2021) are promising in order to ascertain effectiveness of prehabilitation exercise programs to enhance surgical outcomes and patient's recovery after surgery.

8.3.1. Future directions and clinical implications

The data shown in this thesis suggests muscle size is related to 1-year and 3-year mortality, it is therefore, instructive that resistance training may be a viable strategy to stimulate muscle growth in order to reduce the rate of mortality within 3 years after surgery. Meta-analysis presented in chapter 7 was focussed on outcomes that are dependent on cardiopulmonary fitness, including VO_2 peak or 6MWD (Ross et al., 2010). Most of the studies included in the meta-analysis included resistance training as part of the prehabilitation program. However, only handgrip strength was reported as a measure of muscular strength in two of the studies showing a lack of effect in this measure in the prehabilitation group compared to the usual care group. Christensen et al. (2018) have reported an effective increase of lower leg strength after a prehabilitation program. However, this was only observed after a training period greater than the usual prehabilitation length of 4 to 6 weeks, with patients training for 11 to 19 weeks in this study (Christensen et al., 2018). It is therefore, also necessary to evaluate the effect of prehabilitation programs on overall muscle strength with more RCTs. A program focusing on the development of strength (in combination with aerobic fitness) may further improve the prognosis of major abdominal surgical outcomes, as previous studies have also reported the relationships between muscle mass and density (Aleixo et al., 2020, Jones et al., 2017). These in turn influence muscle strength and power (Goodpaster et al., 2001, Reggiani and Schiaffino, 2020) as well as surgical outcomes.

The meta-analysis presented in chapter 7 determines the minimum frequency of supervised exercise that is needed to promote physiological changes and thus reduce the rate of post-operative complications. It is the first meta-analysis with a subgroup analysis that aims to determine the optimal frequency of supervised prehabilitation exercise sessions per week to improve fitness on patients and reduce the risk of adverse events after abdominal surgeries. Next steps should explore the optimal intensity for resistance and aerobic training to inform and deliver effective and safe prehabilitation programs. In addition, studies assessing the optimal mode of exercise are also needed. At the moment only one randomized intervention trial has assessed this (Minnella et al., 2020), showing that patients that were involved in HIIT had a higher AT 2 months after surgery compared to MCET. This finding is important as the available time to train before operation is usually short, controlling for this, is crucial to offer an optimum exercise stimulus that promote physiological adaptations that aid patients to recover faster and reduce the risk of poor surgical outcomes.

Even though the meta-analysis performed in chapter 7 and other previous studies (Aleixo et al., 2020, Jones et al., 2017) have reported relationships between muscle mass, muscle density, muscle function and cardiopulmonary fitness with short-term surgical outcomes, it is not the case in the results of this thesis of chapter 5 and chapter 6. In these chapters, the capability of muscle and cardiopulmonary derived measures to predict the risk of long-term mortality (ignoring the weak relation between VO_2 peak with LOS and the limited relationship of AT with LOS in critical care reported in chapter 5 and 6) is limited. Based on the latest evidence from prehabilitation exercise programs, long-term post operative exercise interventions may provide an effective strategy to reduce sedentary behaviours associated with frail adults (Kehler and Theou, 2019). Combined, these strategies may be effective in ameliorating the degeneration of muscle mass, muscle density, muscle function and cardiopulmonary fitness, potentially reducing the negative impacts on the long-term survival rate of patients postoperatively. Even though this argument may be against the findings of chapter 4, where it was found the same VL-MT and VL-MQ in MAs and older healthy adults, there is plenty of evidence that supports that sustained physical activity during the last stages of life improve muscle mass, muscle density, muscle function and cardiopulmonary fitness (McKendry et al., 2018, Ramírez-Vélez et al., 2021, Pearson et al., 2002).

Programs such as Manchester's Prehab4Cancer program (Moore et al., 2021) offers an exciting opportunity to examine the effect of supervised prehabilitation programs in a large cohort of patients from different surgical populations and have beneficial effects on long term outcomes of surgical recovery. This program is ongoing and was run during the Covid-19 pandemic with remote supervision which gives an excellent opportunity to assess the efficacy of remote supervision in these programs as a cost-effective method of intervention in surgical populations compared with in-person supervision.

8.4. GENERAL LIMITATIONS

In chapter 4, data from three different cohort studies was examined. The aim of this study was to assess differences in VL-MT and VL-MQ between patients waiting for a hepatobiliary surgery with MAs and old healthy population. For this study, it was assumed that MAs have a habitual regime of physical activity and structured exercise which is of a higher volume than age matched healthy adults. This assumption has been made due to the national and international level of competition the athlete group are participating in. Nevertheless, the amount of time of these two different cohorts spent in weekly physical activity was not assessed, which may bring about a misinterpretation of the differences between MAs and older healthy adults. Differences between these two cohorts are interpreted in discussion of chapter 4 acknowledging this limitation. In any case, the aim of this study was to examine any differences between patients awaiting major abdominal surgery with MAs and older healthy adults to understand the pathophysiology of patients waiting for major abdominal surgery. Thus, despite of the limitation in the comparison between MAs and old healthy adults, the findings of chapter 4 aid in the understanding of the effects on muscle tissue of the pathophysiology of the patients waiting for a hepatobiliary surgery. Even though preoperative VL-MQ was seen to be a biomarker of physiological resilience with age (chapter 4), it is not related with surgical outcomes. This demands further exploration when long-term mortality data is available due to the reasons exposed above.

Chapter 5 and 6 included patients waiting for a liver resection or a pancreaticoduodenectomy. The current literature considers all major abdominal patients as a whole cohort; however type of surgery involves a variation in the risk due to differing techniques and pathophysiology's (Krautz et al., 2020, Schlösser et al., 2010, Panis et al., 2011), that influence the potential effect of muscle and cardiopulmonary fitness parameters may have on the prognosis of major abdominal surgeries. Despite this, hepatobiliary and liver resection surgeries followed a similar procedure and recovery pathway. In addition, all patients included in chapter 5 had their surgery performed by the same surgeon, which reduces heterogeneity of technique performed in surgery between the patients included in that study. Studies with large datasets stratifying patients depending on the type of surgery, and other relevant parameters that may influence the risk of surgery, should be performed to ascertain if muscle size, muscle density and cardiopulmonary fitness remain as significant predictors of major abdominal surgery risk.

CT scans that were used in chapter 5 to determine abdominal muscle mass and density were manually analysed. However, based on other studies the variation added by operator error is minimal, with the intra-rater reliability for this measure is considered excellent (Rayhel et al., 2020, Lee et al., 2017). With experience, images were accurately analysed by the author in

~15 min. This amount of time for analysis makes this measure unsustainable in clinical practice, with limited appointment times and clinic pressures. Therefore, development of a deep learning technique in the field of computer science which may be able to segment abdominal CT scans automatically and accurately is demanded. Until this is widely utilised, these analyses will be restricted to research purposes.

Chapter 5 proposes cut-offs for P-index and VE/VCO_2 that may be used to prognose the risk of 3-year mortality. However, median values were used as cut-off and a ROC curve analysis would be necessary to optimally find P-index and VE/VCO_2 cut-offs. These findings add significant detail to the literature, in establishing novel measures and their cut-off values that may be used to assess risk for major abdominal surgery. This technique may also be utilised for the prescription of prehabilitation exercise programs that may reduce the risk of undergoing major abdominal surgery and promote recovery in the postoperative period. However, in the literature there is a lack of standardization in established cut-off values in commonly utilised risk assessment measures as well as the specific measures which can be utilised to best predict major abdominal surgery risk (Jones et al., 2017, Moran et al., 2016b). There is a need to conduct large-scale studies that may be able to ascertain the most robust measures and cut-offs to triage patients and add further objectivity to clinical decision making.

Sample size of experimental chapters and the retrospective design of chapter 4 and 5 imply some limitation to the interpretation of the results presented. Findings of the experimental chapters in this thesis are exploratory in nature and aimed to create new hypotheses to be explored with further research. Therefore, p-values should be interpreted with caution along with CIs. Specific limitations in each of these analyses are mentioned in each experimental chapter.

8.5. GENERAL CONCLUSION

Ultrasound imaging can be used to accurately capture bed-side measurements of the VL to assess in-hospital recovery changes in VL size and architecture after major abdominal surgery. Despite a lack of relationship between VL size reduction after in-hospital recovery with 6-month survival, this relationship may be found when survival is assessed after a longer follow-up period. This hypothesis is based on the finding of P-index and VE/VCO_2, in combination (but not independently), predicted patient 3-year survival after surgery.

To ameliorate the negative impacts of major abdominal surgery, chapter 7 suggests that prehabilitation supervised exercise promote physiological changes that enhance VO_2 peak and physical function. It remains unclear as to whether these adaptations are clinically meaningful, as the rate of post-operative complications was not reduced. However, this effect was observed in a subgroup of patients that were involved in supervised exercise programs that included at least 2 sessions per week of supervised exercise. Exercise components of prehabilitation exercise programs require further investigation to ascertain the structure and contents of successful prehabilitation programs in optimising post-operative outcome

Appendices

Appendix 1. Supplementary data (Tables)

Table 11. Participant's characteristics.

	Master athletes	Healthy population	Patients	p-value
N	47	20	34	-
Age (years)	71±6	73±5	73±6	0.091
Height (m)	1.71±0.05	1.74±0.08	1.73±0.07	0.331
Body mass (kg)	71.0±7.2	78.9±14.4^{A}	81.5±11.7^{A}	<0.001
BMI (kg·m^{-2})	24.2±2.1	25.9±2.8	27.3±3.8^{A}	<0.001
VL MT (mm)	18.9±3.8	20.4±3.4	17.8±4.3	0.065
MVC (N)	520±105	539.1±93.3	327.2±103.0^{A,B}	<0.001

Data is presented as mean±SD.

BMI: Body mass index; MT: Muscle thickness; MQ_{MT}*: muscle quality using muscle thickness; MVIC: maximum voluntary isometric contraction; VL: Vastus Lateralis.*

All included participants were male.

^{A}*denotes significant difference with Master athletes' group.*

^{B}*denotes significant difference with healthy adults' group.*

Appendix 2. Supplementary data (Figures)

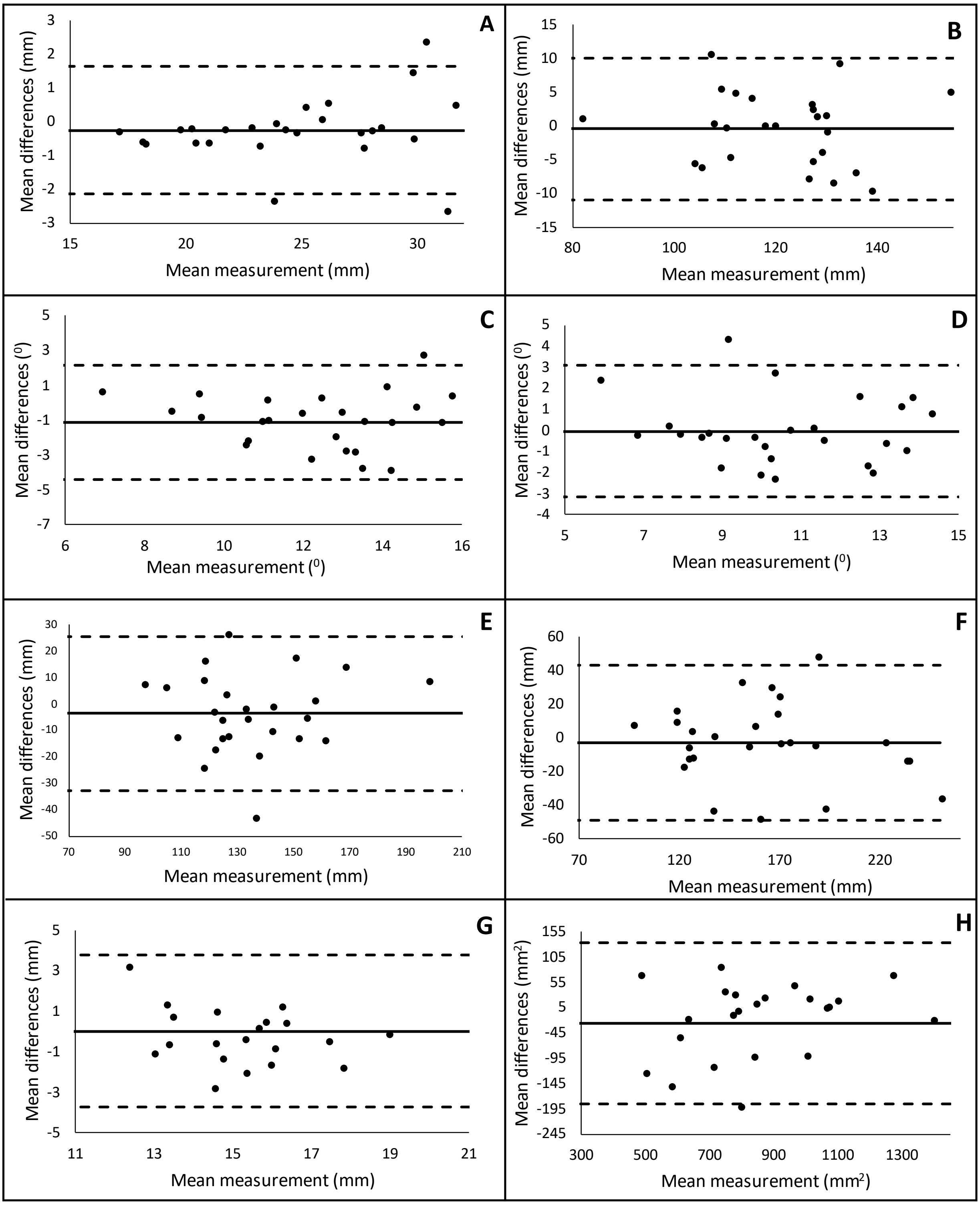


Figure 28. Intra-rater reliability Bland and Altman plots of ultrasound Vastus Lateralis, Vastus Intermedius and Rectus Femoris size measurements and Vastus Lateralis architecture.

A) Vastus Lateralis thickness intra-rater reliability. B) Vastus Lateralis fascicle length intra-rater reliability quantified using EFOV US imaging. C) Vastus Lateralis pennation angle intra-rater reliability quantified using EFOV US imaging. D) Vastus Lateralis fascicle length intra-rater reliability quantified using intercept method. E) Vastus Lateralis pennation angle intra-

rater reliability quantified using intercept method. F) Vastus Lateralis cross-sectional area intra-rater reliability. G) Vastus Intermedius thickness intra-rater reliability. H) Rectus Femoris cross-sectional area intra-rater reliability.

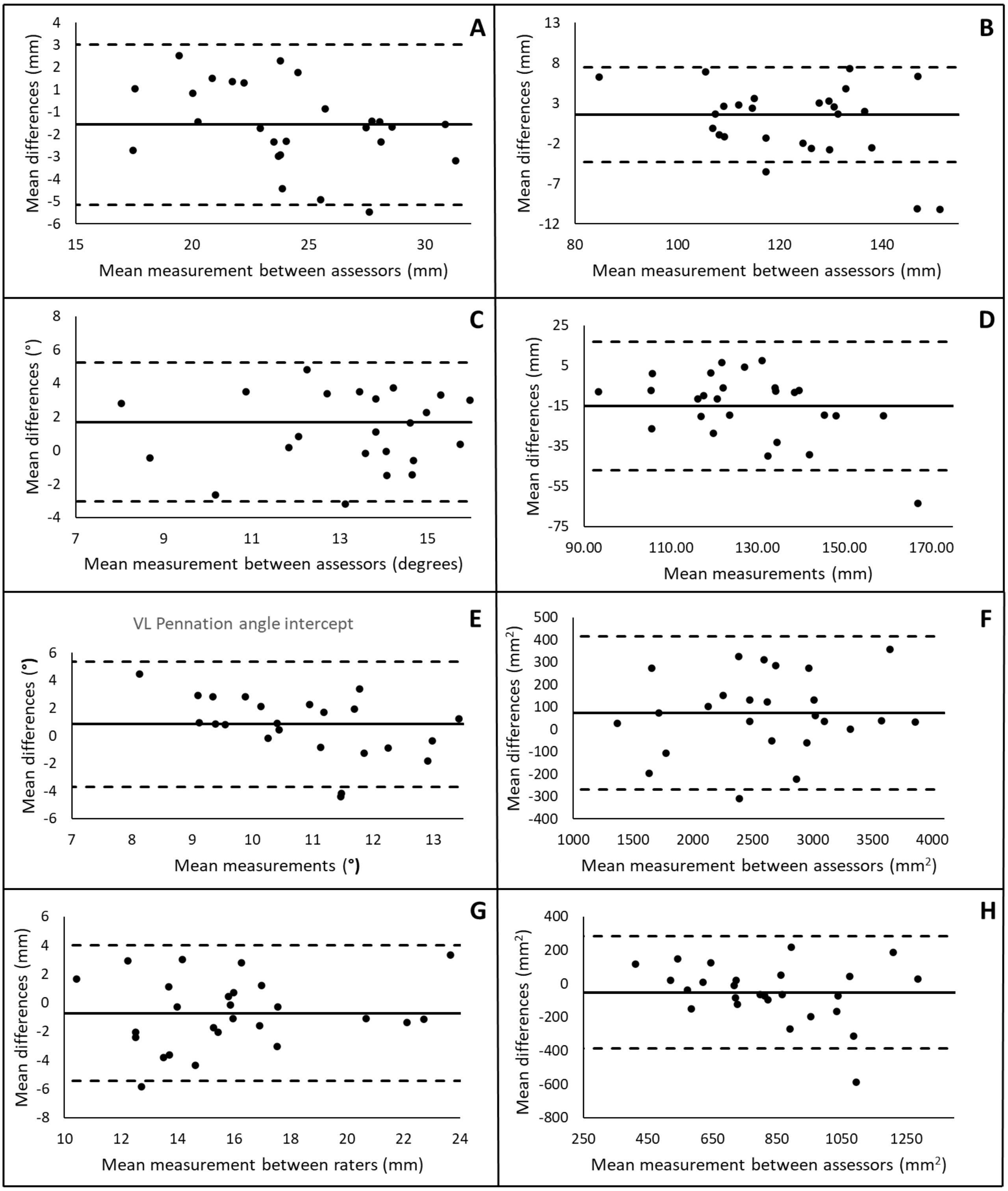


Figure 29. Inter-rater reliability Bland and Altman plots of ultrasound Vastus Lateralis, Vastus Intermedius and Rectus Femoris size measurements and Vastus Lateralis architecture.

A) Vastus Lateralis thickness inter-rater reliability. B) Vastus Lateralis fascicle length inter-rater reliability quantified using EFOV US imaging. C) Vastus Lateralis pennation angle inter-rater reliability quantified using EFOV US imaging. D) Vastus

Lateralis fascicle length inter-rater reliability quantified using intercept method. E) Vastus Lateralis pennation angle quantified using inter-rater reliability intercept method. F) Vastus Lateralis cross-sectional area inter-rater reliability. G) Vastus Intermedius thickness inter-rater reliability. H) Rectus Femoris cross-sectional area inter-rater reliability.

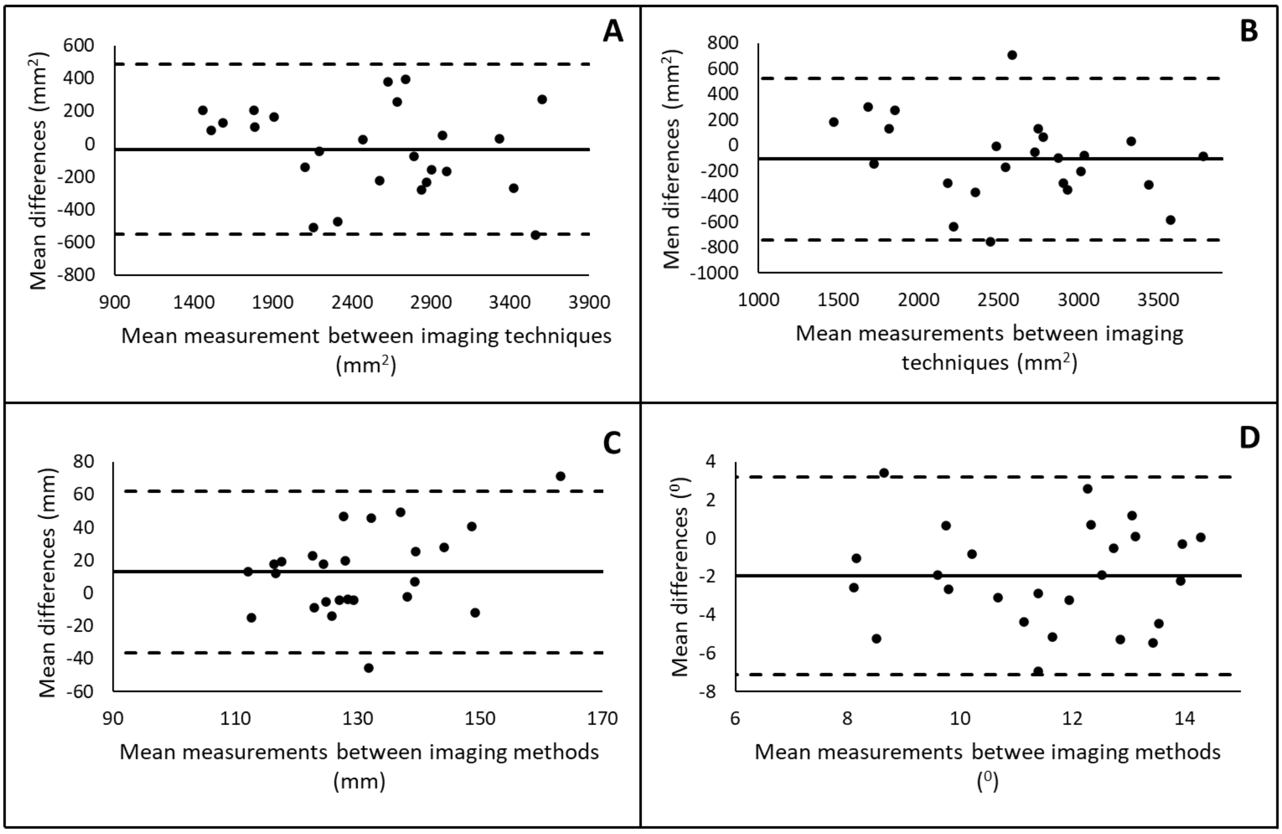


Figure 30. Inter-machine reliability (Ultrasound vs Magnetic resonance imaging) of Vastus Lateralis and Rectus Femoris cross-sectional area measurements and inter-method reliability (Extended field of view ultrasound imaging vs intercept) of Vastus Lateralis architecture, fascicle length and pennation angle Bland and Altman plots.

A) Vastus Lateralis cross-sectional area inter-machine reliability. assessor 1. B) Vastus Lateralis cross-sectional area inter-machine reliability. assessor 2. C) Vastus lateralis fascicle length inter-method reliability. Assessor 1. D) Vastus lateralis pennation angle inter-method reliability.

Appendix 3. Chapter 7 search strategy

MEDLINE

Search *Term*	Field
S1. Digestive System Surgical Procedures+	MH
S2. (Colorectal cancer OR Colorectal neoplasm ORColorectal surgery) OR (Bowel cancer OR Bowel surgery OR Bowel neoplasm) OR (Colon cancer OR Colon neoplasm OR Colon surgery) OR (Liver cancer OR Liver surgery OR Liver neoplasm OR Liver transplantation) OR (Hepatic cancer OR Hepatic surgery OR Hepatic neoplasm OR Hepatic transplantation) OR (Pancreatic cancer OR Pancreatic surgery OR Pancreatic neoplasm) OR (Pancreas cancer OR Pancreas surgery OR Pancreas neoplasm) OR surgery OR cancer OR neoplasm OR transplantation OR surger*	FT
S3. S1 OR S2	FT
S4. exercise+	MH
S5. (Presurgery exercis* OR Presurgery activit* Presurgery OR Presurgery physical activit*) OR (Pre-operative exercis* OR Pre-operative activit* OR Pre-operative physical activit*) OR (Peri-operative exercis* OR Peri-operative activit* OR Peri-operative physical activit*) OR (Pre-surgery exercis* OR Pre-surgery activit* OR Pre-surgery physical activit*) OR (Preoperative exercis* ORPreoperative activit* OR Preoperative physical activit*) OR (Perioperative exercis* OR Perioperative activit* OR Perioperative physical activit*) OR Physical activity OR Exercise program OR supervised physical activity OR supervised exercise program	FT
S6. S4 OR S5	FT
S7. length of stay+	MH
S8. Walk Test	MH
S9. death OR complications OR (Hospital N2 admi*OR Hospitalisation OR Hospitalization) OR (Re-admission OR admission) OR (6 Minutes walk N2 test OR 6MWT OR 6MWD OR Incremental shuttle walk test OR ISWT) OR (Timed up and go test OR TUG OR TUGT) OR (Anaerobic threshold OR	FT

VO2 peak OR VO2 max OR Oxygen consumption OR VE/VCO2 OR equivalence OR death space OR pulmonary reserve OR CPET OR Cardiopulmonary test OR maximal oxygen uptake) OR (Max* force OR Max* knee extension OR Max* isometric voluntary contraction OR MVC OR Max* handgrip OR Max torque OR Max strength OR force production OR force OR Strength) OR morbidity OR morbidities OR mortality	
S10. S7 OR S8 OR S9	FT
S11. randomised OR randomized OR control OR trial	FT
S12. S3 AND S6 AND S10 AND S11	FT

S: search line, MH: MesH term, FT: Full text.

The search was filtered by the next subject major headings to obtain results related to the systematic review and meta-analysis:

kidney transplantation

running

cachexia

obesity, morbid

bariatric surgery

colonic neoplasms

risk reduction behavior

oxygen consumption

physical therapy modalities

health promotion

weight loss

preoperative care

exercise tolerance

health behavior

gait

diet

physical fitness

colorectal neoplasms

prostatic neoplasms

survivors

motor activity

fatigue

life style

muscle strength

cardiovascular diseases

muscle, skeletal

postoperative complications

resistance training

quality of life

walking

obesity

neoplasms

exercise therapy

exercise

Boolean/Phrase

PubMed

(((((randomised) OR randomized) OR control) OR trial)) AND ((("morbidity") OR "morbidities") OR "complication") OR "complications") OR "mortality") OR length of stay[MeSH Terms]) OR "Hospitalisation") OR "hospitalization") OR "re-admission") OR "admission") OR walk test[MeSH Terms]) OR "6 minutes walk") OR "6mwt") OR "6mwd") OR "incremental shuttle walk test") OR "ISWT") OR ("Timed up and go")) OR "TUG") OR "TUGT") OR "Anaerobic threshold") OR "VO2 peak") OR "vo2 max") OR "oxygen consumption") OR "VE/VCO2") OR "equivalence") OR "death space") OR "pulmonary reserve") OR "CPET") OR "cardiopulmonary test") OR "maximal oxygen uptake") OR "maximum oxigen uptake") OR "force") OR "knee extension") OR "isometric voluntary contraction") OR "isometric contraction") OR "handgrip") OR "torque") OR "strength") OR "force production")) AND (((("physical activity") OR (((((((exercise[MeSH Terms]) OR "physical intervention") OR "physical therapy") OR "Exercise intervention") OR "exercise program") OR "training") OR "exercise therapy"))) AND (("abdominal surgery") OR ((((((((((((((((((((((((digestive system surgical procedure[MeSH Terms]) OR "colorectal cancer") OR "colorectal neoplasm") OR "colorectal surgery") OR "bowel cancer") OR "bowel surgery") OR "bowel neoplasm") OR "colon cancer") OR "colon neoplasm") OR "colon surgery") OR "liver cancer") OR "liver neoplasm") OR "liver surgery") OR "liver transplantation") OR "hepatic cancer") OR "hepatic surgery") OR "hepatic neoplasm") OR "hepatic transplantation") OR "pancreatic cancer") OR "pancreatic surgery") OR "pancreatic neoplasm") OR "pancreas cancer") OR "pancreas surgery") OR "pancreas neoplasm"))))

CENTRAL

Search term	*Field*
S1. Colorectal surgery	MH
S2. Colorectal cancer OR Colorectal neoplasm OR Colorectal surgery OR Bowel cancer OR Bowel surgery OR Bowel neoplasm OR Colon cancer OR Colon neoplasm OR Colon surgery OR Liver cancer OR Liver surgery OR Liver neoplasm OR Liver transplantation OR Hepatic cancer OR Hepatic surgery OR Hepatic neoplasm OR Hepatic transplantation OR Pancreatic cancer OR Pancreatic surgery OR Pancreatic neoplasm OR Pancreas cancer OR Pancreas surgery OR Pancreas neoplasm OR Abdominal surgery	FT
S3. S1 OR S2	FT
S4. Exercise	MH

S5. Physical intervention OR Physical therapy OR Exercis* intervention OR Exercis* program* OR Exercis* training OR Exercis* therap* OR Presurgery exercis* OR Presurgery activit* OR Presurgery physical activit* OR Pre-operative exercis* OR Pre-operative activit* OR Pre-operative physical activit* OR Peri-operative exercis* OR Peri-operative activit* OR Peri-operative physical activit* OR Pre-surgery exercis* OR Pre-surgery activit* OR Pre-surgery physical activit* OR Preoperative exercis* OR Preoperative activit* OR Preoperative physical activit* OR Perioperative exercis* OR Perioperative activit* OR Perioperative physical activit* OR Physical activity OR Exercise program OR supervised physical activity OR supervised exercise program	FT
S6. Death OR morbidit* OR Complications OR Mortality OR Hospital admi* OR Hospitalisation OR Hospitalization OR readmission OR admission OR Walk test OR 6 Minutes walk test OR 6MWT OR 6MWD OR Incremental shuttle walk test OR ISWT OR Timed up and go test OR TUG OR TUGT OR Anaerobic threshold OR VO2 peak OR VO2 max OR Oxygen consumption OR equivalence OR death space OR pulmonary reserve OR CPET OR Cardiopulmonary test OR maximal oxygen uptake OR Max* force OR Max* knee extension OR Max* isometric voluntary contraction OR MVC OR Max* handgrip OR Max torque OR Max strength OR force production OR force OR Strength OR length of stay	FT
S7. Length of stay	MH
S8. S4 OR S5	FT
S9. S6 OR S7	FT
S10. randomised OR control OR randomized OR trial	FT
S11. S3 AND S8 AND S9 AND S10	FT

S: search line, MH: MesH term, FT: Full text.

<u>CINAHL</u>

S1. Surgery, Digestive System+	MH
S2. (Colorectal cancer OR Colorectal neoplasm OR Colorectal surgery) OR (Bowel cancer OR Bowel surgery OR Bowel neoplasm) OR (Colon cancer OR Colon neoplasm OR Colon surgery) OR (Liver cancer OR Liver surgery OR Liver	FT

neoplasm OR Liver transplantation) OR (Hepatic cancer OR Hepatic surgery OR Hepatic neoplasm OR Hepatic transplantation) OR (Pancreatic cancer OR Pancreatic surgery OR Pancreatic neoplasm) OR (Pancreas cancer OR Pancreas surgery OR Pancreas neoplasm) OR Abdominal surgery	
S3. S1 OR S2	FT
S4. Exercise+	MH
S5. Physical intervention OR Physical therapy OR (Exercis* intervention OR Exercis* program* OR Exercis* training OR Exercis* therap*) OR (Presurgery exercis* OR Presurgery activit* OR Presurgery physical activit*) OR (Pre-operative exercis* OR Pre-operative activit* OR Pre-operative physical activit*) OR (Peri-operative exercis* OR Peri-operative activit* OR Peri-operative physical activit*) OR (Pre-surgery exercis* OR Pre-surgery activit* OR Pre-surgery physical activit*) OR (Preoperative exercis* OR Preoperative activit* OR Preoperative physical activit*) OR (Perioperative exercis* OR Perioperative activit* OR Perioperative physical activit*) OR (Physical activity OR Exercise program OR supervised physical activity OR supervised exercise program)	FT
S6. S4 OR S5	FT
S7. Length of stay	MH
S8. Death OR morbidit* OR Complications OR Mortality OR (Hospital N2 admi*OR Hospitalisation OR Hospitalization) OR (Re-admission OR admission) OR (Walk test OR 6 Minutes walk N2 test OR 6MWT OR 6MWD OR Incremental shuttle walk test OR ISWT) OR (Timed up and go test OR TUG OR TUGT) OR (Anaerobic threshold OR VO2 peak OR VO2 max OR Oxygen consumption OR VE/VCO2 OR equivalence OR death space OR pulmonary reserve OR CPET OR Cardiopulmonary test OR maximal oxygen uptake) OR (Max* force OR Max* knee extension OR Max* isometric voluntary contraction OR MVC OR Max* handgrip OR Max torque OR Max strength OR force production OR force OR Strength	FT
S9. S7 OR S8	
S10. randomised OR control OR randomized OR trial	
S11. S3 AND S6 AND S9 AND S10	

S: search line, MH: MesH term, FT: Full text.

AMED

S1. (Colorectal cancer OR Colorectal neoplasm OR Colorectal surgery) OR (Bowel cancer OR Bowel surgery OR Bowel neoplasm) OR (Colon cancer OR Colon neoplasm OR Colon surgery) OR (Liver cancer OR Liver surgery OR Liver neoplasm OR Liver transplantation) OR (Hepatic cancer OR Hepatic surgery OR Hepatic neoplasm OR Hepatic transplantation) OR (Pancreatic cancer OR Pancreatic surgery OR Pancreatic neoplasm) OR (Pancreas cancer OR Pancreas surgery OR Pancreas neoplasm) OR Abdominal surgery	FT
S2. Physical intervention OR Physical therapy OR (Exercis* intervention OR Exercis* program* OR Exercis* training OR Exercis* therap*) OR (Presurgery exercis* OR Presurgery activit* OR Presurgery physical activit*) OR (Pre-operative exercis* OR Pre-operative activit* OR Pre-operative physical activit*) OR (Peri-operative exercis* OR Peri-operative activit* OR Peri-operative physical activit*) OR (Pre-surgery exercis* OR Pre-surgery activit* OR Pre-surgery physical activit*) OR (Preoperative exercis* OR Preoperative activit* OR Preoperative physical activit*) OR (Perioperative exercis* OR Perioperative activit* OR Perioperative physical activit*) OR (Physical activity OR Exercise program OR supervised physical activity OR supervised exercise program)	FT
S3. Death OR morbidit* OR Complications OR Mortality OR (Hospital N2 admi*OR Hospitalisation OR Hospitalization) OR (Re-admission OR admission) OR (Walk test OR 6 Minutes walk N2 test OR 6MWT OR 6MWD OR Incremental shuttle walk test OR ISWT) OR (Timed up and go test OR TUG OR TUGT) OR (Anaerobic threshold OR VO2 peak OR VO2 max OR Oxygen consumption OR VE/VCO2 OR equivalence OR death space OR pulmonary reserve OR CPET OR Cardiopulmonary test OR maximal oxygen uptake) OR (Max* force OR Max* knee extension OR Max* isometric voluntary contraction OR MVC OR Max* handgrip OR Max torque OR Max strength OR force production OR force OR Strength	FT
S4. randomised OR control OR randomized OR trial	

S5. S1 AND S2 AND S3 AND S4	

S: search line, FT: Full text.

PeDro

P. Abdominal surger*

Clinical trials. Gov and WHO international clinical trials registry platform

Condition: Surgery

Other terms: prehabilitation exercise OR preoperative exercise.

Appendix 4. Risk of bias assessment of chapter 7

First author	Sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data. Dichotomous	Incomplete outcome data. Continuous	Free of selective reporting	Other bias
Berkel 2022	**Adequate.** **“**They were randomly assigned to the prehabilitation group or the usual care group by block-stratified randomization ”.	**Adequate**. “A nurse who did not help recruit patients or perform data analyses performed the randomization by using sealed opaque envelopes”.	**Adequate.** **“**Participants and care providers were not masked to randomization, because of the type of intervention”	**Not adequate** **“**28/39 patients were intended to treat analysis in the prehabilitation”.	**Not adequate** **“**28/39 patients were intended to treat analysis in the prehabilitation”.	**Adequate.**	**Adequate.**

First author	Sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data. Dichotomous	Incomplete outcome data. Continuous	Free of selective reporting	Other bias
Fulop 2021	**Adequate.** “Patients were randomly allocated using computerised random numbers to treatment groups by a study coordinator who was not involved in the clinical management of the patients”.	**Not mentioned.**	**Not mentioned.**	**Adequate.**	**Adequate.**	**Adequate.**	**Adequate.**

First author	Sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data. Dichotomous	Incomplete outcome data. Continuous	Free of selective reporting	Other bias
Steffens 2021	**Adequate.** "We used a computer-based, random sequence generator, stratified by surgical procedure".	**Adequate.** "Numbered, sealed, opaque envelopes containing the group allocation".	**Adequate.** "The study research officer and the physiotherapist who conducted the self-reported questionnaires and physical assessments were blinded to group allocation".	**Adequate.**	**Adequate.**	**Adequate.**	**Adequate.**

First author	Sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data. Dichotomous	Incomplete outcome data. Continuous	Free of selective reporting	Other bias
Loughney 2021	**Adequate.** “Trans European Network for patient randomisation in clinical trials system. (TENAELA System) and concealed by the research team”.	**Adequate.** “Trans European Network for patient randomisation in clinical trials system. (TENAELA System) and concealed by the research team”.	**Not mentioned.**	**Adequate.**	**Adequate.**	**Adequate.**	**Adequate.**

Blackwell 2020	**Adequate.** “Randomisation was to either the control group (CON; consisting of standard care) or a four week fully-supervised HIIT intervention (HIIT) using a computer-generated list of random permuted block sizes, stratified according to	**Adequate.** “Allocation concealment was ensured by using opaque sealed envelopes with participant group allocation performed on the first study visit”.	**Adequate.** “CPET interpretation was conducted by two experienced assessors blinded to time-point and group allocation”	**Not reporting dichotomous data**	**Not adequate.** 18/19 and 16/21 patients in prehabilitation group and usual care group completed the follow-up assessment.	**Adequate.**	**Adequate.**

First author	Sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data. Dichotomous	Incomplete outcome data. Continuous	Free of selective reporting	Other bias
	age and gender”.						
Carli 2020	**Adequate.** “Randomization was achieved via computer-generated random numbers composed of 12 blocks of 10”	**Adequate.** “Allocations were placed in sealed, opaque, consecutively numbered envelopes by an independent researcher”	**Adequate.** “Outcome assessors (G.B.-D. and R.A.), surgeons (S.L., M.B., B.S., P.C., G.G., andN.M.), and statisticians (J.F.F.) were blinded to group assignment.”	**Adequate.**	**Not Adequate.** 47/55 and 38/54 patients in prehabilitation group and rehabilitation group completed follow-up before surgery and 38/55 and 30/54 completed follow-up after 4 weeks of surgery in 6MWDT	**Adequate**	**Adequate**

Wallen 2019	**Adequate.** “Patients were randomized and stratified (by age and hepatocellular carcinoma) to an exercise training group or usual care group by an individual external to the investigation using a computer-generated allocation program. The same	**Not mentioned.**	**Not mentioned.**	**Adequate.**	**Adequate.**	**Adequate**	**Adequate**

First author	Sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data. Dichotomous	Incomplete outcome data. Continuous	Free of selective reporting	Other bias
	individual who allocated participants also generated the randomization code.”						

First author	Sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data. Dichotomous	Incomplete outcome data. Continuous	Free of selective reporting	Other bias
Northgraves 2019	**Adequate.** "Participants were randomised 1:1 to either prehabilitation or standard care using a random number sequence"	**Adequate**. "with assignments sealed in sequentially numbered opaque envelopes"	**Not mentioned.**	**Adequate**	**Adequate**.	**Adequate.**	**Adequate.**

Banerjee 2018	**Adequate.** “Randomisation was undertaken using a pre-generated random sequence, which was held by a research administrator not involved in the day to day running of the study”	**Not mentioned.**	**Adequate.** “CPETs and post-operative recovery outcomes were blindly assessed by an exercise physiologist who was not directly involved in the supervision of exercise sessions and clinical staff at the treating hospital who were unaware of group allocation, respectively”	**Adequate.**	**Adequate.**	**Adequate.**	**Adequate.**

First author	Sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data. Dichotomous	Incomplete outcome data. Continuous	Free of selective reporting	Other bias
Bousquet-Dion 2018	**Adequate** “patients were randomly assigned on a 1:1 ratio by computer-generated random numbers.”	**Adequate**. “In sealed envelopes to receive either the supervised prehabilitation (PREHAB) or the rehabilitation (REHAB) program”	**Not mentioned**	**Not adequate.** Complications and severe complications are reported only of 26/39 patients in the rehabilitation group.	**Not Adequate.** 32/39 patients in the rehabilitation group completed the follow-up before surgery and 26/39 the follow-up 4 weeks after the surgery.	**Adequate.**	**Adequate**

First author	Sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data. Dichotomous	Incomplete outcome data. Continuous	Free of selective reporting	Other bias
Barberan-Garcia 2017	**Adequate.** “Assignment to group allocation was carried out by means of a computer-generated random number”	**Adequate.** “The randomization was done by means of the SAS Proc Plan System procedure (version 9.1.3 Service Pack 3 or superior)”	**Not mentioned.**	**Adequate.**	**Adequate.**	**Adequate.**	**Adequate**

First author	Sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data. Dichotomous	Incomplete outcome data. Continuous	Free of selective reporting	Other bias
Tew 2017	**Adequate.** “Minimization was performed using Minim software24, with a 1:1 allocation ratio and equal weighting for the three minimization factors”.	**Adequate. “**Allocation was concealed from those assessing eligibility and recruiting patients, with eligible patients allocated remotely via e-mail by the trial statistician”.	**Not mentioned.**	**Adequate.**	**Not adequate.** “Loss follow-up in cardiorespiratory capacity 22/27 exercise group”.	**Adequate.**	**Adequate.**

First author	Sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data. Dichotomous	Incomplete outcome data. Continuous	Free of selective reporting	Other bias
Barakat 2016	**Adequate.** “computer-generated sequence prepared by an independent professional”	**Adequate.** “Randomization was performed using opaque, sealed, identical envelopes containing the treatment allocation”.	**Not mentioned.**	**Adequate.**	**Not Adequate.** 33/62 and 15/62 patients in prehabilitation and usual care group respectively lost follow-up before surgery for measuring VO_2 max and anaerobic threshold.	**Adequate.**	**Adequate**

First author	Sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data. Dichotomous	Incomplete outcome data. Continuous	Free of selective reporting	Other bias
Dunne 2016	**Adequate.** “By means of a block randomization list created at the trial outset”	**Adequate.** “An individual independent of the study group held this list and provided e-mail results of randomization following recruitment”	**Not mentioned.**	**Adequate.**	**Adequate.**	**Adequate.**	**Adequate.**

First author	Sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data. Dichotomous	Incomplete outcome data. Continuous	Free of selective reporting	Other bias
Soares 2013	**Adequate.** **“**participants were randomly allocated”	**Adequate.** **“**participants were randomly allocated, by means of sealed envelope randomization”	**Not adequate.** “Neither patients nor physical therapists were blinded to group assignment, and the investigators responsible for data collection were aware of allocation.”	**Not Adequate.** Severe complications of 12/16 patients in the prehabilitation group are reported.	**Not Adequate.** 12/16 and 8/16 patients in the prehabilitation and usual care group completed the follow-up of 6MWT before surgery and 4 weeks after the surgery.	**Adequate**	**Adequate**

First author	Sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data. Dichotomous	Incomplete outcome data. Continuous	Free of selective reporting	Other bias
Dronkers 2010	**Adequate.** “Participants were randomly assigned (Block randomization)”	**Adequate.** “Using prepared envelopes”	**Adequate.** “Preoperative outcome measures (T=1) and the postoperative course (T=2) were assessed by an investigator who was unaware of the treatment allocation until after data analysis was completed.”	**Adequate.**	**Adequate.**	**Adequate.**	**Not adequate.** VO_2 max was not measured with a breath by breath analyser.

First author	Sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data. Dichotomous	Incomplete outcome data. Continuous	Free of selective reporting	Other bias
Kim 2009	**Adequate.** “Persons were assigned to these two groups by a random process using a two-to-one ratio of intervention to control”.	**Not mentioned.**	**Not mentioned.**	**N/A.**	**Adequate.**	**Adequate.**	**Adequate.**

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