The prognostic capabilities of a preoperative six-minute walk test to inform cardiovascular risk after noncardiac surgery: a pragmatic prospective cohort study.

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ABSTRACT

OBJECTIVES: Postoperative cardiovascular complications are associated with increased morbidity and mortality and may be preventable. The revised cardiac risk index (RCRI) is a commonly used clinical tool to estimate the risk of postoperative cardiovascular complications but has limitations in its predictive ability. Alternatively, the six-minute walk test (6MWT) is a simple, objective measure of functional capacity that has previously been associated with postoperative complications. This study examined whether the addition of a preoperative 6MWT to the RCRI improved its ability to predict death, myocardial infarction, or cardiac arrest 30 days after elective noncardiac surgery.

METHODS: This prospective cohort study included 967 patients aged ≥ 50 years who were scheduled for elective noncardiac surgery under general and/or regional anaesthesia at two sites of the McGill University Health Centre (MUHC) in Montreal, Quebec, Canada. Patients were recruited from the preoperative assessment clinic and completed a 6MWT on the same day. Participants were then followed up at 30 days postoperatively, with the primary outcome being death, MI, or cardiac arrest. Secondary outcomes included all-cause death, individual cardiovascular complications, and length of stay. Non-cardiovascular complications were also examined, and we compared subjectively assessed functional capacity to the metabolic equivalents (METs) calculated from the 6MWT result. Multivariable logistic regression was used to examine the relationship between the 6MWT and the RCRI on the primary outcome.

RESULTS: After enrolment, 819 patients remained eligible for outcome analysis, and completed the 30-day follow-up postoperatively. Participants were predominantly male (58.2%) and had an ASA score of 2 or 3 (97%), with a mean age of 69 years and mean BMI 29.0. The most common comorbidities were hypertension (81.1%), dyslipidemia (65.9%), diabetes (33.3%), and 43.5% of patients underwent surgery for cancer. The mean (SD) 6MWT distance across the cohort was 389 (111) meters. The primary outcome of death, MI, or cardiac arrest within 30 days of index surgery occurred in 17 patients (2.1%), comprising 10 deaths, 8 MIs, and 1 cardiac arrest. Multivariable logistic regression indicated that the RCRI was associated with the primary outcome (OR [95% CI] = 2.085 [1.233, 3.462], p = 0.005), whereas the 6MWT was not (OR [95% CI] = 0.996 [0.992, 1.001], p = 0.099). Further, the 6MWT was not predictive of any cardiovascular complications postoperatively, but it was associated with a decreased risk of all-cause death and suffering any non-cardiovascular complication at 30-days postoperatively. We also observed a significant discrepancy between subjectively assessed METs and calculated METs from the 6MWT.

CONCLUSION: The 6MWT was not associated with the primary outcome of death, MI, or cardiac arrest at 30 days after elective noncardiac surgery, and thus did not improve the predictive abilities of the RCRI. Otherwise, this study was consistent with previous literature in finding that the 6MWT was associated with non-cardiovascular complications postoperatively. Further research is required to clarify the role of objective measures of functional capacity in the perioperative period.

RÉSUMÉ

OBJECTIFS: Les complications cardiovasculaires postopératoires sont associées à une morbidité et une mortalité accrues et peuvent être évitables. Le score « revised cardiac risk index » (RCRI) est un outil clinique fréquemment utilisé pour estimer le risque de complications cardiovasculaires postopératoires suite à une chirurgie non cardiaque. Toutefois, ce score a une capacité prédictive limitée. D'autre part, le test de marche de six minutes (6MWT) est une test simple qui mesure objectivement la capacité fonctionnelle. Des études antérieures ont démontré qu'une mesure du 6MWT basse est associé à des complications postopératoires. Conséquemment, nous avons effectué une étude qui a examiné l'impact de l'ajout de la mesure préopératoire du 6MWT au score RCRI sur la prédiction de complications postopératoires telles que la mort, l'infarctus du myocarde (IM) ou l'arrêt cardiaque, en dedans de 30 jours après une chirurgie non cardiaque élective.

MÉTHODE: Cette étude de cohorte prospective a inclus 967 patients âgés de ≥ 50 ans qui ont subit une chirurgie non cardiaque élective sous anesthésie générale et/ou régionale dans deux sites du centre universitaire de santé McGill (CUSM) à Montréal, Québec, Canada. Les patients ont été recrutés à la clinique préopératoire. Les patients ont effectué le 6MWT au courant de cette même visite en clinique. Les participants ont ensuite été suivis pendant 30 jours après l'opération. L'issue principal est la mort, l'IM ou l'arrêt cardiaque. Les issus secondaires comprennent la mort de toutes causes confondues, les complications cardiovasculaires individuelles et la durée du séjour hospitalier. Les complications non cardiovasculaires ont également été examinées. De plus, nous avons comparé la capacité fonctionnelle évaluée subjectivement aux équivalents métaboliques (METs) calculés à partir de la mesure du 6MWT.

Une régression logistique multivariée a été effectuée pour examiner la relation entre le 6MWT et le RCRI sur l'issu principal.

RÉSULTATS: Suite au recrutement, 819 patients sont demeurés éligibles pour l'analyse des résultats et tous ont complété le suivi postopératoire à 30 jours. Les participants étaient majoritairement des hommes (58.2 %) et avaient un score ASA de 2 ou 3 (97 %), avec un âge moyen de 69 ans et un IMC moyen de 29.0. Les comorbidités les plus fréquentes étaient l'hypertension (81.1%), la dyslipidémie (65.9%), le diabète (33.3%) et 43.5 % des patients ont subi une chirurgie pour un cancer. Parmi tous les participants de la cohorte, la distance moyenne (ET) du 6MWT était de 389 (111) mètres. L'issu principal de décès, d'IM ou d'arrêt cardiaque dans les 30 jours suivant la chirurgie est survenu chez 17 patients (2.1%) : 10 décès, 8 IM et 1 arrêt cardiaque. La régression logistique multivariée a indiqué que le RCRI était associé l'issu principal (OR [IC à 95 %] = 2.085 [1.233, 3.462], p = 0.005), alors que le 6MWT ne l'était pas (OR [IC à 95 %] = 0.996 [0.992, 1.001], p = 0.099). De plus, le 6MWT n'était pas prédictif de complications cardiovasculaires postopératoires, mais il était associé à une diminution du risque de décès toutes causes confondues et de toutes complications non cardiovasculaires à 30 jours postopératoire. Nous avons également observé un écart significatif entre la valeur de MET subjective reportée par le patient et celle calculée à partir du 6MWT.

CONCLUSION: Le 6MWT n'était pas associé à l'issu principal de décès, d'IM ou d'arrêt cardiaque à 30 jours après une chirurgie non cardiaque élective. Donc, nos résultats ont démontré que le 6MWT n'a pas amélioré les capacités prédictives du RCRI. D'autre part, les résultats de cette étude sont cohérents avec la littérature antérieure en constatant que le 6MWT est associé à

des complications non cardiovasculaires. Des études supplémentaires futures sont nécessaires pour clarifier le rôle des mesures objectives de la capacité fonctionnelle dans la période périopératoire.

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CONTRIBUTION OF AUTHORS

The entirety of this thesis research has been conducted and written by Stefan Saric (SS), with contributions from Dr Amal Bessissow (AB; supervisor) and Berson Augustin (BA; research assistant), as indicated below:

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LIST OF ABBREVIATIONS

6MWT: Six-Minute Walk Test

6MWD: Six-Minute Walk Test Distance

ACS-NSQIP: American College of Surgeons National Surgical Quality Improvement Program

AF: Atrial Fibrillation

ASA: American Society of Anesthesiologists Functional Status

AT: Anaerobic Threshold

ATS: American Thoracic Society

AUC: Area-Under-the-Curve

BMI: Body Mass Index

CABG: Coronary Artery Bypass Graft

CHF: Congestive Heart Failure

CI: Confidence Interval

CKD: Chronic Kidney Disease

COPD: Chronic Obstructive Pulmonary Disease

CPET: Cardiopulmonary Exercise Test

DASI: Duke Activity Status Index

DM: Diabetes Mellitus

DVT: Deep Venous Thrombosis

EAC: Event Adjudication Committee

ECG: Electrocardiogram

ENT: Ear, Nose, and Throat

HR: Hazard Ratio

ICU: Intensive Care Unit

IRB: Institutional Review Board

IQR: Interquartile Range

LOS: Length of Stay

M_{diff}: Mean Difference

METs: Metabolic Equivalents

METS: Measurement of Exercise Tolerance Before Surgery Study

MI: Myocardial Infarction

MINS: Myocardial Injury after Non-cardiac Surgery

MUHC: McGill University Health Centre

NSCLC: Non-Small Cell Lung Cancer

NSTEMI: Non-ST Elevation Myocardial Infarction

NT-pro-BNP: N-terminal Pro B-type Natriuretic Peptide

OHA: Oral Hypoglycemic Agent

OR: Odds Ratio

OSA: Obstructive Sleep Apnea

PCI: Percutaneous Coronary Intervention

PE: Pulmonary Embolism

POISE: Perioperative Ischaemic Evaluation trial

PVD: Peripheral Vascular Disease

RCRI: Revised Cardiac Risk Index

RCT: Randomized Controlled Trial

ROC: Receiver-Operator-Characteristic curve

RR: Relative Risk

SD: Standard Deviation

STEMI: ST Elevation Myocardial Infarction

TIA: Transient Ischemic Attack

VISION: Vascular Events in Noncardiac Surgery Patients Cohort Evaluation

VO2: Volume of Oxygen

VTE: Venous Thromboembolism

INTRODUCTION

Globally, it is estimated that between 200 to 300 million patients undergo surgery each year (1, 2). Despite the widespread benefits of surgery, an estimated seven million patients suffer major cardiovascular complications after surgery, and approximately one million patients die within 30 days (2). It is well established that perioperative cardiovascular complications are associated with increased morbidity and mortality and increase the costs of care. Notably, almost half of postoperative adverse events are believed to be preventable (2).

Postoperative cardiovascular complications are a leading cause of perioperative morbidity and mortality and confer a poorer prognosis after noncardiac surgery. Devereaux, et al. (3) examined an international cohort of 8,351 patients undergoing noncardiac surgery and found that 5% of patients experienced perioperative myocardial infarction (MI); this was associated with a 12% risk of 30-day mortality after surgery compared to a 2% mortality risk in patients who did not experience MI. Other cardiovascular complications have also been associated with increased risk of 30-day mortality postoperatively, including myocardial injury after noncardiac surgery (MINS; hazard ratio (HR)= 2.2) , congestive heart failure (CHF; HR = 2.4), stroke (HR = 3.7), new atrial fibrillation (AF; HR = 1.4), and venous thromboembolism (VTE; HR = 2.2) (4). These risks may be further compounded in the future given the increasing age and comorbidities of patients undergoing surgery (5-7). Thus, rigorous preoperative risk assessment and perioperative monitoring are required to reduce the impact of postoperative cardiovascular complications. Expert-lead, evidence-based guidelines have been published to aid clinicians in this process (6, 8). In particular, the use of preoperative risk assessment tools to identify high-risk patients is recommended (6, 8). One of these tools is the revised cardiac risk index (RCRI).

The RCRI (9, 10) is one of the most commonly used tools for estimating risk of cardiovascular complications (death, MI, or cardiac arrest) after noncardiac surgery (8). It's a simple, 6-item tool that has been externally validated across multiple large prospective studies (11-13). However, one of the weaknesses of the RCRI is that its discriminative abilities appear to be weaker than initially indicated (11, 14).

An aspect of perioperative risk assessment that is not captured by the RCRI is the functional capacity assessment. Functional capacity is an assessment of a patient's ability to perform their activities of daily living, and thus reflects the health and integrated functioning of their cardiac, pulmonary, musculoskeletal, and metabolic systems. Consequently, functional capacity assessment has been considered a crucial step the in perioperative assessment process. Guidelines suggested that physicians use the functional capacity assessment to determine whether further cardiac evaluation was required prior to proceeding with moderate to high-risk surgery (15, 16). Traditionally, a patient's functional capacity was assessed subjectively by clinicians during the preoperative clinic interview (15, 16). In fact, Buse, et al. (17) demonstrated that the addition of a simple question ("can you climb 2 flights of stairs?") to the RCRI improved the prediction of postoperative cardiovascular complications after noncardiac surgery. However, another large study argued that subjective functional capacity assessment was unreliable, given that it was not associated with postoperative outcomes and did not correlate with validated objective measures of functional capacity (18). This suggests that the use of a simple objective measure of functional capacity, such as the six-minute walk test (6MWT), may be a better candidate for addition to the RCRI to improve its predictive capabilities.

The 6MWT is a safe, easy-to-administer, and reproducible test that involves measuring the total distance a patient is able to walk on flat ground in 6 minutes, following the provision of standardised instructions and feedback as outlined by the American Thoracic Society guidelines (19). Further, the 6MWT is simple and well-tolerated by patients (20, 21), and has been shown to correlate with more physically demanding measures of functional capacity, such as the gold-standard cardiopulmonary exercise test (CPET) (18). There is also growing evidence that the 6MWT alone may be used to predict postoperative complications. In particular, a reduced preoperative 6WMT has been associated with increased risk of complications after noncardiac (22), colorectal (23), abdominopelvic(24) (25), and thoracic surgery (26-29).

Thus, given the respective strengths of the RCRI and the 6MWT, the aim of this study is to assess whether the addition of a preoperative 6MWT to the RCRI would improve its ability to identify patients at risk of major cardiovascular complications at 30 days after noncardiac surgery.

This monograph will be divided into four chapters: **Chapter 1:** Literature review related to surgery and perioperative complications, perioperative risk assessment, functional capacity assessment, and the 6-minute walk test; **Chapter 2:** 6MWT study: study rationale & methods; **Chapter 3:** 6MWT study: results & discussion; and **Chapter 4:** Conclusion.

CHAPTER 1 – LITERATURE REVIEW

1.1 Surgery & perioperative complications

The global volume of surgery is increasing. Weiser, et al. (1) examined surgical volume data from over 50 countries in 2004 and again in 2012 – they found that the number of surgeries had increased from approximately 226 million to 313 million cases per year, respectively. This is an increase of 38%, and the upward trend is expected to continue. Further, initially Weiser, et al. (2) estimated that close to 7 million patients undergoing surgery experienced major complications, and that 1 million patients would die during or shortly after their surgery. With their latest projections, this would suggest that by 2012, approximately 9 million patients suffered perioperative complications, and over 1.5 million may have died postoperatively. However, even these figures may be underestimates, as updated figures for global perioperative mortality are closer to 1.8% (4), rather than the conservative 0.5% mortality rate assumed by Weiser, et al. (2). Evidently, this large global volume of surgery also carries with it a significant burden of perioperative morbidity and mortality. This may be further compounded by the increasing age and comorbidities of surgical candidates (5-7).

Smilowitz, et al. (5) examined over 10 million hospital admissions for noncardiac surgery in patients aged ≥ 45 years between 2004 and 2014. Their key finding was that the presence of at least 2 cardiovascular risk factors in surgical candidates increased from 40.5% in 2008 to 48.2% in 2013. Specifically, by 2013, 63% of patients undergoing noncardiac surgery had hypertension, 37% had dyslipidemia, 27% diabetes, and 18% had a history of coronary artery disease; each of these having incremented since 2004. Given that the frequency of cardiovascular risk factors is known to increase with age (5), the ageing population (and thus increasing age of surgical

candidates) is likely to continue this trend of operating on patients with an increasing number of comorbidities. It is estimated that by the year 2030, 20% of patients > 75 years of age will undergo surgery each year (6). This also necessitates a higher degree of vigilance for perioperative complications, given that elderly patients are at greater risk than younger patients (30). Evidence-based, expert-lead guidelines (6, 8) have been published to aid clinicians in approaching the challenge of perioperative risk assessment that is posed by an ageing and more comorbid surgical population.

Cardiovascular complications are common leading causes of perioperative morbidity and mortality (31, 32). In an international study of 8,351 patients undergoing noncardiac surgery, Devereaux, et al. (3) found that 5% of patients experienced perioperative myocardial infarction (MI); this conferred a 12% risk of death 30-days after surgery compared to 2% mortality risk in patients who did not experience MI. Furthering this research, an interim analysis (32) of The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) study identified that 8% of patients suffered myocardial injury after noncardiac surgery (MINS). Importantly, MINS is a more clinically "silent" complication than MI which can be easily missed without active surveillance for myocardial ischaemia, with just under 16% of patients experiencing ischaemic symptoms (32). Nevertheless, MINS was identified to be highly prognostically significant, as it was associated with increased 30-day mortality (HR = 3.87). This has been corroborated by other studies (33), and MINS has also been associated with increased risk of death at 1-year after surgery (34). The final VISION cohort included over 40,000 patients aged ≥ 45 years who underwent noncardiac surgery across 14 countries (4). The aim of this study was to examine the association between perioperative complications and death at 30-days

postoperatively. The overall mortality rate was 1.8%, and the VISION study investigators identified further cardiovascular complications that conferred an increased risk of 30-day death. These included: congestive heart failure (CHF; HR = 2.4), stroke (HR = 3.7), new atrial fibrillation (AF; HR = 1.4), and venous thromboembolism (VTE; HR = 2.2).

In addition to the clinical consequences of perioperative cardiovascular complications, the additional costs to the health-system should also be considered. This added cost has been shown to culminate in an increased length of hospital stay for patients who suffer MINS, MI, new or worsened CHF, and arrhythmia postoperatively (33, 35). Specifically, a study by van Waes, et al. (33) examined over 2000 patients undergoing noncardiac surgery, and found that patients who experienced MINS stayed twice as long in hospital (median length of stay 5 versus 10 days). Mackey, et al. (35) found that the same was true for patients who suffered perioperative MI, CHF, or arrhythmia. These complications also increased the risk of ICU admission and ICU length of stay, and were associated with a greater chance of readmission to an emergency department after discharge from hospital (35). Accordingly, this increased resource utilisation and requirement for further treatment is associated with increased costs of care (36). Thus, an imperative exists at the patient, health-system, and population levels to identify, intervene, and monitor patients at high-risk of postoperative cardiovascular complications.

Unfortunately, attempts by the POISE (37) and POISE-2 (38, 39) trials to identify perioperative interventions to reduce the risk of cardiovascular complications have been unsuccessful. However, early identification and monitoring of patients at high-risk of cardiovascular complications may reduce perioperative morbidity and mortality after noncardiac surgery (4).

Accordingly, several perioperative risk assessment strategies and tools exist to aid in the preoperative assessment of patients.

1.2 Perioperative risk assessment tools

To identify patients at higher risk of postoperative morbidity and mortality, several preoperative risk predictor tools are available. Currently, the American Society of Anesthesiology (ASA) physical status, the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) surgical risk calculator, and the Revised Cardiac Risk Index (RCRI) are the most commonly used tools.

The ASA physical status classification system was first introduced in 1941(40), and then later revised in 1961(41), and again in 2014 (42). The aim of the ASA score is to describe a patient's preoperative health status (and/or the degree of functional impairment) on a scale of 1 to 5. The ASA classes range from normal healthy patient (ASA 1) to a moribund patient who is not expected to survive without surgery (ASA 5); further, an "E" qualifier may be added to indicate emergency surgery (e.g., 2E) (see Appendix 1.1). Today, the ASA score is routinely documented for all patients undergoing surgery with anaesthesia (43). The advantages of the ASA are its simplicity, longevity in clinical practice, and association with postoperative morbidity and mortality (43-45). A large retrospective cohort study of over 2 million noncardiac surgery cases concluded that ASA was independently associated with postoperative complications and mortality (43). The ASA score has also been shown to be associated with cardiovascular complications after hip fracture surgery, namely heart failure, MI, and death (46). However,

conflicting evidence exists (47). When receiver operating characteristic (ROC) area under the curve (AUC) analysis is used to examine the ability of the ASA score to discriminate between patients who would (versus would not) suffer major cardiac events perioperatively, it has been shown to perform poorly (AUC 0.59; 95% CI: 0.47 – 0.71) (48). Generally, an AUC 0.5 to 0.7 indicates that a discriminatory tool has no to low discriminatory power (49) (see Appendix 1.2).

The ASA score has also been heavily criticized for its subjectivity and low inter-rater reliability (50-53), with agreement between clinicians ranging widely from 40-90% (54). Further, in its inception, the ASA was not intended to be used as a predictor of operative risk, and many authors have presented arguments reminding clinicians of that (55, 56). Collectively this suggests that although the ASA provides insights into a patient's preoperative health status, and correlates with some postoperative complications, it is not an optimal risk stratification tool when used alone (54). Nevertheless, the ongoing use of the ASA in clinical practice is testament to its value, and as a result, it has been incorporated into other risk prediction models – one of which is the ACS-NSQIP surgical risk calculator (57).

The ACS-NSQIP was developed by Bilimoria, et al. (57), and uses a complex proprietary model of 21 predictor variables to provide procedure-specific estimates of eight complications within 30 days of surgery. The complications include: death, pneumonia, cardiac complications, surgical site infection, urinary tract infection, venous thromboembolism, renal failure, and a composite outcome of "any complication". The ACS-NSQIP risk calculator was developed by examining over 1.4 million patients undergoing surgery across multiple specialties from the vast and ongoing NSQIP database (58). Importantly, the discriminative ability of the risk calculator is

excellent, with the AUC for all eight outcomes ranging from 0.81 to 0.94 (57). Further, the ACS-NSQIP risk calculator can be applied to over 1500 different procedures. However, a few limitations exist: the calculator is based entirely on US data, is yet to be extensively validated using external datasets, and it requires clinicians to use a web-based calculator to input all required data – a much slower process when compared to a simple ASA assignment. Finally, its most significant limitation is that the model likely underestimates the risk of perioperative cardiovascular complications (8). The reason for this is two-fold: 1) a narrow definition of symptomatic MI or cardiac arrest was used, and 2) the NSQIP derivation cohort did not include prospective surveillance for myocardial ischaemia (such as using serial postoperative troponin measurements) (8). This is a significant limitation because up to half of perioperative MIs may be undetected if screening is not performed (59). Unfortunately, the model has also received criticism for not publishing the prediction equations utilised (60), thereby limiting validation with external datasets. For these reasons, the Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery (8) still recommend use of the Revised Cardiac Risk Index (RCRI) (10) when assessing and communicating cardiovascular risk preoperatively.

The RCRI is a widely used tool for estimating risk of cardiovascular complications (death, MI, or cardiac arrest) after noncardiac surgery. The cardiac risk index was first developed in 1977 by Goldman, et al. (9) who examined 1001 patients undergoing noncardiac surgery, and identified nine predictors of perioperative death, MI, arrhythmia, and pulmonary oedema. Years later, due to advances in cardiac disease diagnosis and management, the risk index was revised by Lee, et al. (10). The revised score (i.e., “RCRI”) was derived from a prospective cohort study of 4315

patients aged ≥50 years who were undergoing major elective noncardiac surgery (10). Lee's RCRI consists of six equally weighted items: history of ischaemic heart disease, heart failure, cerebrovascular disease, diabetes mellitus requiring insulin therapy, renal insufficiency with preoperative serum creatinine >177 μmol/L, and/or undergoing high-risk surgery. Examples of high-risk surgery include supra-inguinal vascular surgery, open intra-peritoneal surgery, and intra-thoracic surgery. Adding each risk factor produces a total score (0, 1, 2, or ≥3) which corresponds to the 30-day risk of postoperative cardiovascular complications: 0.5%, 1.3%, 4%, and 9%, respectively. The authors remarked at the discriminative ability of the RCRI at the time, using ROC analysis to estimate the AUC to be between 0.78 to 0.81 (10).

Since then, the RCRI has been externally validated and examined by multiple large prospective studies (11-13), with the general trend being that the cardiovascular complication rates were significantly higher than that initially thought. A pooled analysis of 5 studies by Duceppe, et al. (8) indicated that RCRI scores of 0, 1, 2, or ≥3 corresponded to estimated event rates of 3.9%, 6.0%, 10.1%, and 15%, respectively, for risk of MI, cardiac arrest, or death within 30 days of non-cardiac surgery (see Appendix 1.3). This is significantly higher than the initial estimates by Lee, et al. (10), and is likely due to two major factors: 1) the use of more sensitive troponin assays to capture myocardial ischaemia (as opposed to older creatine kinase or brain isoenzyme assays), and 2) inclusion of emergency surgery patients in newer studies (8). These additional studies and external validation have contributed to the robustness and uptake of the RCRI.

However, the downside is that the predictive and discriminatory ability of the RCRI has been found to be more variable than initially demonstrated. The systematic review by Ford, et al. (61)

examined over 790,000 patients across 24 studies and concluded that the discriminative ability of the RCRI to identify patients at low versus high risk of perioperative cardiovascular complications was lower than previously reported, with an AUC of 0.69 [95% CI 0.62 to 0.75]. More recently, Roshanov, et al. (62) also reported a similarly weak discriminative ability for the RCRI. This is a major weakness of the RCRI, despite its simplicity and widespread use. However, a significant aspect of perioperative risk stratification that is not captured by the RCRI is functional capacity assessment. We hypothesise that the addition of a functional capacity measure to the RCRI may improve the prediction of cardiovascular complications after noncardiac surgery.

1.3 Functional capacity assessment

Routine preoperative assessment of surgical patients involves evaluation by a treating physician, including a medical, anesthetic, and surgical history, focused physical examination, and review of relevant investigations (63, 64). In addition, assessment of the patient's functional capacity during the clinical interview may also be considered an essential part of this preoperative evaluation, as it was previously found to be a reliable indicator of perioperative risk (15, 16). Functional capacity refers to a patient's ability to complete their activities of daily living, and is dependent on healthy, integrated functioning of the cardiovascular, pulmonary, musculoskeletal, and metabolic systems (Arena et al., 2007). Functional capacity is measured in metabolic equivalents (METs), where 1 MET is equal to the oxygen consumption of a 40–year-old, 70-kg male at rest (15). Traditionally, functional capacity was assessed using subjective, self-reported measures during the preoperative assessment interview (see Appendix 1.4 for examples). Patients who reported being able to achieve at least 4 METs (e.g. "can you walk up two flights of

stairs?") were generally considered suitable to proceed to surgery without further cardiac investigations or stress-testing (15, 16). However, two recent large studies (17, 18) have provided conflicting evidence on the reliability of subjective functional capacity assessment.

Buse, et al. (17) conducted an international, multicenter, prospective cohort study of 4560 patients undergoing noncardiac surgery, with the aim to assess whether the self-reported ability to climb two flights of stairs was associated with reduced cardiac complications at 30 days and 12 months postoperatively. The patient population studied were patients aged ≥ 65 years or patients aged ≥45 years with a history of cardiovascular disease. The key finding was that the self-reported inability to climb two flights of stairs preoperatively was associated with an increased risk of cardiac complications and death at 30-days and 1-year postoperatively. Further, when the subjective functional capacity assessment (i.e., "yes" or "no") was added to the RCRI, it improved the predictive abilities of the RCRI. This evidence supported the continued use of simple, subjective functional capacity assessments preoperatively.

Conversely, the study performed by Wijeysundera, et al. (18) came to the opposite conclusion. This was also a large, international, multicenter prospective cohort study, enrolling 1401 patients aged at least 40 years with cardiovascular risk factors who were undergoing noncardiac surgery. Functional capacity was similarly subjectively assessed, but the classification considered all responses during the preoperative interview (as opposed to a single discriminating question) and patients were categorized into three functional capacity groups: "poor" (i.e., METs achieved < 4), "moderate" (METs 4-10), or "good" (METs > 10). However, Wijeysundera, et al. (18) concurrently assessed functional capacity using three other, more objective measures: the Duke Activity Status Index (DASI) questionnaire, cardiopulmonary exercise testing (CPET), and

serum NT-pro-BNP. The primary outcome was death or MI within 30-days of surgery, and the secondary outcome was death at 12-months postoperatively. The key finding was that subjective functional capacity assessment was not associated with any outcome, whereas the DASI predicted 30-day death and myocardial infarction, NT-pro-BNP was associated with 30-day death and myocardial injury, and lower peak oxygen consumption (as measured by CPET) was associated with increased risk of postoperative complications. Further, subjective assessment was only able to correctly identify 16% of patients who had a METs < 4 according to their CPET result. Based on this evidence, Wijeysundera, et al. (18) argued that subjective assessment of functional capacity should not be used for preoperative risk stratification.

This divergent evidence has now been reflected in newer European (6) and Canadian (8) perioperative assessment guidelines – which no longer strongly recommend subjective functional capacity assessment preoperatively. However, the study by Wijeysundera, et al. (18) did provide further evidence that objective measures of functional capacity may still play a role in preoperative assessment. Traditionally, the gold-standard non-invasive method for functional capacity assessment has been CPET (65).

Cardiopulmonary exercise testing (CPET) involves patients exercising on a cycle ergometer against a progressively increasing resistance, until maximum workload is achieved (66). During the test, patients require continuous cardiac monitoring (blood pressure, heart rate, electrocardiogram) as well as gas exchange analysis for accurate interpretation (66). The key measures of functional capacity are peak oxygen consumption ("VO2 max" or "peak VO2") and anaerobic threshold (AT). A trained interpreter is then able to synthesize the data obtained during

CPET to diagnose the cause of any limitations in exercise capacity (66). Whilst this provides further insight into patient's cardiopulmonary comorbidities (and thus perioperative risk profile), the requirement for specialized equipment and highly trained personnel to administer and interpret the test are two major drawbacks. Further, it is a demanding workout for most patients, and Wijeysundera, et al. (18) speculated that this may have contributed to the low 27% consent rate in their study. An alternative method of objective cardiopulmonary fitness assessment which is better tolerated by patients, simple, cheap, and safe to perform is the six-minute walk test.

1.4 The Six-Minute Walk Test (6MWT)

Field tests for the measurement of exercise capacity were first described in the 1960s by Balke (67) who designed a 15-minute run test for military aviation personnel to obtain standardized measures of physical fitness. Cooper (68) extended this by performing a similar 12-minute run test, as well as conducting treadmill exercise tests and measuring peak VO2 in male air force officers. Their key finding was that performance on the run test was highly correlated with peak VO2 during the treadmill exercise test. This concept was then transferred to the patient context by McGavin, et al. (69), who simplified the run test to a 12-minute walking test for patients with chronic bronchitis and conducted bicycle ergometer exercise tests – again finding that performance on a field test correlated with peak VO2. With evidence building that field tests were reliable and simple measures of exercise capacity, Butland, et al. (70) then examined whether the 12-minute walk could be substituted for shorter 2- or 6-minute walk tests in patients with chronic airflow obstruction. Although longer walking tests were able to better discriminate between patients with differing levels of exercise capacity, shorter tests were better tolerated, as reproducible, had less of a "training effect", and were more practical for investigators to perform.

On the balance of advantages and disadvantages, Butland, et al. (70) suggested the 6-minute walk test as a reasonable compromise. Guyatt, et al. (20) then validated the 6-minute walk test in a small cohort of patients with chronic heart failure or chronic lung disease, and similarly found that the test was reproducible and well-tolerated by patients. Notably, Guyatt, et al. (20) also confirmed the provision of encouragement during the test improved the walking scores for patients compared to those who weren't encouraged. This set the scene for the establishment of a standardised six-minute walk test (6MWT).

The American Thoracic Society (19) provides guidelines for the administration of a standardised 6MWT. Patients are instructed to walk continuously and as far as possible between two markers 30-metres apart on a flat indoor track for six minutes. The assessor notes each lap completed, and provides standardized feedback and encouragement cues each minute until the completion of the test. Patients are specifically informed to complete the test walking as fast as they can, without jogging or running. Vital signs and baseline dyspnea or fatigue (using the Borg scale) are assessed prior to the test, and again at the end. Any symptoms developed during the test (e.g., chest pain, dyspnea, claudication) are noted. Patients may take breaks to rest during the test but are instructed to continue walking when (or if) they are able. If unable, the test may be terminated early (i.e., prior to completion of the 6 minutes). In these cases, the distance completed at that point constitutes the final 6MWT distance (6MWD). The 6MWT has now been extensively studied in many patient populations, and has been found to be simple, cheap, and safe to perform (21). The 6MWT reliably correlates with CPET findings (71) and can be converted to a MET score using the following formula (72): METs = (0.1 * (6MWD / time

taken to complete the test in minutes)) + 3.5) ÷ 3.5. Further, the 6MWT has been extensively studied as a potential predictor of postoperative complications.

Following a comprehensive review of several databases (Medline, PubMed, Embase), we identified 15 studies of various designs over the past 10 years examining the association between a preoperative 6MWT and complications after noncardiac surgery. Table I displays a summary of the studies reviewed. The most consistent evidence for the association between a preoperative 6MWT and postoperative complications are in the following contexts: 1) thoracic surgery, 2) outcomes examining composite scores of postoperative complications or pulmonary complications specifically, and 3) in cohorts of patients undergoing surgery for cancer.

Firstly, in the context of thoracic surgery, patients with a reduced 6MWT distance have been consistently shown to be at increased risk of postoperative complications, including atelectasis, pneumonia, respiratory failure, reintubation, arrhythmia, blood transfusion, and death (26-29, 73). Although similar associations have been observed in patients undergoing colorectal (23, 74) or abdominal surgery (24) (25, 75), conflicting evidence also exists. Specifically, Paisani, et al. (76) examined 137 patients undergoing upper abdominal surgery, and did not find an association between the preoperative 6MWT and postoperative pulmonary complications. However, this study may have been underpowered due to observing a very low incidence of pulmonary complications (7.2%), Arruda, et al. (73) also reported lower than expected complication rates, namely 17% for patients undergoing upper abdominal surgery, and 10% for patients undergoing thoracic surgery. This is in comparison to the 20-50% complication rates captured in other studies (23-25, 75). Despite this, Arruda, et al. (73) were still able to identify an association

between the preoperative 6MWT and postoperative complications in the thoracic surgery cohort, but there was no such relationship observed in the upper abdominal surgery cohort. Bearing in mind the heterogeneity in the complication data captured across all these studies, on balance it appears that the evidence is more consistent in thoracic surgery cohorts.

Second, most studies report an association between 6MWT and a composite endpoint of postoperative complications, with varying definitions. When these postoperative complications are reported or teased out by systems, only pulmonary complications have been consistently associated with a low preoperative 6MWD (24, 26, 29, 73, 77).When examined as a dichotomous variable, 6MWT results between 400m to 500m are common cutoffs for increased risk of postoperative complications. Regarding other systems, Ramos, et al. (22) examined postoperative cardiac complications but were unable to demonstrate an association between 6MWT and 30-day death or myocardial injury. However, this was a secondary outcome in a substudy analysis, and the authors suggested that their study may have suffered from a selection bias for "fitter" patients as two exercise tests were required, many of which were administered on the same day. Otherwise, as seen in Table 1, most studies focus on capturing composite outcomes postoperatively, with definitions spanning medical and surgical complications across multiple systems.

Finally, a recent systematic review and meta-analysis of 379 patients having abdominopelvic cancer surgery revealed that patients who were able to walk ≥ 400m were at reduced risk of postoperative complications (78). This is supported by an abundance of evidence for patients having surgery for esophageal (28) or lung cancer (26, 27, 29), with the latter significantly

overlapping with the evidence from thoracic surgery. Thus, the 6MWT appears to be more consistently associated with predicting complications in patients after cancer surgery.

Overall, as the evidence for the ability of a preoperative to 6MWT to predict postoperative complications continues to grow, it is worth more thoroughly examining its performance in conjunction with the RCRI to predict cardiovascular complications in a broadly generalizable cohort of patients undergoing noncardiac surgery.

Table 1: Summary of studies examining the relationship between a preoperative 6WMT and postoperative complications

Author(s)	Year	Study Design	Population studied	Outcome(s)	Key finding(s)
Makker, et al. (78)	2022	Systematic review and meta-analysis	379 patients (across 5 studies) undergoing gastrointestinal tract cancer surgery	• Incidence postoperative complications • LOS	• 6MWD ≥400m was associated with reduced risk of complications • No association between 6MWD and LOS
Ramos, et al. (22)	2021	Prospective cohort study – secondary subgroup analysis	545 adults (≥ 40 years) undergoing elective noncardiac surgery	• Moderate-severe in-hospital complications • 30-day death or myocardial injury	• A 100m decrease in 6MWD associated with moderate-severe complications (OR 1.32 [95% CI 1.01, 1.73]) • No association between 6MWD and 30-day death or myocardial injury
Gillis, et al. (74)	2021	RCT – secondary analysis	47 patients (>65 years and Fried frailty ≥2) undergoing surgery for colorectal cancer	• Postoperative complications within 30 days of hospital discharge	• 6MWD <400m was associated with increased risk of postoperative complications (OR 6.2, p = 0.041)
Soares and Nucci (24)	2021	Cross-sectional cohort study	50 adults undergoing elective abdominal surgery	• Postoperative pulmonary complications within 7 days	• 6MWD > 400m associated with lower risk of postoperative pulmonary complications (OR 0.978, p = 0.010)
Lee, et al. (29)	2020	Prospective cohort study	416 adults undergoing lobectomy for NSCLC	• Cardiopulmonary complications within 30 days of surgery	• Moderate risk patients walking <400m were more likely to develop postoperative complications (OR 7.84 [95% CI 2.24, 27.46])

Inoue, et al. (28)	2020	Retrospective cohort study	111 patients undergoing thoracic surgery for oesophageal cancer	• Clavien-Dindo grade ≥2 postoperative complications	• Higher 6MWD was associated with lower risk of Clavien-Dindo grade ≥ II complications (OR 0.994 [95% CI 0.989, 0.999]) • 6MWD AUC for prediction of postoperative complications was 0.622, 95% CI [0.514, 0.730]
Wesolowski, et al. (27)	2020	Retrospective cohort study	555 patients undergoing single lobectomy for lung cancer	• In-hospital or 30-day cardiopulmonary complications	• 6MWD ≥400m was associated with reduced risk of complications (OR 0.53 [95% CI 0.35, 0.81])
Miccichè, et al. (25)	2019	Prospective cohort study (pilot)	42 adults (≥ 18 years) undergoing major upper abdominal surgery	• Cardiopulmonary complications within 28 days of surgery	• 6MWD of 489m had a sensitivity of 83.3% and a specificity of 60% to predict a cardiopulmonary complications • AUC was 0.718 (p = 0.029)
Hayashi, et al. (75)	2017	Prospective cohort study	81 patients undergoing hepato-pancreato-biliary cancer surgery	• Clavien-Dindo postoperative complications (grade ≤2 vs ≥ 3)	• 6MWD < 400m associated with increased risk of grade ≥ 3 complications.
Keeratichananont, et al. (77)	2016	Prospective cohort study	78 adults (≥ 18 years) undergoing major noncardiac surgery	• Postoperative pulmonary complications within 30 days	• 6MWD ≤ 325m associated with increased risk of postoperative pulmonary complications (HR 1.59 [95% CI 1.21, 2.13])
Awdeh, et al. (79)	2015	Prospective cohort study	117 adults undergoing thoracotomy, sternotomy, or laparotomy	• Severity of complications within 30 days of surgery • LOS	• 6MWD was negatively correlated and with severity of postoperative complications ($p < 0.0001$) and with LOS ($p < 0.0001$)

Marjanski, et al. (26)	2015	Retrospective cohort study	253 adults undergoing lobectomy for non-small-cell lung cancer	• Postoperative in-hospital general and cardiopulmonary complications	• 6MWD ≤ 500m associated with increased risk of postoperative cardiopulmonary complications (OR 2.6 [95% CI 1.28, 5.30])
Lee, et al. (23)	2013	RCT – subgroup analysis	112 adults undergoing elective colorectal surgery	• Postoperative complications within 30 days of surgery	• 6MWD associated with decreased risk of postoperative complications (OR 0.995 [95% CI 0.990, 0.999])
Arruda, et al. (73)	2013	Prospective cohort study	78 adults undergoing upper abdominal or thoracic surgery	• In-hospital cardiopulmonary postoperative complications	• 6MWD associated with postoperative pulmonary complications in thoracic surgery patients only
Paisani, et al. (76)	2012	Prospective cohort study	137 adults undergoing elective upper abdominal surgery	• In-hospital postoperative pulmonary complications	• 6MWD was not significantly associated with postoperative pulmonary complications

6MWD, 6-minute walk test distance; *AUC*, area-under-the-curve; *CI*, confidence interval; *OR*, odds ratio*; HR*, hazard ratio; *LOS*, length of hospital stay; *NSCLC,* non-small-cell lung cancer; *RCT,* randomized controlled trial

CHAPTER 2 – 6MWT STUDY RATIONALE & METHODS

2.1 Rationale

Surgery continues to grow globally, and more operations are being performed on older patients with increasing cardiovascular risk factors. Given this, it is possible that perioperative cardiovascular complications will similarly increase. Thus, prevention and surveillance for perioperative complications must be informed by accurate and easy-to-use risk stratification tools. Although the routine use of RCRI is common, it remains an imperfect tool given the deficits in its discriminative capabilities, and it does not account for a patient's functional capacity. The addition of an objective measure of functional capacity to the RCRI could be of significant clinical value if it improves perioperative risk prediction of cardiovascular complications. However, assessment of functional capacity should remain cheap, safe, and reliable, and thus places the 6MWT as a perfect candidate over subjective assessment or CPET. Finally, as the literature for the predictive abilities of the 6MWT continues to grow, a gap remains: a large study primarily examining the association between a preoperative 6MWT and postoperative cardiovascular complications in a general noncardiac surgery cohort is required.

Thus, the primary aim of this study is to investigate the additive value of the 6MWT alongside the RCRI in predicting a composite outcome of death, MI, or cardiac arrest at 30 days after noncardiac surgery. The secondary aim is to investigate the association between 6MWT and all-cause death or individual cardiovascular complications (MI, cardiac arrest, MINS, congestive heart failure, new AF, DVT, PE, and stroke) 30 days after noncardiac surgery, and whether 6MWT distance is associated with hospital length of stay (LOS). The tertiary aim of this study is to examine the association between 6MWT distance and non-cardiovascular complications

postoperatively. The final aim is to compare the subjectively assessed functional capacity (in METs) to the calculated METs obtained from the 6MWT distance.

2.2 Methods

Study design

We conducted a prospective cohort study of 967 patients aged ≥ 50 years who were scheduled for elective noncardiac surgery under general and/or regional anaesthesia at two sites (Montreal General Hospital; MGH, and Royal Victoria Hospital; RVH) of the McGill University Health Centre (MUHC) in Montreal, Quebec, Canada. All patients attending their preoperative assessment clinic appointment were screened for eligibility and invited to participate if they satisfied the inclusion criteria. Consenting patients then completed a 6-minute walk test (6MWT) at this same preoperative clinic appointment. Participants were then followed-up via chart review and phone call at 30 days postoperatively. Recruitment for this study commenced in January 2016 and finished in February 2022. This study was approved by the MUHC Research Ethics Board (protocol number: 2017-2622).

Participants

Inclusion criteria were:

i. Patients aged ≥ 50 years old, and
ii. Patients scheduled for elective noncardiac surgery within 3 months of the preoperative clinic visit, and
iii. Patients undergoing general and/or regional anaesthesia, and

iv. Patients with at least one of the following comorbidities: hypertension, diabetes mellitus, dyslipidaemia, coronary artery disease, chronic kidney disease, cerebrovascular disease, or peripheral vascular disease.

Patients were considered ineligible if they:

i. declined participation,

ii. had previously been enrolled in the study, or

iii. had significant cardiopulmonary comorbidities (e.g., unstable angina, severe aortic stenosis, severe pulmonary disease) or physical limitations (e.g., wheelchair-bound) which prevented them from completing a 6MWT.

Study procedures, data collection & follow-up

After the provision of written informed consent, patient contact details, expected surgery date, and baseline demographic data were recorded at the preoperative assessment clinic appointment. Functional capacity was also subjectively assessed by study investigators based on the patient's self-reported exercise capacity (as per Appendix 1.4), with the maximum recorded score being >4 METs. The 6MWT was then performed according to the American Thoracic Society (ATS) guidelines (80), with one exception: for pragmatic reasons, a 20 metre corridor adjacent to the preoperative assessment clinic was used as the walking track, rather than the recommended 30 metre track. Patients were instructed to walk as far as possible in six minutes in a flat indoor corridor between two orange cones 20 metres apart, with 1 metre intervals marked. Standardized instructions, feedback, and encouragement cues were provided. A practice test was not performed. At the completion of the test, the total distance walked (i.e., the six-minute walk distance or "6MWD") and the time taken to complete the test (including if terminated prior to six

minutes) were recorded. Patient symptoms and reasons for early termination of the test were also recorded. The 6MWD was converted to a calculated functional capacity METs score using the following formula (72): METs = (0.1 * (6MWD / time taken to complete the test in minutes)) + 3.5) ÷ 3.5.

Patient medical charts were reviewed to obtain American Society of Anesthesiologists' (ASA) status, comorbidities, surgical and anaesthetic details, and to calculate the Revised Cardiac Risk Index (RCRI) (8). The RCRI is a perioperative risk prediction tool, consisting of six, equally weighted components: coronary artery disease, heart failure, cerebrovascular disease, diabetes requiring insulin, serum creatinine >177 μmol/L, and high-risk surgery. The additive score for each risk factor indicates the risk of postoperative cardiovascular complications (see Appendix 1.3).

Complications and outcome data during index hospitalization and at 30 days postoperatively were also collected (see Appendix 2). Data for laboratory (e.g., haemoglobin, serum creatinine, serum troponin), microbiological (e.g., wound swabs, blood cultures) or radiological investigations (e.g., angiography, echocardiography, computed tomography) requested by the treating team during the index hospitalisation or follow-up period were also recorded. No surveillance investigations (e.g., daily serum troponin or electrocardiogram) were prescribed by the study protocol. However, in 2018 the MUHC implemented the Canadian Cardiovascular Society (8) recommendations to perform preoperative NT-pro-BNP screening in high-risk patients, as well as obtaining a postoperative electrocardiogram and measuring daily serum troponin for 48-72 hours postoperatively.

Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at The McGill University Health Centre, Montreal Qc, Canada (81, 82). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

Outcomes

The primary outcome was a composite of death, cardiac arrest, or MI within 30 days of index surgery. Secondary outcomes were all-cause death and the incidence of individual cardiovascular complications within 30 days of surgery (cardiac arrest, MI, MINS, stroke, DVT, PE, new AF, and CHF). Length of hospital stay was also a secondary outcome. Tertiary outcomes were individual non-cardiovascular complications within 30 days postoperatively, including: readmission to hospital, life-threatening bleeding, major bleeding, sepsis, pneumonia, surgical site infection (SSI), and delirium (see Appendix 2 for all outcome definitions). Finally, the fourth aim was to compare subjectively assessed functional capacity to the calculated METs achieved during the 6MWT.

After data collection, three clinicians with expertise in perioperative medicine independently adjudicated the following outcomes: death, cardiac arrest, and the cause of any elevated postoperative serum troponin (including diagnosis of MI and MINS). The adjudicators were

blinded to the participants' 6MWD, demographics, surgical and/or anesthetic details, RCRI, and to one another's adjudication decisions.

Statistical analysis

All participants who completed the 6MWT and underwent surgery at the study sites were included in the descriptive analyses at baseline. Categorical data are reported as a number (percent), continuous normally-distributed data are reported as mean (SD), and continuous non-parametric data as median [25th – 75th centile]. Continuous variables were compared using analysis of variance (ANOVA) with Tukey's post-hoc test or the Kruskal–Wallis test, and categorical variables were compared using Chi-square or Fisher's exact test. Type 1 error was set to 0.05.

Only participants who underwent surgery at the study sites within 3 months of their completed 6MWT were included in the outcome analyses. To examine the relationship between 6MWT distance (continuous variable; meters) and postoperative outcomes, binomial logistic and linear regression were performed for categorical and continuous outcome measures, respectively. Bootstrapping was applied to linear regressions to account for any deviations from normality. Binomial logistic regression was only performed for categorical outcomes with at least 10 events. Regression estimates were reported with a 95% confidence interval and type 1 error was set to 0.05. All regressions were adjusted for age and sex; regressions for the primary outcome also adjusted for the RCRI. Spearman's rank correlation was used to examine multicollinearity between the RCRI and 6MWT distance variables. Statistical analyses were performed using R

statistical software package (Version 4.1.2, R Foundation for Statistical Computing, Vienna, Austria).

The sample size calculation for this study was based on events per predictor for logistic regression. Specifically, the four predictor variables for the primary outcome were: age, sex, RCRI, and the 6MWD. Simulation studies have shown that logistic regression models require 12 to 15 events per predictor to produce stable estimates (83, 84). Therefore, an estimated 60 (i.e., 4 x 15) primary outcomes events were required. Based on a previous study (12), it was estimated that the incidence of the primary outcome would 6.3%. Thus, this study aimed to recruit a sample of N = 953 patients (60/ 0.063).

CHAPTER 3 – 6MWT RESULTS & DISCUSSION

3.1 Results

Recruitment & follow-up

Between January 2016 and February 2022, 967 patients were recruited in the study. Of these, only 927 patients completed the preoperative 6MWT, as 25 patients were subsequently found to be ineligible after initial consent, and 15 patients left the clinic prior to completion of the test. Following this, a further 4 patients died prior to surgery, 28 patients never had their surgery, and 12 patients were referred to external hospitals to have their surgery. This left 883 eligible patients who proceeded to elective surgery (see Figure 1: patient flow diagram). At this baseline, 525 (59.5%) patients were recruited from the MGH and 358 (40.5%) from the RVH. However, 64

patients exceeded the 3-month waiting period between their 6MWT and surgery date, leaving 819 patients eligible for outcome analysis. All 819 patients completed the 30-day follow-up.

The target sample size of N = 953 was not achieved because interim analyses revealed that the incidence of the primary outcome was significantly lower than the projected 6.3% upon which the sample size calculation was based. Consequently, the study would have to recruit over 2500 patients to remain adequately powered. Study investigators were aware that limitations in study funding and resources prohibited them from achieving this significantly larger recruitment target. Further, completing recruitment to reach the original target of 953 patients would not significantly change the incidence of the primary outcome or complications, and would not improve the power or validity of the study. Therefore, study recruitment ceased early.

6MWT data

The 6MWT was prematurely terminated (i.e., prior to completion of 6 minutes) by 38 patients (4.3%). Reasons for stopping the test early included: chest pain in 2 patients, 14 patients experienced dyspnea, 1 patient had a cough, 25 patients experienced lower limb pain or claudication, and 1 patient was too fatigued to continue. No patients suffered any harm or required further medical treatment after ceasing the test. The mean (SD) 6MWT distance across the cohort was 389 (111) meters.

Participant characteristics & surgical details

Table 2 shows the baseline patient characteristics for all patients who completed the 6MWT and underwent surgery (N = 883). Participants were predominantly male (58.2%) and had an ASA score of 2 or 3 (97%), with a mean age of 69 years and mean BMI 29.0. Most patients had an

RCRI score of 0 (51.2%) or 1 (35.9%), with only 28 (3.1%) patients having an RCRI score of ≥3. The most common comorbidities were hypertension (81.1%), dyslipidemia (65.9%), diabetes (33.3%). Twelve percent of patients were current smokers, and 43.5% of patients were having surgery for an active malignancy. Most patients received general anaesthesia (84.9%), and the most common surgical specialties were general (20.8%), orthopaedic (18.6%), thoracic (17.7%), and urological (12.9%) surgery. Most patients spent 2 nights in hospital (22.3%), and 169 patients (19.1%) were discharged home on the same day of surgery.

6MWT and type of surgery

An ANOVA indicated a significant difference in mean 6MWT distance between surgical groups ($F(9, 809) = 6.928$, $p < 0.01$) (Figure 2). Specifically, patients undergoing ENT surgery had a significantly higher mean 6MWT distance than those undergoing orthopaedic surgery (mean difference, M_{diff} [95%CI] = 95 [40, 149] metres, p <0.001), plastics/ maxillofacial surgery (M_{diff} [95%CI] = 72 [3, 141] metres, p = 0.04), vascular surgery (M_{diff} [95%CI] = 109 [37, 180] metres, p <0.001), and general surgery (M_{diff} [95%CI] = 59 [5, 114] metres, p =0.02). Patients having vascular surgery had a significantly lower mean 6MWT than those undergoing urological surgery (M_{diff} [95%CI] = -81 [-144, -18] metres, p =0.002), thoracic surgery (M_{diff} [95%CI] = -70 [-131, -10] metres, p = 0.01), or gynaecological surgery (M_{diff} [95%CI] = -91 [-172, -10] metres, p = 0.02).

6MWT and RCRI

Patients with RCRI scores of 0, 1, 2, and ≥3 had a mean 6MWD of 401 meters, 387 meters, 359 meters, and 313 meters, respectively. A Spearman's rank correlation indicated a weak negative

correlation (r = -0.114) between RCRI and 6MWT. An ANOVA was performed ($F(3, 879) = 8.447$, $p < 0.01$) to examine the relationship between RCRI and mean 6MWD (see Figure 3). Patients with an RCRI of 2 had a significantly lower mean 6MWD than patients with RCRI of 0 (M_{diff} [95%CI] = -42 [-75, -9] meters, p = 0.006), and those with RCRI ≥3 had a significantly lower mean 6MWD than patients with an RCRI of 0 (M_{diff} [95%CI] = -88 [-143, -33] meters, p < 0.001) or RCRI score of 1(M_{diff} [95%CI] = -74 [-129, -18] meters, p = 0.004).

Complications

Table 3 shows the complication data for the 819 patients who had surgery within 3 months of their 6MWT. The primary outcome of death, MI, or cardiac arrest within 30 days of index surgery occurred in 17 patients (2.1%), comprising 10 deaths, 8 MIs, and 1 cardiac arrest. Regarding secondary outcomes: any cardiovascular complication occurred in 79 (9.6%) patients, 33 (4.0%) patients experienced MINS, 11 (1.3%) patients developed new clinically significant AF, and 16 patients (1.9%) had a DVT or PE postoperatively. The median length of hospital stay was 3 days. For tertiary outcomes, 108 patients (13.2%) were readmitted to hospital after index surgery and 157 patients (19.2%) suffered any non-cardiovascular complication after index surgery.

Baseline characteristics and complications according to 6MWT tertiles

Table 4 re-examines baseline characteristics and complications, now stratified according to the 6MWD tertiles: “low” <348 meters, “medium” 349-444 meters, and “high” >445 meters. Patients in the lowest tertile (<348m) were more likely to be older and female, have a higher BMI, ASA, and RCRI, and were more likely to have had the following comorbidities: previous

CABG, peripheral vascular disease, AF, CHF, COPD, and osteoporosis. Patients in the lowest tertile were also less likely to undergo general anesthesia, and more likely to receive spinal anesthesia. The likelihood of death ($p = 0.031$) and likelihood of delirium ($p < 0.001$) within 30-days postoperatively were also significantly different between the 6MWD tertiles.

Prediction of Outcomes

In assessing whether the 6MWT distance improved the predictive capability of the RCRI for the primary outcome, three binary logistic regression models were constructed (Table 5). With age and sex as covariates, the 6MWT distance was not predictive of death, MI, or cardiac arrest (Model 1), whereas the RCRI was (OR [95% CI] = 2.085 [1.233, 3.462], $p = 0.005$) (Model 2). When both 6MWT and RCRI are included as predictors (Model 3), RCRI remains significantly associated with the primary outcome (OR [95% CI] = 1.954 [1.148, 3.273], $p = 0.011$), whereas the 6MWT distance is not significantly associated.

For individual complications (Table 6), the 6MWT distance (with age and sex as covariates) was significantly associated with a lower risk of death (OR [95% CI] = 0.994 [0.988, 0.9996], $p = 0.033$), readmission (OR[95% CI] = 0.998 [0.996, 0.9995], $p = 0.014$), delirium (OR[95% CI] = 0.995 [0.990, 0.999], $p = 0.032$), and any non-cardiovascular complication (OR[95% CI] = 0.998 [0.996, 0.9995], $p = 0.010$). There was no association between 6MWT distance and individual cardiovascular complications, or length of hospital stay.

Subjective versus objective functional capacity assessment

Finally, according to subjective functional capacity assessment, 88% of patients were deemed to be able to achieve >4 METs; however, only 8 patients (0.9%) achieved >4 METs according to the calculations from their 6MWD ($p <0.001$) (Table 7).

3.2 Discussion

The primary aim of this study was to examine whether a preoperative 6MWT improved the ability of the RCRI to predict postoperative death, MI, and cardiac arrest within 30 days of noncardiac surgery. However, the 6MWD was not associated with this primary outcome in our cohort. Thus, the addition of the 6MWT did not improve the predictive abilities of the RCRI. Secondly, we examined whether a preoperative 6MWT was associated with all-cause death, postoperative cardiovascular complications, or length of stay. The 6MWD was significantly associated with a decreased risk of all-cause death within 30 days of surgery, but it was not associated with any cardiovascular complications or hospital length of stay. The third aim of the study was to examine whether the 6MWT was associated with non-cardiovascular complications – the data suggested that a higher 6MWD was associated with a reduced the risk of: readmission to hospital after discharge, postoperative delirium, and suffering any non-cardiovascular complication within 30 days of surgery. Finally, we compared the METs achieved during the 6MWT to the subjective functional capacity assessment performed during the preoperative consultation. The key finding was that only 8 patients (0.9%) achieved > 4 METs during their 6MWT, whereas 88% of patients were assessed as being able to achieve >4 METs according to the subjective assessment based on self-reported exercise capacity.

This is the first large study that primarily examines the prediction of cardiovascular complications after noncardiac surgery using the 6MWT, with the overarching aim being to supplement the predictive abilities of the RCRI. Although the RCRI remained significantly associated with an increased risk of death, MI, or cardiac arrest within 30 days of surgery in our cohort, the 6MWT was not associated with this primary outcome. Further, the 6MWT was not

associated with any cardiovascular complications individually or as a composite outcome. This suggests that the 6MWT (as a surrogate marker of functional capacity) is not associated with postoperative cardiovascular complications. These results support the findings from the larger METS study (18) and the 6MWT METS substudy (22). Although the larger METS study examined the functional capacity of 1401 patients using CPET rather than the 6MWT, the authors found that peak VO2 was associated with increased risk of in-hospital postoperative complications, most of which were non-cardiovascular complications (18). Notably, there was no association between functional capacity and 30-day death, myocardial infarction, or myocardial injury after noncardiac surgery. More specifically, the METs substudy (22) included 545 patients who also completed the 6MWT preoperatively and found that the 6MWT was again associated with postoperative complications, but no association was evident between the 6MWT and 30-day death or myocardial injury.

Five other recent studies examined postoperative cardiovascular complications using the 6MWT but have combined them with pulmonary complications to create a composite "cardiopulmonary complications" endpoint. These studies also examined specific surgical cohorts, namely thoracic surgery (26, 27, 29), upper abdominal surgery (25), or both (73). All five of these studies found the preoperative 6MWT to be significantly associated with postoperative cardiopulmonary complications, with 6MWD cut-offs for risk classification ranging from 400 to 500 metres. However, significant limitations exist in the interpretation of the cardiac (or cardiovascular) contribution to these complications and subsequent association with the preoperative 6MWT. Firstly, the only cardiac complication observed by Marjanski, et al. (26) and Lee, et al. (29) was atrial arrhythmia. Secondly, Arruda, et al. (73) only observed an association between 6MWD and

pulmonary complications in the thoracic surgery cohort, because no cardiac complications occurred. As for the studies by Wesolowski, et al. (27) and Miccichè, et al. (25), the authors did not specify the incidence of individual complications as part of their composite cardiopulmonary outcome. Further, three of these studies examined patients undergoing thoracic surgery for lung cancer – in this cohort, patients are already at high risk of developing atrial arrhythmia postoperatively due to the type of surgery (85), and consistent evidence exists for the prediction of pulmonary complications with the 6MWT (24, 77). Thus, the association between the 6MWT and "cardiopulmonary" complications in these studies is unsurprising, but the significance of the cardiovascular complications included is unclear. Overall, the evidence from the METS studies (18, 22) and our study is much more convincing that the 6MWT does not appear to be associated with postoperative cardiovascular complications.

The only contradictory finding in our study was that we observed a significant negative association between 6MWD and risk of all-cause death at 30 days postoperatively, whereas the METS study did not. However, this discordance is unsurprising given that only 5 patients died in the METS study, leaving the investigators underpowered to examine this relationship. Previously, CPET measures of functional capacity have been associated with postoperative mortality (86), suggesting that perhaps either measure of functional capacity is representative of a patient's overall morbidity or deconditioning, and thus may be associated with their risk of postoperative mortality. However, given that only 10 deaths were observed in our study, the significance of this association is difficult to interpret and warrants further investigation in future studies. Lastly for secondary outcomes, our study did not find an association between 6MWD and LOS. This is consistent with previous meta-analysis findings (78), and suggests that LOS is

dependent on a wide range of clinical and institutional variables, making it difficult to predict with a single preoperative 6MWT.

The most significant positive finding in our study was that a higher baseline 6MWD was associated with a decreased risk of readmission to hospital, postoperative delirium, or suffering any non-cardiovascular complication postoperatively. Although no other recent studies specifically reported an association between 6MWD and hospital readmission or risk of delirium, a decreased risk of postoperative complications (as a composite outcome) has been observed in numerous other studies (22, 23, 28, 74, 75, 78, 79). This appears to be a highly reproducible signal in the literature, despite the significant heterogeneity in which complications are captured and how they are defined or categorised. Common trends appear to be capturing both surgical (e.g. surgical site infection, reoperation, bleeding) and medical complications (e.g. pneumonia, respiratory failure, acute kidney injury), as well as using severity grading systems such as the Clavien-Dindo system (87). Further, some studies choose to dichotomize the 6MWD into a "threshold" variable, with <400 metres being a common cut-off point for increased risk of complications (24, 26, 27, 74, 75), whereas others evaluate the 6MWD as a continuous variable (22, 23, 28, 79). Irrespective of the methodology, the association between 6MWD and postoperative complications appears to be most consistent with composite postoperative outcomes that aren't necessarily specific to the cardiovascular system. Again, this evidence suggests that the 6MWT is likely a "big picture" or blunt instrument that assesses a patient's overall preoperative fitness or degree of impairment and is not necessarily related to individual systems. This may provide some explanation as to why we observed the same association between 6MWD and readmission and postoperative delirium – essentially, patients with a lower

6MWD preoperatively have a greater functional limitation at baseline, and thus are more likely to experience complications in their recovery after surgery.

Finally, our study provided further evidence to the unreliability of subjective functional capacity assessment. This was thoroughly investigated in the METS study (18), where subjective functional assessment only correctly categorised 16% of patients who achieved < 4 METs as per their CPET result. Our study similarly demonstrated a stark contrast between the subjective functional capacity assessment based on self-reported exercise tolerance, and the METs achieved when calculated from their 6MWT result. To explain this discrepancy, we suggest that perhaps subjective assessment biases clinicians towards selecting the patients "best" response regarding their physical activities (or what the patient thinks they could achieve) rather than selecting a more representative response based on the physical tasks the patient regularly performs on a daily basis. Additionally, the training effect observed with field walking tests (70) should be considered. For pragmatic reasons, a practice 6MWT is often omitted from studies such as ours or the METS study, however, it is possible that patients are pacing themselves too conservatively, having not performed the test previously. The training effect suggests that patients would perform better in subsequent tests, and perhaps this would be more representative of their true functional capacity and may improve the matching between subjective and objective assessments. Although, this wouldn't negate the fact that the METS study did not find subjective functional capacity assessment to be associated with any postoperative outcomes. Instead, alternative simple measures such as the Duke Activity Status Index (DASI) or serum NT-pro-BNP proved much more informative (18).

Our study has several strengths, including the prospective enrolment of a large cohort of patients undergoing both cancer and non-cancer surgery across a wide variety of surgical specialties, and capturing a broad range of clinically important outcome data. Also, our key findings in that the 6MWT was associated with composite non-cardiovascular postoperative complications, and that the RCRI remained predictive of the primary outcome were consistent with other large bodies of literature and adds to the validity to the patient cohort studied. Our outcomes were also adjudicated by independent blinded assessors, reducing the risk of detection bias. Further, consistent with the approach adopted by Ramos, et al. (22), we examined the 6MWT as a continuous variable in our statistical analyses rather than identifying a "cut-off" threshold and creating a dichotomous 6MWT variable. The advantage of this approach is that it maximises the power of analyses and reduces the risk of residual confounding, bias, or type I error (88, 89). Finally, by performing the 6MWT in the preoperative clinic setting, we maintained a pragmatic study design that minimally inconvenienced patients or staff, and minimised costs.

Limitations of our study must also be considered, namely: the lack of mandatory prospective monitoring for cardiac complications, the fact that one-fifth of our sample comprised lower risk day-surgery patients, and the observation of a much lower than expected primary outcome event rate. The rationale not to include prospective cardiac monitoring (such as routine postoperative electrocardiogram and daily serum troponin measurement) was to maintain a pragmatic, real-world study design whilst operating with minimal funding, instead relying on clinicians to request cardiac investigations based on their routine clinical practice. The disadvantage of this approach was that it was possible that some cardiac events or complications were not captured by our study, as up to two-thirds of patients may experience perioperative MI in the absence of

ischaemic symptoms (59). However, in 2018 the study sites adopted the Canadian Cardiovascular Society (8) recommendations to perform daily serum troponin measurements and an immediate postoperative electrocardiogram in high-risk patients. This may have helped to reduce missed cardiac complications in our study cohort. Regarding the inclusion of day surgery cases, the authors felt that this was an often-excluded and under-studied cohort of surgical patients, despite the increasing volume of day surgery cases over time (90). However, this inclusion of day surgery patients and the lack of mandatory postoperative cardiac surveillance may have also contributed to the lower-than-expected event rate for the primary outcome (2.1%). This was significantly lower than the 6.3% reported in the VISION pilot study, and upon which the sample size calculation was based. A significant consequence of this discrepancy was that our study became underpowered. In an interim analysis, we repeated the same sample size calculation based on events per predictor for logistic regression and used the observed 2.1% incidence for the primary outcome. This revealed that our study would have to recruit 2858 patients (i.e. 60/0.021) to remain adequately powered. Knowing that this figure was not achievable given our funding and resources, and that further recruitment below this target would not improve the validity or power of the data, the study investigators opted to terminate recruitment early and report the results as they are. However, newer data suggests that the incidence of death, MI, or cardiac arrest within 30 days of noncardiac surgery is 3.3% (62). This estimate is much closer to the primary outcome event rate observed in our study and suggests that the VISION pilot study figure was a significant overestimate. Finally, our study did not account for baseline pain scores which may have affected the 6MWD (91), and the single-center study design limited the generalisability of our findings.

Nevertheless, scope remains to improve the predictive ability of RCRI via the inclusion of other simple measures of functional capacity such as the DASI, which correlates with peak VO2 and has been associated with postoperative mortality and cardiovascular complications (18). Further, the DASI is a 12-item questionnaire (92) that is likely even simpler to administer in the preoperative clinic than a 6MWT. Thus, future studies could employ a similar methodology to ours, substituting the DASI over the 6MWT to examine any incremental improvement in the predictive abilities of the RCRI. Alternatively, future studies could focus on elucidating the prediction of specific non-cardiovascular complications with the 6MWT and aim to develop risk calculation tools based on the absolute 6MWD or embed the 6MWD into existing risk prediction tools. However, it is also possible that due to the non-specificity of the 6MWT as an assessment tool, it's strongest application may be as a marker of exercise prehabilitation (74, 93, 94) or rehabilitation (95), rather than in perioperative risk prediction. Finally, future studies should also consider evaluating other types of field walking tests for perioperative risk prediction, such as the incremental shuttle walk test (96), which has been associated with increased postoperative complications and length of stay (97, 98).

CHAPTER 4 – CONCLUSION

Overall, our study findings are consistent with existing literature examining the predictive capabilities of the 6MWT in patients undergoing elective noncardiac surgery. Specifically, we were unable to demonstrate an association between objective functional capacity assessment and postoperative cardiovascular outcomes, and thus were unable to improve upon the predictive capabilities of the RCRI alone. Although we did identify a significant association between the 6MWT and all-cause death and composite non-cardiovascular complications at 30 days postoperatively, the lack of robustness and non-specificity of these findings, respectively, make it difficult to use the 6MWT as a risk prediction tool that would meaningfully change perioperative patient management. Accordingly, there is insufficient evidence at present to recommend the addition of a routine 6MWT as part of the preoperative assessment for patients undergoing elective surgery. Ongoing research to clarify the role of objective measures of functional capacity in the perioperative period is required.

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FIGURES & TABLES

Figure 1: Patient flow diagram

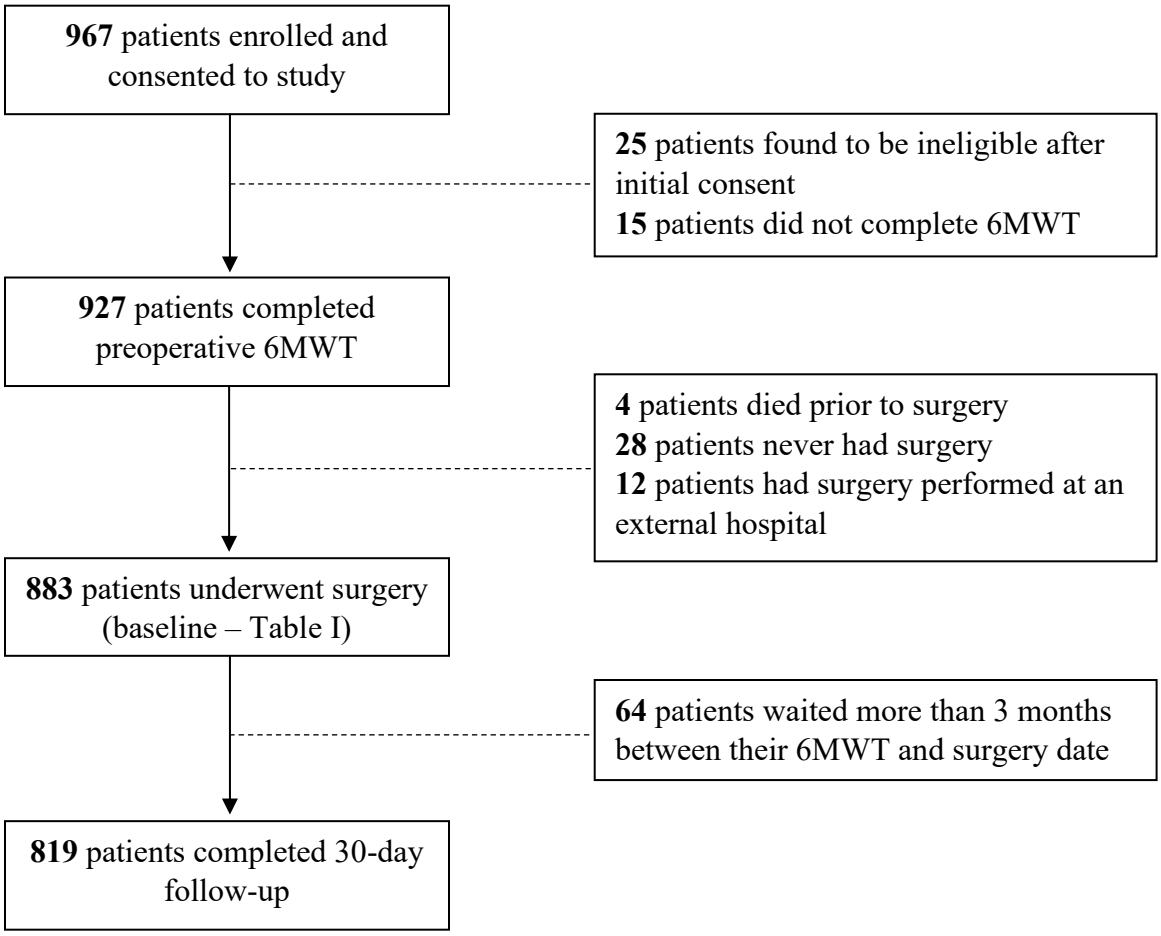

Figure 2: Mean 6-minute walking test (6MWT) distance by type of surgery. Error bars indicated standard error.

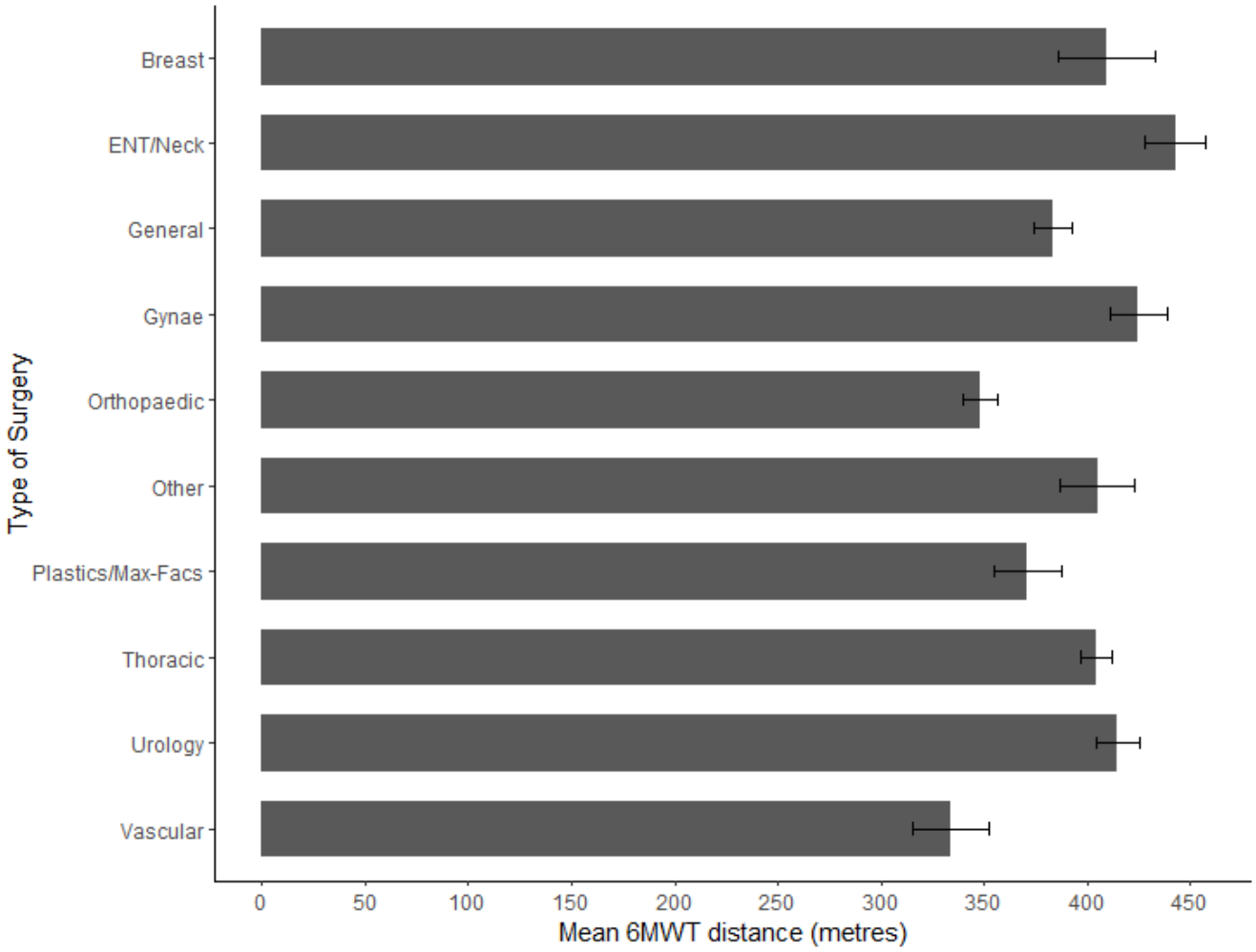

Figure 3: Mean 6-minute walking test (6MWT) distance by RCRI score. Error bars indicate standard error.

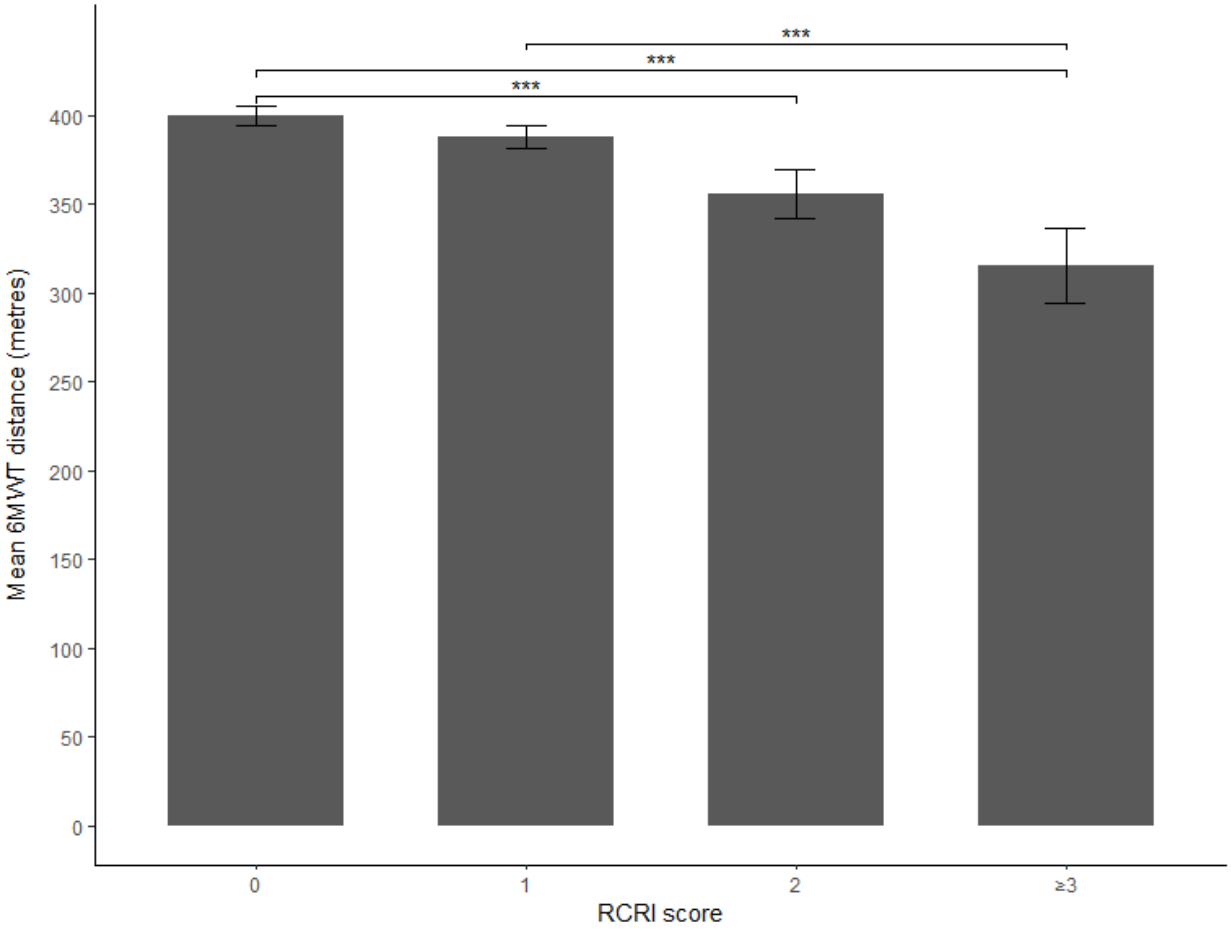

Table 2. Baseline cohort demographics and comorbidities. Data presented as number (percent) unless stated otherwise.

Demographics	**Total N = 883**
Age, years (mean ± SD)	68.8 ± 9.3
Female sex	369 (41.8)
BMI, kg/m^2 (mean ± SD)	29.0 ± 6.8
ASA Score	
1	5 (0.6)
2	361 (40.9)
3	495 (56.1)
4	22 (2.5)
RCRI Score	
0	452 (51.2)
1	317 (35.9)
2	86 (9.7)
≥ 3	28 (3.1)
Comorbidities	
Currently smoking	105 (11.9)
Hypertension	716 (81.1)
DM on OHA or diet	232 (26.3)
DM on insulin	62 (7.0)
Dyslipidemia	582 (65.9)
Stable angina	15 (1.7)
Unstable angina	0 (0.0)
MI	81 (9.2)
PCI	70 (7.9)
CABG	49 (5.5)
PVD	59 (6.7)
Aortic stenosis	6 (0.7)
Atrial fibrillation	77 (8.7)
CHF	44 (5.0)
OSA	128 (14.5)
COPD	100 (11.3)
Asthma	82 (9.3)
ILD	3 (0.3)
Osteoporosis	42 (4.8)
Stroke	37 (4.2)
TIA	36 (4.1)
Dementia	4 (0.5)
Active malignancy	384 (43.5)
PE	25 (2.8)
DVT	42 (4.8)
CKD	105 (11.9)
CKD on dialysis	16 (1.8)

Surgical Details	
Anaesthesia type	
General	750 (84.9)
Spinal	129 (14.6)
Other regional	254 (28.8)
Surgery type	
Breast	29 (3.3)
ENT/ Head & Neck	58 (6.6)
General	184 (20.8)
Gynaecology	33 (3.7)
Orthopaedic	164 (18.6)
Plastics / Maxillofacial	49 (5.5)
Thoracic	156 (17.7)
Urology	114 (12.9)
Vascular	52 (5.9)
Other	44 (5.0)
Estimated blood loss, mL	
Mean ± SD	329 ± 470
Median [IQR]	200 [300]
Minimum to maximum	0 to 5300

Table 3: Post-operative complications within 30 days of surgery; N = 819.

Primary outcome	**N (%)**
Death, MI, or cardiac arrest	17 (2.1)
Secondary outcomes	
Death	10 (1.2)
MINS	33 (4.0)
MI	8 (1.0)
Cardiac arrest	1 (0.1)
New AF	11 (1.3)
CHF	1 (0.1)
Stroke	1 (0.1)
PE	6 (0.7)
DVT	10 (1.2)
Any cardiovascular complication[1]	79 (9.6)
Length of hospital stay (days), median [IQR]	3 [4]
Tertiary outcomes	
Readmission	108 (13.2)
Major bleeding	34 (4.2)
Life-threatening bleeding	3 (0.4)
Sepsis	22 (2.7)
Pneumonia	15 (1.8)
SSI	52 (6.3)
Delirium	15 (1.8)
Any non-cardiovascular complication[2]	157 (19.2)

[1] "Any cardiovascular complication" is a composite outcome of death, MI, MINS, cardiac arrest, new atrial fibrillation, CHF, DVT, PE or stroke.
[2] "Any non-cardiovascular complication" is a composite outcome readmission to hospital, life-threatening bleeding, major bleeding, sepsis, pneumonia, surgical site infection (SSI), or delirium.

Table 4. Baseline demographics and comorbidities (N = 883), and postoperative complications at 30-days (N = 819), displayed across 6MWD tertiles. Data presented as number (percent) unless stated otherwise.

Demographics	**Low <348m**	**Medium 349 – 444m**	**High >445m**	**Total N = 883**	**P value**
Age, years (mean ± SD)	72.6 ± 9.7	68.4 ± 8.6	65.4 ± 8.0	68.8 ± 9.3	< 0.001
Female sex	151 (40.9)	116 (31.4)	102 (27.6)	369 (41.8)	< 0.001
BMI, kg/m^2 (mean ± SD)	30.2 ± 8.5	29.2 ± 6.5	27.6 ± 4.7	29.0 ± 6.8	< 0.001
ASA Score					
1	0 (0)	0 (0)	5 (100.0)	5 (0.6)	<0. 001
2	76 (21.1)	118 (32.7)	167 (46.3)	361 (40.9)	
3	201 (40.6)	177 (35.8)	117 (23.6)	495 (56.1)	
4	16 (72.7)	4 (18.2)	2 (9.1)	22 (2.5)	
RCRI Score					
0	139 (30.8)	143 (31.6)	170 (37.6)	452 (51.2)	<0. 001
1	99 (31.2)	123 (38.8)	95 (30.0)	317 (35.9)	
2	37 (43.0)	24 (27.9)	25 (29.1)	86 (9.7)	
≥ 3	18 (64.3)	9 (32.1)	1 (3.6)	28 (3.2)	
Comorbidities					
Currently smoking	33 (31.4)	42 (40.0)	30 (28.6)	105 (11.9)	0.345
Hypertension	249 (34.8)	251 (35.1)	216 (30.1)	716 (81.1)	0.001
DM on OHA or diet	86 (37.1)	78 (33.6)	68 (29.3)	232 (26.3)	0.258
DM on insulin	30 (48.4)	22 (35.5)	10 (16.1)	62 (7.0)	0.005
Dyslipidemia	207 (35.6)	182 (31.3)	193 (33.2)	582 (65.9)	0.042
MI	36 (44.4)	26 (32.1)	19 (23.5)	81 (9.2)	0.052
PCI	27 (38.6)	26 (37.1)	17 (24.3)	70 (7.9)	0.267
CABG	30 (61.2)	16 (32.7)	3 (6.1)	49 (5.5)	< 0.001
PVD	34 (57.6)	18 (30.5)	7 (11.9)	59 (6.7)	< 0.001
Aortic stenosis	5 (83.3)	1 (16.7)	0	6 (0.7)	0.035
Atrial fibrillation	42 (54.5)	21 (27.3)	14 (18.2)	77 (8.7)	< 0.001
CHF	28 (63.6)	12 (27.3)	4 (9.1)	44 (5.0)	< 0.001
OSA	47 (36.7)	44 (34.4)	37 (28.9)	128 (14.5)	0.517
COPD	49 (49.0)	30 (30.0)	21 (21.0)	100 (11.3)	< 0.001
Asthma	31 (37.8)	31 (37.8)	20 (24.4)	82 (9.3)	0.222
Osteoporosis	26 (61.9)	7 (16.7)	9 (21.4)	42 (4.8)	< 0.001
Stroke	18 (48.6)	13 (35.1)	6 (16.2)	37 (4.2)	0.048
TIA	16 (44.4)	12 (33.3)	8 (22.2)	36 (4.1)	0.253
Dementia	2 (50.0)	0 (0)	2 (50.0)	4 (0.5)	0.404
Active malignancy	110 (28.6)	139 (36.2)	135 (35.2)	384 (43.5)	0.043
PE	11 (44.0)	8 (32.0)	6 (24.0)	25 (2.8)	0.462
DVT	22 (52.4)	11 (26.2)	9 (21.4)	42 (4.8)	0.024
CKD	43 (41.0)	44 (41.9)	18 (17.1)	105 (11.9)	0.001
CKD on dialysis	8 (50.0)	5 (31.2)	3 (18.8)	16 (1.8)	0.303
Surgical Details					

Anesthesia type					
General	225 (30.0)	268 (35.7)	257 (34.3)	750 (84.9)	<0.001
Spinal	69 (53.5)	29 (22.5)	31 (24.0)	129 (14.6)	<0.001
Other regional	79 (31.1)	93 (36.6)	82 (32.3)	254 (28.8)	0.519
Surgery type					
Breast	7 (24.1)	7 (24.1)	15 (51.7)	29 (3.3)	<0.001
ENT/ Head & Neck	9 (15.5)	17 (29.3)	32 (55.2)	58 (6.6)	
General	61 (33.2)	65 (35.3)	58 (31.5)	184 (20.8)	
Gynaecology	2 (6.1)	16 (48.5)	15 (45.5)	33 (3.7)	
Orthopaedic	84 (51.2)	44 (26.8)	36 (22.0)	164 (18.6)	
Plastics / Maxillofacial	20 (40.8)	20 (40.8)	9 (18.4)	49 (5.5)	
Thoracic	41 (26.3)	63 (40.4)	52 (33.3)	156 (17.7)	
Urology	29 (25.4)	37 (32.5)	48 (42.1)	114 (12.9)	
Vascular	28 (53.8)	16 (30.8)	8 (15.4)	52 (5.9)	
Other	12 (27.3)	14 (31.8)	18 (40.9)	44 (5.0)	
Estimated blood loss, mL					
Mean ± SD	350 ± 428	332 ± 527	303 ± 457	329 ± 470	0.626
Median [IQR]	200 [300]	200 [300]	150 [200]	200 [300]	0.221
Minimum to maximum	-	-	-	0 to 5300	
All postoperative outcomes				**N = 819**	
Death, MI, or cardiac arrest	7 (41.2)	6 (35.3)	4 (23.5)	17 (2.1)	0.620
Death	4 (40.0)	5 (50.0)	1 (10.0)	10 (1.2)	0.031
MINS	17 (51.5)	9 (27.3)	7 (21.2)	33 (4.0)	0.078
MI	3 (37.5)	1 (12.5)	4 (50.0)	8 (1.0)	0.261
Cardiac arrest	0 (0)	1 (100)	0 (0)	1 (0.1)	-
New AF	2 (18.2)	6 (54.5)	3 (27.3)	11 (1.3)	0.304
CHF	1 (100)	0 (0)	0 (0)	1 (0.1)	-
Stroke	0 (0)	0 (0)	1 (100)	1 (0.1)	-
PE	1 (16.7)	5 (83.3)	0	6 (0.7)	-
DVT	6 (60.0)	3 (30.0)	1 (10.0)	10 (1.2)	0.132
Any cardiovascular complication[1]	33 (41.8)	29 (36.7)	17 (21.5)	79 (9.6)	0.052
Length of stay (days), median [IQR]	3 [4]	3 [3.25]	3 [3.75]	3 [4]	-
Readmission	38 (35.2)	40 (37.0)	30 (27.8)	108 (13.2)	0.392
Major bleeding	17 (50.0)	9 (26.5)	8 (23.5)	34 (4.2)	0.106
Life-threatening bleeding	2 (66.7)	1 (33.3)	0 (0)	3 (0.4)	0.442
Sepsis	10 (45.5)	6 (27.3)	6 (27.3)	22 (2.7)	0.474
Pneumonia	4 (26.7)	5 (33.3)	6 (40.0)	15 (1.8)	0.901
SSI	19 (36.5)	19 (36.5)	14 (26.9)	52 (6.3)	0.587
Delirium	12 (80.0)	2 (13.3)	1 (6.7)	15 (1.8)	<0.001
Any non-cardiovascular complication[2]	62 (39.5)	53 (33.8)	42 (26.8)	157 (19.2)	0.089

[1] "Any cardiovascular complication" is a composite outcome of death, MI, MINS, cardiac arrest, new atrial fibrillation, CHF, DVT, PE or stroke.

[2] "Any non-cardiovascular complication" is a composite outcome readmission to hospital, life-threatening bleeding, major bleeding, sepsis, pneumonia, surgical site infection (SSI), or delirium.

Table 5: Binary logistic regression models for the prediction of the primary outcome (death, MI, or cardiac arrest) by the 6MWT and RCRI.

Regression Model	**OR [95% CI]**	**p-value**
Model 1		
Age	1.031 [0.977, 1.089]	0.276
Sex	2.799 [0.959, 10.186]	0.080
6MWT distance	0.996 [0.992, 1.001]	0.099
Model 2		
Age	1.046 [0.993, 1.102]	0.092
Sex	2.045 [0.705, 7.380]	0.220
RCRI	2.085 [1.233, 3.462]	0.005*
Model 3		
Age	1.033 [0.978, 1.093]	0.248
Sex	2.361 [0.790, 8.719]	0.150
RCRI	1.954 [1.148, 3.273]	0.011*
6MWT distance	0.997 [0.993, 1.002]	0.247

Table 6: Association of secondary and tertiary outcomes with 6MWD. OR [95% CI] reported for binary logistic regression, β [95% CI] reported for linear regression. N = 819.

Outcome	**N (%)**	**OR [95% CI]**	**p-value**
Death	10 (1.2)	0.994 [0.988, 0.9996]	0.033*
Any troponin elevation	56 (6.8)	0.999 [0.996, 1.001]	0.319
MINS	33 (4.0)	1.000 [0.995, 1.005]	0.970
Non-ischaemic	10 (1.2)		
New AF	11 (1.3)	1.002 [0.996, 1.008]	0.527
PE	6 (0.7)	-	-
DVT	10 (1.2)	0.995 [0.989, 1.000]	0.049
Any cardiovascular complication[1]	79 (9.6)	0.998 [0.996, 1.000]	0.059
Length of stay (days)		**β [95% CI]**	
Hospital, median [IQR]	3 [4]	-0.004 [-0.009, 0.001]	0.084
		OR [95% CI]	
Readmission	108 (13.2)	0.998 [0.996, 0.9995]	0.014*
Major bleeding	34 (4.2)	0.997 [0.994, 1.000]	0.079
Life-threatening bleeding	3 (0.4)	-	-
Sepsis	22 (2.7)	0.999 [0.995, 1.003]	0.509
Pneumonia	15 (1.8)	1.001 [0.996, 1.007]	0.632
SSI	52 (6.3)	0.999 [0.997, 1.002]	0.537
Delirium	15 (1.8)	0.995 [0.990, 0.999]	0.032*
Any non-cardiovascular complication[2]	157 (19.2)	0.998 [0.996, 0.9995]	0.010*

[1] "Any cardiovascular complication" is a composite outcome of death, MI, MINS, cardiac arrest, new atrial fibrillation, CHF, DVT, PE or stroke.

[2] "Any non-cardiovascular complication" is a composite outcome readmission to hospital, life-threatening bleeding, major bleeding, sepsis, pneumonia, surgical site infection (SSI), or delirium.

Table 7: Subjective METs assessment versus calculated METs according to 6MWT; N = 883

Metabolic Equivalents (METs)	Subjective N (%)	Calculated[1] N (%)	p-value
<2	3 (0.3)	40 (4.5)	
2 to 3	72 (8.2)	483 (54.7)	
3 to 4	29 (3.3)	343 (38.8)	
>4	777 (88.0)	8 (0.9)	< 0.001

[1]6MWD was converted to a calculated METs using the following formula: METs = (0.1 * (6MWD / time taken to complete the test in minutes)) + 3.5) ÷ 3.5 (72)

APPENDIX 1

1.1: American Society of Anesthesiologists (ASA) Physical Status

Score	Definition	Examples
1	Healthy	No comorbidities, non-smoker, no or minimal alcohol consumption
2	Mild systemic disease	Mild disease only without significant functional limitations: smoker, well-controlled hypertension or diabetes, obesity (BMI 30 to 40), mild lung disease.
3	Severe systemic disease	Significant functional impairment with ≥1 moderate to severe comorbidities: poorly controlled hypertension or diabetes, COPD, obesity with BMI ≥ 40, ESRF, alcohol dependence, liver failure.
4	Severe systemic disease that is a constant threat to life	Recent (< 3 months) MI, stroke, TIA, coronary revascularization; cardiac ischaemic symptoms; severe cardiac valvular dysfunction; sepsis.
5	Moribund; patient is not expected to survive without surgery	Ruptured AAA, massive trauma, intracranial haemorrhage with mass effect, ischaemic bowel, multi-organ dysfunction.
6	Brain-dead organ donor	

1.2: Receiver-operator-characteristic (ROC) area-under-curve (AUC) interpretation

AUC	Interpretation (i.e., ability to discriminate between groups)
≥ 0.9	Excellent
0.7 to 0.9	Moderate
0.5 to 0.7	None to low
0.5	No discrimination

1.3: Revised cardiac risk index (RCRI) calculation and interpretation

Parameter	
Undergoing high risk surgery	1 point
History of ischemic heart disease	1 point
History of compensated or prior heart failure	1 point
History of cerebrovascular disease	1 point
Diabetes mellitus on insulin therapy	1 point
Preoperative serum creatinine >177 μmol/L	1 point

RCRI Score	Risk of death, MI, or cardiac arrest at 30 days after surgery (95% CI)
0	3.9% (2.8-5.4%)
1	6.0% (4.9-7.4%)
2	10.1% (8.1-12.6%)
≥3	15% (11.1-20.0%)

1.4: Estimated energy requirements to calculator metabolic equivalents (METs)

METs	Activities
1.0 to <2.0	Standing, reading, talking on the phone, sitting in class.
2.0 to <3.0	Walking at a slow pace, playing musical instrument, cooking, bowling, fishing, slow dancing.
3.0 to <4.0	Standing doing light/moderate work, washing car, scrubbing floors.
4.0 to <5.0	Walking at a very brisk pace, climbing stairs two flights of stairs, raking lawn, moderately heavy lifting, slow swimming.
5.0 to <6.0	Tennis, dancing, using heavy power tools.
≥6.0	Slow jogging, doubles tennis, hiking, rowing, bicycling, swimming, jogging/running.

APPENDIX 2: OUTCOME DEFINITIONS

Any cardiovascular complication: a composite outcome of death, MI, MINS, cardiac arrest, new atrial fibrillation, CHF, DVT, PE or stroke.

Any non-cardiovascular complication: a composite outcome of readmission to hospital, life-threatening bleeding, major bleeding, sepsis, pneumonia, surgical site infection (SSI), or delirium

Atrial fibrillation (AF): the diagnosis of new, clinically important AF required documentation on an ECG or rhythm strip, and had to be associated with angina, congestive heart failure, symptomatic hypotension, or required treatment with a rate controlling drug, antiarrhythmic drug, or electrical cardioversion.

Cardiac arrest (non-fatal): defined as successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation.

Congestive heart failure (CHF): diagnosis required a clinical sign (i.e., at least one of the following: elevated jugular venous pressure, respiratory rales/crackles, crepitations, or presence of S3) and a radiographic finding (i.e., at least one of the following: vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema).

Death: clearly documented death (i.e., death certificate or certification of death progress note in medical chart) within 30 days of index surgery or during the index hospitalization, due to any cause.

Deep vein thrombosis: diagnosis required any one of the following:

1. A persistent intraluminal filling defect on contrast venography;

2. Non-compressibility of one or more venous segments on ultrasonography; or,

3. A clearly defined intraluminal filling defect on contrast enhanced CT.

Delirium: documented acute alteration in cognition, attention or consciousness within 30 days of index surgery.

Infection: a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by a pathogenic organism.

Length of stay: number of days admitted in hospital, with the date of index surgery being day 1.

Life-threatening bleeding: bleeding event that was fatal or led to:

1. Significant hypotension that required inotrope or vasopressor therapy,

2. Emergent (within 24 hours) surgery (other than superficial vascular repair), or

3. Intracranial hemorrhage.

Major bleeding: bleeding event that was not specified under life- threatening bleeding and resulted in any one of the following:

1. a hemoglobin ≤70 g/L and a transfusion of ≥2 units of red blood cells;

2. a hemoglobin drop of ≥50 g/L and a transfusion of ≥2 units of red blood cells;

3. a transfusion of ≥4 units of red blood cells within a 24 hour period;

4. any one of the following interventions (i.e., embolization, superficial vascular repair, nasal packing); or

5. retroperitoneal, intraspinal, or intraocular bleeding

Myocardial Infarction (MI): diagnosis of MI required at least one of the following (1 to 5):

1. Detection of a rise and/or fall of an elevated troponin measurement with at least one of the following:

- Signs or symptoms of ischemia (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema);
- New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; or,
- Identification of an intracoronary thrombus by angiography or autopsy.

2. Cardiac death, with symptoms suggestive of myocardial ischemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

3. Percutaneous coronary intervention (PCI) related myocardial infarction is defined by elevation of a troponin value (>5 x 99th percentile URL) in patients with a normal baseline troponin value (≤99th percentile URL) or a rise of a troponin measurement >20% if the baseline values are elevated and are stable or falling. In addition, i. symptoms suggestive of myocardial ischaemia or ii. new ischaemic ECG changes or iii. angiographic findings consistent with a procedural complication or iv. imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

4. Stent thrombosis associated with myocardial infarction when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one of value above the 99th percentile URL.

5. Coronary artery bypass grafting (CABG) related myocardial infarction is defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with a normal baseline troponin value (≤99th percentile URL). In addition, i. new pathological Q waves or new LBBB, or ii. angiographic documented new graft or new native coronary artery occlusion, or iii. imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

MINS (Myocardial Injury after Non-Cardiac Surgery): diagnosis required the following criteria:

1. Evidence of at least one cardiac troponin value above the 99th percentile upper reference limit for the assay (i.e., either >17.5ng/L for HS-TnI assay or >0.04ug/L for TnI assay in this study), with a rise/fall pattern.

2. Occurred within 30 days after index surgery, and

3. No evidence of non-ischaemic aetiology (e.g., sepsis, rapid atrial fibrillation, pulmonary embolism, cardioversion, chronically elevated troponin).

NB. Symptoms or ECG findings indicative of cardiac ischemia were not required for the diagnosis of MINS.

Pneumonia: diagnosis required the presence of new respiratory symptoms (e.g., cough, dyspnoea, or pleuritic chest pain) with at least one of the following: pulmonary infiltrate or consolidation seen on X-ray, fever, or treatment with antibiotics.

Pulmonary embolism: diagnosis required any one of the following:

1. A high probability ventilation/perfusion lung scan;

2. An intraluminal filling defect of segmental or larger artery on a helical computed tomography (CT) scan;

3. An intraluminal filling defect on pulmonary angiography; or

4. A positive diagnostic test for deep venous thrombosis (e.g., positive compression ultrasound) and one of the following:

A. non-diagnostic ventilation/perfusion lung scan, or

B. non-diagnostic (i.e., subsegmental defects or technically inadequate study) helical CT.

Readmission: return to hospital and requiring at least an overnight admission within 30 days of index surgery.

Sepsis: was defined by the presence of both infection and a systemic inflammatory response (SIRS). SIRS required 2 or more of the following factors: core temperature >38°C or heart rate ≥90 beats per minute; respiratory rate >20 breaths/minute; white blood cell count >12 x 10^9/L or <4 x 10^9/L.

Stroke: new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting more than 24 hours or leading to death.

Surgical site infection (SSI): infection within 30 days of the index surgery, with at least one of the following:

1. Diagnosis by the attending physician or surgeon documented in the medical chart, or

2. Documented purulent discharge from the surgical wound, or

3. Organisms isolated/ cultured from a wound swab, or

4. Presence of pain, tenderness, heat, swelling, or erythema at the surgical site.

Transient ischemic attack (TIA): New focal neurological deficit thought to be vascular in origin with signs and symptoms lasting less than 24 hours.

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Appendix 1.1: Table displaying American Society of Anesthesiology (ASA) Physical Status with examples has been adapted from (99).

Appendix 1.2: Table displaying receiver-operator-characteristic (ROC) area-under-curve (AUC) interpretation has been adapted from (49).

Appendix 1.3: Table displaying RCRI scoring adapted from (8).

Appendix 1.4: Table displaying estimated energy requirements, with metabolic equivalents (METs) descriptions adapted from (15) and (16).

Appendix 2: Outcome definitions were adapted from the POISE-2 trial (39).