Successful Multimodal Prehabilitation Prior to Elective Colorectal Cancer Resection: A Recursive Partitioning Analysis of Pooled Trial Data

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List of Abbreviations

6MWD (T): six-minute walk distance (test)
95% CI: 95% confidence interval
ASA: American Society of Anesthesiologists
AT: anaerobic threshold
AUROC: area under the receiver operating curve
BIA: bioelectrical impedance analysis
BMI: body mass index
CCI: Comprehensive Complication Index
CDC: Clavien-Dindo classification
CRC: colorectal cancer
COPD: chronic obstructive pulmonary disease
CPET: cardiopulmonary exercise test
CRP: C-reactive protein
DASI: Duke Activity Score Index
ERAS: Enhanced Recovery After Surgery
FC: functional capacity
FFMI: fat-free mass index
GAD-7: Seven-item General Anxiety Disorder screening tool
GLIM: Global Leadership on Malnutrition
Hb: hemoglobin
HbA1c: hemoglobin A1c
ICF: International Classification of Functioning, Disability, and Health
ICU: intensive care unit
LOS: length of stay
LBM: lean body mass
MACE: major adverse cardiac events
MP: multimodal prehabilitation
NSQIP: National Surgical Quality Improvement Program of the American College of Surgeons
OR: odds ratio
O_2: oxygen
PG-SGA: Patient-Generated Subjective Global Assessment
RCT: randomized controlled trial
RPA: recursive partitioning algorithm
SF-36: Rand 36-item Quality of Life Short Form Questionnaire
SF-36 PFI: Physical Functioning Index (in SF-36 questionnaire)
STS: 30-Second Sit-to-Stand test
TUG: Timed-Up and Go test
VO_2 : oxygen consumption
VO_2 AT: oxygen consumption at anaerobic threshold
VO_2 peak: oxygen consumption at peak exercise
WHO: World Health Organization

Glossary

Functioning

"…How well one lives (i.e. one's level of functioning). Data about functioning is important for determination of the efficacy, effectiveness, and cost-effectiveness of health services." page 566 (1)

"Umbrella term encompassing all body functions, activities and participation; positive aspects of disability, from the World Health Organization's International Classification of Functioning, Disability and Health (WHO ICF)."(2)

Functional Capacity

A qualifier for the 'Activities and Participation' functional classification in the WHO ICF that separates the client's "inherent capacity to perform actions within a domain, and performance in his or her actual environmental context."(1)

Response Indicators

"…the indicator term here is a synonym for "*indicans*", i.e. a measure or component from which conclusions on the phenomenon of interest (the "*indicandum*") can be inferred.(3)

The phenomenon of interest in this thesis is the response to multimodal prehabilitation, and the indicators are the metrics and measures that change during multimodal prehabilitation from which we can draw conclusions about the state of participants.

"A response indicator is a measure or metric used to assess the effectiveness or impact of a specific intervention, program, or action. They are used to track progress towards achieving specific goals or objectives and are typically designed to reflect changes or outcomes that result directly from the evaluated intervention. Response indicators help stakeholders monitor progress, identify areas of improvement, and make informed decisions about programmatic adjustments and resource allocation to improve the intervention." (4)

Model

"Models are the way theories are operationalized in order to develop methods to test hypotheses that arise from theory; they tend to focus on explaining a phenomenon; using the road map analogy, it is the trip plan that uses the map and a basis for planning. Models can be simple, such as the model to derive degrees Fahrenheit from degree Centigrade ($^oF = 32 + 9/5^oC$), or complex, such as modeling quality of life as a function of personal factors, environmental factors, symptoms, function, and health perception as in the Wilson-Cleary model." (2)

Outcome

"In the context of health, an outcome is an aspect of an individual's physical, emotional, mental, or social health that is expected to change owing to a deliberate intervention or to vary in the presence of another personal, health or environmental factor. Kerr White coined the term 'the 5Ds' for health outcomes: death; disease; discomfort; disability; and dissatisfaction (5). A more modern list would include mortality (death), morbidity (disease), disability (encompassing discomfort), dissatisfaction, and cost (destitution of person or health care system) (6)." (2, 7),

Resilience

The intrinsic ability of a system to adjust its functioning prior to, during, or following changes and disturbances. Resilient systems have been defined as those that (1) rapidly acquire information about their environments, (2) quickly adapt their behaviours and structures to changing circumstances, (3) communicate easily and thoroughly with others, and (4) broadly mobilize networks of expertise and material support.304, 305 At the individual level, resilience is the process of negotiating, managing and adapting to significant sources of stress or trauma. Assets and resources within the individual, their life and environment facilitate this capacity for adaptation and 'bouncing back' in the face of adversity (2).

Theory

An organized, heuristic, coherent, and systematic articulation of a set of statements related to significant questions that are communicated in a meaningful whole. It describes observations, summarizes current evidence, proposes, explanations, and yields testable hypotheses. It is a symbolic depiction of aspects of reality that are discovered or invented for describing, explaining, predicting, and controlling a phenomenon. Simply spoken, it is akin to a road map, and as such it is context specific. (2)

Abstract

Background: Undergoing multimodal prehabilitation (MP) is associated with improved outcomes after elective colorectal surgery. However, the beneficiaries of MP and the indicators of MP response that are associated with optimal preparation have yet to be defined. We sought to create preliminary descriptions of successful MP by defining characteristics of MP participants who avoided 30-day postoperative complications.

Methods: Using a pooled sample of participants randomized to the MP arms of six trials, recursive partitioning classification tree models were generated to identify subgroups with reduced complication risk. Candidate predictors in these models were modifiable by MP and associated with surgical outcomes. Two tree models were generated, one using baseline and another using post-prehabilitation characteristics.

Results: Among a sample of 135 (58.4%) men and 96 (41.6%) women, 34.2% experienced 30-day postoperative complications. Of the four terminal nodes in the baseline tree model, those with the largest reductions in complication risk had a Six-Minute Walk Distance (6MWD) ≥519 m with a RAND Short Form 36-Item Physical Functioning Score (SF-36 PFI) ≥56 (14.9% risk; 95% CI: [8.3-25.3%]) or had a combination of SF-36 PFI ≥56, 6MWD 314-518 m, and Patient-Generated Subjective Global Assessment Score < 3 indicating adequate nutrition (6.2% risk; 95% CI [1.1-28.3%]). In the post-MP tree, the lowest 30-day complication risk was realized among patients who achieved a 6MWD ≥487 m at MP completion (22.2% risk; 95% CI [15.4-30.9%]). For those who could not reach this distance, ≥41 days of prehabilitation offset an otherwise elevated risk, reducing risk from 46.4% to 31.8% (95% CI [19.5-45.7%]).

Conclusions: This study delineates several patient profiles with low postoperative complication risk as targets for successful MP programs. These profiles could be used as descriptors of successful MP in this population.

Keywords: multimodal prehabilitation, preoperative, colorectal cancer, pre-surgery, Enhanced Recovery After Surgery, clinical outcomes, postoperative complications, classification tree, functional capacity

Résumé

Introduction et Objectif: Suivre une préadaptation multimodale (PM) est associé à des résultats améliorés après une chirurgie colorectale élective. Cependant, les bénéficiaires de la PM et les indicateurs de réponse au PM qui indiquent une préparation optimale n'ont pas encore été définis. Nous avons donc cherché à créer des descriptions préliminaires de la PM réussie avec les caractéristiques des participants à la PM qui ont évité des complications post-opératoires à 30 jours.

Méthode: En utilisant un échantillon regroupé de participants qui ont été randomisés aux groupes d'intervention de six essais cliniques, des arbres dichotomiques utilisant un algorithme de partitionnement récursif ont été créés pour identifier des sous-entités associés avec un moindre risque de complications post-opératoires. Les variables prédictives candidats dans ces arbres sont modifiables par le biais de la PM et influencent les résultats chirurgicaux. Deux arbres ont été créés, le premier utilisant des variables prédictives mesurées au début de la PM, et l'autre avec celles-ci mesurées post-PM.

Résultats: Parmi les 135 hommes (58,4 %) et les 96 femmes (41,6 %), 34,2 % ont présenté des complications à 30 jours. Parmi les quatre feuilles de l'arbre du début de la PM, ceux ayant les réductions de risque les plus importantes avaient une distance de marche pendant le 6MWT (6MWD) ≥ 519 m avec un Score de Fonctionnement Physique du Formulaire Court de Rand à 36 Items (SF-36 PFS) ≥56 (risque de 14,9 % ; IC à 95 % [8,3-25,3 %]) ou présentaient une combinaison de SF-36 PFS ≥56, 6MWD de 314 à 518 m, et un Score d'Évaluation Globale Subjective Générée par le Patient (PG-SGA) < 3, indiquant une nutrition adéquate (risque de 6,2 % ; IC à 95 % [1,1-28,3 %]). Dans l'arbre post-MP, une réduction du risque de complications à 30 jours a été observée chez les patients ayant atteint une 6MWD ≥ 487 m à la fin de la PM (risque de 22,2 % ; IC à 95 % [15,4-30,9 %]). Pour ceux qui n'ont pas pu atteindre cette distance, ≥41 jours de préadaptation ont compensé un risque par ailleurs élevé, réduisant le risque de 46,4 % à 31,8 % (IC à 95 % [19,5-45,7 %]).

Conclusions : Cette étude décrit plusieurs profiles cliniques qui caractérise les patients qui ont du potentiel d'amélioration pendant la PM et ceux qui ont atteint des conditions cibles associés à une réduction de risque de complications à 30 jours après une chirurgie colorectale élective. Ces profiles pourraient être utiles pour définir la PM réussie dans cette population.

Mots-clés : préadaptation multimodale, préparation préoperatoire, cancer colorectale, pré-chirurgicale, récuperation améliorée après chirurgie, résultats cliniques post-opératoires, complications post-opératoires, arbre dichotomiques, capacité fonctionnelle

Preface

I have always identified as 'atypical.' As a child, I wore jeans from Hong Kong labelled "Indigestion Jeans." In my twenties, I hiked the Inca Trail, Mount Cotopaxi, and Mount Kilimanjaro, and I cycle-camped from Vancouver, British Columbia to San Francisco, California over a span of 6 weeks in my thirties. Now in my forties, I am completing a Master's program in Experimental Surgery. This Master's degree journey, beginning in December 2020, qualifies as atypical because of the clinical workload I maintained throughout my degree as a staff anesthesiologist at the Montreal General Hospital, completing my coursework or this thesis during my overnight call shifts. However atypical my journey to this point, I follow in the footsteps of many generations of graduate students who are proud to present their theses on the eve of degree completion, mine entitled "Successful Multimodal Prehabilitation Prior to Elective Colorectal Cancer Resection: A Recursive Partitioning Analysis of Pooled Trial Data" as part of my degree requirements at McGill University.

Since my graduation from the McGill Anesthesiology residency program in 2009, I have been fascinated by the idea that patient outcomes after surgery could be significantly improved through thorough and holistic pre-operative preparation. After my first exposure to the concept of multimodal prehabilitation (MP) in 2016, I was fired up, convinced that this intervention was the future of preoperative preparation with immense potential to improve outcomes after surgery. A year later, I attended an MP conference with a peripherally-inserted central catheter (PICC)-line in my left arm, receiving intravenous penicillin for a severe osteomyelitis. The following year I came back to attend another MP workshop while 24 weeks pregnant with my third child. Very little deterred me from learning as much as I could about this program. In 2020, I was given an opportunity to return to McGill University and the Montreal General Hospital when a colleague and friend, Dr. Gabriele Baldini, offered me the opportunity I had been looking for: to join the department of anesthesiology, pursue a Masters' degree to deepen my knowledge of MP, and contribute to MP development. With the invaluable support of my entourage, I seized this opportunity.

This thesis is written for health care workers who strive to improve perioperative care and who derive great joy from empowering patients in their healing and health. My thesis begins with

Chapter 1, the introduction, and Chapter 2, a review of colorectal cancer (CRC), the etiology of postoperative complications and an overview of mitigating strategies. It also addresses selected key knowledge gaps in prehabilitation science, thereby providing a rationale and objective for my thesis research. Chapter 3 is the manuscript prepared for submission to the journal Anesthesiology and is the core of this thesis. Concluding the work are Chapters 4 and 5, an in-depth discussion of the manuscript findings, their implications on pre-operative preparation, and concluding statements. I hope that this thesis will enlighten and inspire readers as much as it enlightened me to write it.

Reflecting on this expansive journey, I am filled with gratitude for all the people I met who challenged, inspired, and encouraged me. It catalyzed growth beyond my wildest expectations. I never imagined that I would learn to program in R, to understand regression analysis, acquire knowledge and skills on how to contribute significantly to science, and to meet so many passionately curious people united in their desire to understand and foster that understanding in others. Most importantly, I met the researcher in me. I suspect that this thesis represents the beginning of my academic journey, one that promises further meaningful pursuits, connections, and growth.

Acknowledgments

I would like to express my sincere gratitude to Dr. Gabriele Baldini, whose vision and confidence in me was the catalyst for this academic journey. My journey could not have continued without my supervisor Dr. Chelsia Gillis and co-supervisor Dr. Nancy Mayo, whose experience, wisdom, oversight, and collaboration were the wings for my project to take flight. I also offer deep gratitude to Dr. Franco Carli, Dr. Francesco Donatelli, and Dr. Miquel Coca Martinez for their unwavering support, for protecting the time I needed to complete this endeavor, for helping me juggle the responsibilities of a practicing anesthesiologist and those of a graduate student, and for the constant stream of encouragement that fueled my tank.

I also express my profound gratitude to my husband Yves who has not only shouldered our family responsibilities to allow me to pursue this dream, but has also been a paragon of patience, devotion, and grace. Finally, I dedicate this work and the lessons learned from its creation to my sons Evan, Colin, and Nolan so that they can navigate the world with a passion for learning.

I also thank my research advisory committee members and associate members: Dr. Elie Girsowicz (chair), Dr. Nandini Dendukuri, Dr. Amal Bessissow, and Dr. Heather Gill for their time and support. I acknowledge the invaluable assistance provided by Rashami Awasthi, Anh Thy Le Quang, research assistant Dr. Bhagyha Tahasildar, and medical archivist Lavaughn Lashley who helped me with the initial data collection. Lastly, I would like to recognize Dr. Ibon Tamayo Uria, Professor of Statistics at the Universidad de Navarra (Spain), Dr. David Stephens from the Computation and Data Science Initiative at McGill University, and Dr. Daniel McIsaac, University of Ottawa for their help in my development as an R programmer.

Contributorship Statement

The initial study question was conceived by Dr. Gabriele Baldini and subsequently refined by Dr. Nancy Mayo and Dr. Chelsia Gillis. Dr. Mayo, Dr. Nandini Dendukuri, and I planned the analysis. Anh Thy Le Quang collected the initial data which I subsequently verified, supplemented with additional data through chart reviews, and cleaned. Dr. Gillis contributed additional data. I performed the analysis in R using RStudio, with guidance from Dr. Ibon Tamayo Uria and Dr. Dendukuri. For my thesis, I performed the literature review and wrote the introduction, manuscript, discussion, and conclusion. Dr. Chelsia Gillis and Dr. Nancy Mayo co-supervised, contributed to the interpretation of the data, reviewed, and edited the manuscript that I prepared.

1. Introduction

1.1 Statement of the Problem

At the beginning of this decade, CRC was listed as having the third highest incidence among cancers and as the second leading cause of cancer mortality globally (8). While common, patients diagnosed with this class of cancer have also benefited from multiple advances in both diagnosis and treatment that have increased the likelihood of early detection, definitive treatment, and improved survivorship. Of these treatment advances, surgical resection remains a mainstay of treatment. Paradoxically, despite technological innovations such as Enhanced Recovery After Surgery (ERAS) care bundles and minimally-invasive surgery, overall complication rates after CRC resection remain between 23 to 28% (9-12) Among the various hypotheses considered to explain this discrepancy, insufficient preoperative patient functioning has been shown to be a be a critical determinant affecting the risk of postoperative complications (13, 14).

The patient's preoperative level of functioning is likely to be a proxy for the resilience needed to recover after the stress of CRC surgery (15). As a result, multimodal prehabilitation was conceived with the goal of optimizing preoperative function and surgical resilience. By improving nutritional status, cardiorespiratory function, and emotional stress management in addition to medical optimisation, it aims to improve a patient's intrinsic capacity to withstand the stress of colorectal surgery, thereby decreasing complication rates and increasing the likelihood of meaningful recovery from surgery. However, details of optimal effectiveness, its target population, and the indicators of adequate response to MP have not been described.

1.2 Thesis rationale

Consequently, the rationale for this study was to examine cases of MP that were associated with benefit, or 'successful', to identify the key components and potential relationships that underpin the benefit. For this study, the chosen outcome was an important reduction (≥ 10%) in 30-day postoperative complication risk. Since multimodal prehabilitation is a complex intervention, this study aimed to profile baseline and post-prehabilitation characteristics of participants successfully undergoing MP instead of focusing on the effects of individual risk factors. This approach provides interpretable information corresponding to observed phenomena in the clinical setting and proposes preliminary descriptions of patients who may develop adequate resilience to avoid complications.

1.3 Research questions

Among MP participants preparing for elective colorectal surgery between 2012 and 2021 at an ERAS-compliant surgical center, what profiles of pre- and post-multimodal prehabilitation characteristics describe participants who lowered their 30-day postoperative complication risk? If successful MP is defined as "multimodal prehabilitation that results in lowered complication risk," which of these characteristics, individually or combined, are most important and influential for success?

2. Review of Relevant Literature

Sir Ronald A. Fisher, a titan of science, is credited with 43 seminal concepts in the fields of statistics and genetics, each bearing his name. To some, Fisher is the illustrious British polymath who stands as a pillar of modern scientific inquiry, while to others, he is the bane who introduced the null hypothesis and significance tests. While his life is undeniably fascinating, to an anesthesiologist specializing in perioperative medicine such as myself, the events surrounding his death are the most remarkable. Following surgery for colon cancer in 1962, Sir Ronald A. Fisher tragically died of postoperative complications at the age of 72. It is for him, and others like him, that I embark on this thesis journey.

2.1 Colorectal Cancer

Cancers of the colon, rectum, and anus together have the third highest incidence among cancers, accounting for 10% of all new cancer diagnoses globally in 2020 and ranking as the second leading cause of cancer mortality (8). In the US and Canada, an estimated 175,000 new cases of CRC were diagnosed in 2020, the equivalent of 49 to 68 new cases per day (16, 17). Notably, this cancer has a strong association with socioeconomic status, with incidence rates rising uniformly with a country's Human Development Index (HDI) (18, 19). Within high HDI zones, the incidence of CRC is increasing by 1-4 % per year among adults aged < 50 years, suggesting a rising burden of early-onset CRC likely rooted in lifestyle-related factors and an effect of CRC screening programs in adults > 50 years (8, 16). Mortality from this cancer has also decreased due to improvements in treatment among adults ≥ 65 years old (16), suggesting that with increased survivorship among the elderly and increased incidence among younger adults, the overall burden of disease on health systems is likely to increase.

Treatment of Colorectal Cancer

Definitive treatment of CRC consists of surgical and non-surgical options, along with palliation of symptoms caused by the presence of the tumor. Surgery is the mainstay of CRC treatment, with most patients undergoing tumor resection as part of definitive treatment. In the US and Canada, approximately 110,000 patients undergo elective colorectal surgery per year (20, 21). Adjunctive medical treatments of chemotherapy, immunotherapy, and radiotherapy often complement CRC excision. Patients are often at risk of a 'double hit': cancer treatment superimposed on an increased disease burden. This ‘double hit’ becomes a significant factor in their recovery trajectory and quality of life. To manage this burden, symptom palliation is an integral part of CRC treatment. Treating iron deficiency anemia, malnutrition, and sarcopenia significantly contributes to improving the patient’s quality of life, maintains physiological reserve during neoadjunctive and adjunctive therapies, and increases resilience towards surgical stress, thus increasing the likelihood of favourable overall outcomes.

2.2 Complications after CRC Resection

With surgery comes the risk of complications. Surgical complications are any deviation from the normal postoperative course (22). Each complication’s severity can be graded using the widely-adopted Clavien-Dindo Classification, which describes a complication in terms of the therapy used to treat it and the presence of enduring patient disability (22). A patient’s total complication burden over a given period can then be calculated using the Comprehensive Complications Index (CCI) (23), where multiple Clavien-Dindo grades are combined to produce a score ranging from 0 (no complications) to 100 (postoperative death). The CCI not only accurately captures the clinical consequences of complications but also correlates with the health care costs accrued with the morbidity (24). Minnella et al proposed a CCI ≥ 22.6 as indicative of clinically-significant morbidity after colorectal surgery based on the 75th percentile score in their sample distribution (25). This is consistent with findings from Slankamenac et al showing that a CCI score between 20-40 captures the most common combinations of Clavien-Dindo complications after elective abdominal surgery (23).

Complications have also been differentiated by surgical or medical etiology. Kauppila et al define surgical complications as directly related to the surgical procedure or the operated organ system (hemorrhage, surgical site infection), while medical complications relate to adverse events in other organ systems following surgery, such as major adverse cardiovascular events, pulmonary embolus, or stroke (26). This distinction is also based on what measures are required to prevent the complication: for surgical complications, an improvement in surgeon case volume and skill could prevent surgical complications, while for medical complications, preoperative optimisation of patient comorbidities and overall health could contribute to avoiding the complication (26). This is not a consensus definition, but it reflects real-world clinical practice and some studies have used this distinction in outcomes reporting (25, 27, 28).

After CRC resection, the most common surgical complications are infections (surgical site or deep organ space, sepsis) and gastrointestinal motility pathologies, namely bowel obstruction and ileus (28). Significant medical complications common to most surgical procedures also occur after these resections and include acute kidney injury, MACE, pneumonia, thromboembolic events, and stroke with neurological deficit. Overall occurrence rates of both classes of complications range between 22 and 28% percent (9-12), such that approximately 1 in 4 patients undergoing this surgery are expected to develop a complication.

Despite technical advances, these morbidity rates have remained stable over the last 25 years (23-28%) (9-12), suggesting that technology and surgeon factors alone are not enough to reduce complications. Moreover, the prevalence of CRC is not expected to decrease despite an overall reduction in incidence owing to screening. Due to increased incidence among adults < 50 years of age (29, 30), increased survivorship from improved treatment (16, 31), potential for recurrence, and overall aging of the population, the potential for increased numbers of colorectal surgery exists. As such, there is great need for innovations in reducing complications after CRC surgery.

2.2.1 Etiology of Complications After Colorectal Surgery

Complications after colorectal surgery have been linked to hospital, surgeon, and patient factors. Patient factors appear to be the primary determinant of complication risk (13). For illustration, Bamdad et al found that 35% of the variance in complication risk after colorectal surgery was attributable to patient factors, compared to surgeon (2.4%) and hospital (1.8%) factors (13). Individual patient comorbidities such as atrial fibrillation, COPD (32), diabetes (33), obesity (34), and sarcopenia (35, 36) have been identified in historical cohort studies as independent risk factors for complications after colorectal surgery. The current approach to mitigating these comorbidities' negative impact on surgical outcomes is reductionist, focussing on the minimizing the negative contribution of each comorbidity to a patient's overall functioning. However, this reductionist approach to reducing complications may have reached a plateau of efficacy, since complication rates post-colorectal surgery have not changed drastically in the last decade despite advances in medical treatment of the abovementioned comorbidities (12, 37).

At present, there is no unified theory that explains why patients develop postoperative complications, and as such, no accurate way to predict in whom they may develop. However, two major concepts have emerged as foundations for answering this question. The first is the concept of surgical stress, which results from the therapeutic damage from surgery and the body's response. The second concept is surgical resilience, a patient's capacity to recover from surgical stress. Ostensibly, when the stress of surgery exceeds the patient's capacity to restore homeostasis for recovery, postoperative complications are more likely to develop (38).

Surgical Stress

Surgical stress is defined as "a pattern of physiological and pathophysiological changes that occur in response to the stimulus of surgery"(39). Unlike major trauma, surgical incision and manipulation is a controlled physical insult. However, the body does not differentiate this disturbance of body integrity from major trauma and responds to defend and repair itself. Tissue trauma, loss of effective circulating blood volume, hypoperfusion, anoxia, and contamination derange homeostasis (40). This amplitude of this response has been observed to correlate with the extent of surgery (40, 41). In addition to the stress induced by the surgical incision, the definition of surgical stress has been broadened to include indirect stressors present in the perioperative period, such as prolonged fasting and hypothermia (42). In particular, prolonged perioperative fasting has been found to induce and prolong catabolism (43).

Surgical Resilience

The second concept underlying the development of complications relates to what Bamdad et al term 'patient factors,' or the patient's ability to recover after surgery. In general, resilience is a biological system's ability to maintain homeostasis when challenged by external stressors (2, 44). It is a dynamic construct most observable when an external stimulus induces measurable changes in the system. In a medical context, this dynamic response is more likely to differentiate individuals with resilience from those without, and it also implies that resilience cannot be assessed accurately when the individual is in their non-stressed, baseline state (45, 46). Loss of resilience is hypothesized to underlie catastrophic declines in health and function which result from dysregulated interactions either within and/or between multiple physiological regulatory functions. This chronic dysregulation then compromises the body's ability to maintain homeostasis in response to an external stimulus (46, 47).

This concept can easily be translated to the development of postoperative complications. Patients at high risk of complications and frail individuals show an increased vulnerability to external stressors such as major surgery or illness (48). In both populations, dysregulated interactions between multiple physiological components have been observed, resulting in an increased risk of functional decline and poor health (49). Finally, assessing resilience is notoriously imprecise because current assessment paradigms evaluate the patient in an unstressed state rather than in a stressed state where a dynamic construct such as resilience is most evident (44).

The patient's level of functioning prior to surgery is considered to be a proxy of resilience (37, 50). It is more easily measured, since a measurement tool for resilience is still under development (51). Functioning is the ability of the individual to perform defined tasks (52). In the I*nternational Classification of Functioning, Disability and Health,* the World Health Organization (WHO) defines 'functional capacity' as "how well one lives in a standard environment" versus 'functional performance,' which is "how well one lives in their actual environment" (1). In the context of perioperative medicine, 'functional capacity' could be defined as 'how well one lives in their actual environment as an assessment of how well one might live through a surgery.' Functional capacity is a multidimensional construct including metabolic, neuroendocrine, musculoskeletal, and behavioral factors (53). Higher levels of functioning can indicate a greater adaptability to stressors. Carli & Zavorsky proposed that increased functional capacity and attendant reserves create a safety margin that may be necessary to meet the demands of surgical stress (15).

To support this proposition, a relationship between poor baseline physical functional capacity and increased risks of complications after major noncardiac surgery has been consistently demonstrated (54-57). Stabenau et al showed that return to postoperative wellness is greatly influenced by pre-existing disability. Among 269 elderly patients (age 82.4 ± 5.5 years) who underwent major surgery, those who were moderately or severely disabled were more likely to deteriorate, or at best, remain at their preoperative state of disability. Those who were most likely to follow favourable recovery trajectories were those who were also most functional prior to surgery (14). Thus, a key component of resilience to surgical stress appears to be linked to functional capacity.

A lack of resilience may be attributed to dysregulation or deficiencies in patients' biological, psychological, and environmental support systems. Considering this imbalance could elucidate the causes of inter-patient variability in postoperative complication risk (58).

Dysregulation and Deficits May Underlie Lack of Resilience

Several studies investigating the presence of dysregulation and deficit in various physiological systems may support the idea that such faults contribute to a loss of resilience to surgical stress. Dysregulation and deficits in oxygen delivery, including anemia (59-62), in nutritional reserve and metabolism (63, 64), in the hypothalamic-pituitary-adrenal (HPA) endocrine stress response (65), and in pro- and anti-inflammatory processes (66-68) are being advanced as potential determinants of complication risk and surgical recovery.

Deficient oxygen delivery

The ability to deliver oxygen effectively during surgical stress is related to an individual's cardiopulmonary fitness (CRF), and impairments have been associated with adverse postoperative outcomes (61, 69). Shoemaker et al documented a surgery-induced oxygen debt among 253 high-risk patients who underwent abdominal surgery (70). In this study, the degree of oxygen debt corresponded with the likelihood of postoperative morbidity and mortality. Surgical stress is similar to exercise in that they both exact increased adenosine triphosphate production to fuel essential processes (59). Therefore, an inability to fulfill the increased oxygen demand from surgical stress hypermetabolism (71) could underlie the relationship between impaired O_2 delivery and adverse postoperative outcomes. If a patient's ability to deliver oxygen is chronically compromised with low CRF or anemia, the oxygen debt could contribute to the development of ischemia, organ dysfunction, or suboptimal immune response leading to impaired healing or infection (70).

Dysregulated Nutrition & Deficient Reserves

Malnutrition is known to influence postoperative outcomes of CRC surgery (72, 73). Malnutrition in surgical patients is "a nutritional state where nutrient intake does not match nutrient needs…leading to losses in lean tissue and diminished function" (74). Re-establishing homeostasis can be more difficult without sufficient substrates to meet the demands of surgery-induced hypermetabolism. In fact, decreased metabolic reserves seen in malnourished, frail, and sarcopenic patients increase vulnerability to complications (73, 75). Insufficient reserves with unchecked catabolism have also been shown to weaken vital respiratory or core musculature, impairing effective pulmonary secretions and mobilization efforts, and thereby increasing the risk of pulmonary and thrombotic complications (63).

Dysregulated hypothalamic-pituitary-adrenal (HPA) axis function

In addition to substrate deficit, Manou-Stathopoulos et al present evidence that decreased resilience to surgical stress could be linked to dysregulated HPA endocrine axis function (65). The proposed dysregulations in the HPA axis negatively impact surgical resilience by causing sustained and possibly excessive cortisol secretion during the unstressed, pre-surgery state. As opposed to healthy ultradian pulses superimposed on circadian cycles, cortisol secretion patterns show blunted variability in these patients. Chronically-elevated cortisol levels might cause pathology by facilitating deleterious interactions with mineralocorticoid receptors (MR) in susceptible tissues such as the myocardium, renal glomeruli, and vascular smooth muscle. Inappropriate MR activation from constant cortisol exposure activates injury-promoting gene transcription that produces myocardial failure and acute kidney injury during surgical stress. As such, they suggest that frail, deconditioned, or depressed patients with such HPA axis dysfunction, are therefore more likely to develop postoperative complications, delirium, and cognitive dysfunction.

Dysregulated immune response

Finally, immune system dysregulations may also influence the risk of postoperative complications. The surgical injury provokes concurrent pro- and anti-inflammatory processes, and the more pronounced the initial cytokine spike from injury, the more pronounced the counterbalancing immunosuppressive response (68). Dysregulation in either direction is likely to contribute to severe morbidity either from aseptic systemic inflammatory response syndrome or sepsis from bacterial pathogens (76). Links between dysregulated immune responses and complications have been demonstrated among cardiac surgery patients, where those who had upregulated pro-inflammatory gene expression had a greater likelihood of postoperative complications (77). With the advent of high-throughput omic technologies, the potential relationship between immune system regulation and surgical outcomes is now being investigated. For example, Fragiadakis et al and Gaudilliere et al connected preoperative immune states with postoperative recovery trajectories in orthopedic surgeries (66, 67). These states, defined by multiple cell-specific, functional signalling changes, figured most prominently among CD14+ monocytes (66). Efforts to optimize patient resilience to surgery may, in the future, involve modulating immune states or balancing pro- and anti-inflammatory responses (68).

Summary

While no unified theory explaining the development of postoperative complications has been advanced, evidence suggests that complications are more likely when a given patient receives a surgical insult that exceeds their level of surgical resilience. Varying levels of surgical resilience could therefore be a more precise conception of the 'patient factors' identified by Bamdad et al. Resilience is a dynamic construct influenced by a patient's functional capacity. Functional capacity has been the most commonly used construct because it is broad and inclusive, referring to the sum of physical, mental, and social factors that allow the patient to 'respond well' in the perioperative environment. The mechanisms that are hypothesized to decrease resilience to surgery involve some degree of chronic dysregulation and deficits in oxygen transport, metabolism, endocrine signalling during stress, and immune system imbalances. These adaptations, which were appropriate for the patient's baseline state, become maladaptive when an acute stressor disrupts the baseline state. As such, they also could impede a person's ability to return to homeostasis.

Ideally, to reduce the risk of postoperative complications, clinicians would have quantitative assessments of a patient's resilience and a given surgery's stress to allow for comparison. The interpretation of the discrepancy between these two quantities would serve as the basis for risk stratification and optimisation strategies. None of these measures yet exist.

Strategies for managing postoperative complication risk currently involve a risk stratification approach and reducing risk with a combination of surgical stress mitigation and patient resilience enhancement.

2.2.2 Current Strategies for Reducing Complication Risk

Pre-Operative Risk Stratification

To increase the likelihood of a favourable outcome, assessing and stratifying operative risk guides decisions on what health care resources will be needed in the perioperative period. For example, allocating critical care resources to a high-risk patient is done to detect and treat any deviations from expected postoperative recovery. Risk stratification also informs shared decision-making about surgery. With an assessment of risk, clinicians and patients decide whether the potential benefits from surgery outweigh the risks of potential harm, and whether the risks are acceptable (78). This exercise can also guide patient expectations for surgery and inform joint decisions on preoperative optimisation strategies (79). Currently, preoperative risk stratification is most often accomplished by assessing functional capacity and by using clinical risk calculators.

Clinicians have empirically observed a positive relationship between a patient's preoperative level of functioning and their likelihood of a good surgical outcome. However, quantification of this empiric relationship began only three decades ago, when investigators linked levels of physical functioning or self-reported exercise tolerance to an increased risk of adverse surgical outcomes (55, 80). Girish et al reported that the inability to climb two flights of 18 stairs had a positive predictive value of 82% for 30-day complications among 83 patients undergoing non-cardiac major surgery (54). However, since this study there has been little evidence in the literature for standardizing the number of stairs to climb for prognostic accuracy (81), and the predictive ability of identifying patients with adequate functional capacity (peak oxygen consumption (peak VO_2) > 16 ml/kg/min) using a single question about stair-climbing was very low (Area Under Receiver Operating Curve (AUROC) = 0.55) (82). Similarly, quantifying functional capacity using unstructured assessments of daily living activities had poor prognostic ability (AUROC of 0.66 for cardiac complications and 0.52 for mortality) (83, 84). Unstructured subjective assessments are limited by non-standardized questioning and, conceptually, by response or social desirability bias, where people provide answers that they perceive as desirable or socially acceptable even if they may not accurately reflect their true behaviours. As a result, to quantify functional capacity, best perioperative practice is to use the Duke Activity Status Index (DASI) questionnaire since it is the only structured and validated subjective assessment method or use objective testing such as the Six-Minute Walk Test (6MWT), Incremental Shuttle Walk Test or cardiopulmonary exercise testing (CPET) (81, 85).

In addition to the assessment of functional capacity, various risk stratification calculators have been developed to quantify risks of general or body system-specific adverse outcomes. The National Surgical Quality Improvement Program (NSQIP) Surgical Risk Calculator is a general-purpose, universal risk calculator providing surgery-guided estimates for 30-day morbidity and mortality (78, 86). This calculator was built from regression and machine learning-based analysis of over 5.0 million operations (87) and is the most tested and mature among several risk assessment tools (88). System-specific or surgery-specific calculators also exist to aid stratification, such as the Revised Cardiac Risk Index for myocardial injury, Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) for pulmonary complications, or Carlisle Vascular Surgery Risk Calculator. While these objective risk quantification tools require adequate time for clinicians to administer, interpret, and discuss with patients, they provide invaluable information that helps all stakeholders plan and mitigate risks accordingly.

Decreasing Surgical Insult and Mitigating Stress Response: Enhanced Recovery After Surgery (ERAS)

Conceived in the late 1990s, the founders of ERAS changed the paradigm for intraoperative and early perioperative care by creating bundles of interventions aiming to attenuate the surgical stress response and enhance return to function (42). While specifics vary between surgical procedures, these care bundles are all multidisciplinary, multimodal, evidence-based, and continually-audited measures (89). ERAS pathways mitigate surgical stress by modifying the hospital and surgeon factors affecting recovery, and ERAS-compliant care decreases the odds of complications after colorectal surgery and reduces hospital stays and readmissions (90-92). ERAS's efficacy rests on the integrated application of care bundles: compliance must be ≥70% for such benefits (90, 91).

ERAS care bundles, or pathways, consist of measures that encourage the resumption of functioning throughout the surgical trajectory (89). Briefly, the main tenets of enhanced recovery pathways are as follows: in the preoperative period, patient education sets expectations and prescribes proactive health-promoting behaviours (i.e. smoking cessation). Fasting is proscribed and replaced with hydration and carbohydrate loading to reduce insulin resistance (93). Intraoperatively, surgeons decrease tissue trauma by using minimally-invasive surgical techniques and reducing use of indwelling drains and catheters, while anesthesiologists provide pre-emptive multimodal analgesia, maintain normothermia and normoglycemia, avoid fluid overload, and provide prophylaxis for infection and thrombosis. Post-operatively, the patients and ward staff mandate eating, drinking, and mobilizing on the day of surgery to mitigate protein catabolism. Stopping intravenous fluids while providing chewing gum and oral nutritional supplementation stimulate effective caloric intake, and multimodal analgesia that minimizes opioid use facilitates early mobilization. Taken together, these interventions aim to reduce surgical stress and stimulate homeostatic mechanisms towards healing and recovery after surgery.

Increasing Patient Resilience

Optimization of Medical Risk Factors

Reducing complication risk through medical optimization involves performing a comprehensive assessment of a patient's comorbidities and then prescribing treatment to ensure optimal conditions for surgery. The comorbidities requiring treatment are either related to the pathology requiring surgery or are chronic, and de novo deteriorations or abnormalities that could negatively impact the patient's ability to withstand surgical stress are addressed. Correcting coagulation or thrombosis abnormalities, optimizing hemoglobin levels, and managing glycemia, blood pressure, and chronic pain are among the goals of preoperative medical risk mitigation. Such optimization and detailed risk assessment in a preoperative clinic have been associated with improved postoperative outcomes. A matched retrospective study of 64,418 patients found reduced odds of in-hospital mortality (OR 0.48, 95% CI, 0.22-0.96) among those who were seen in an anesthesiologist-led preoperative evaluation clinic (94). Preoperative clinics that offer risk mitigation and stratification are invaluable to help clinicians and patients understand potential postoperative trajectories, what health care resources can be mobilized to mitigate risks, and ultimately, the value of surgery.

Multimodal Prehabilitation

Multimodal prehabilitation (MP) is an innovative, complex intervention which aims to build surgical resilience during the preoperative period and potentiates medical optimisation (50, 95). In a recent review, Fleurent-Grégoire et al propose a definition of prehabilitation as: “a process from diagnosis to surgery, consisting of one or more preoperative interventions of exercise, nutrition, psychological strategies and respiratory training, that aims to enhance functional capacity and physiological reserve to allow patients to withstand surgical stressors, improve postoperative outcomes, and facilitate recovery.’ (96). Multimodal prehabilitation is a subset of prehabilitation which integrates exercise, nutrition, and psychological interventions to increase cardiorespiratory fitness, optimize nutrient intake and body reserves, and encourage health-promoting attitudes (97). With information gathered during an initial comprehensive screening and assessment, a multidisciplinary team designs and delivers a personalized program to address identified needs. Since patient participation is a central element for MP efficacy, regular re-assessments and program adjustments are crucial to support the patient’s evolution and to sustain progress. Multimodal prehabilitation provides a structured and personalized program that helps patients in the preoperative period create better conditions for their own recovery. Gillis et al propose that MP elements should be structured along the Wilson-Cleary Health Status framework (52), including the symptom assessments and general health perceptions that influence the overall quality of life (98).

The benefits associated with prehabilitation are likely linked to increasing patient resilience prior to the surgical insult and encouraging the practice of health-promoting behaviours required in the postoperative period (i.e. early mobilization and optimal postoperative nutrition (50, 95)). The increased resilience results in less surgery-induced decline, allowing rehabilitation to build on the skills acquired during MP and promoting recovery to baseline more effectively. While rehabilitation is a vital component of perioperative care, it is insufficient for a good postoperative outcome because it begins when a patient is in a weakened and stressed post-surgical state. For example, physiotherapy in the postoperative period is hampered by surgical site pain, surgical stress catabolism, and bedrest-induced declines in muscle mass and physiological reserve (99). As a result, patients are relatively disadvantaged compared to the preoperative period, with significant physiological barriers to anabolism and healing. Conversely, in the preoperative period, the patient is relatively stronger because the decline associated with surgery has not yet occurred. The time before surgery is when people are more primed to assume an active role in managing their health, thus increasing the likelihood of physical and psychological gains (100). These gains increase patient resilience, the ability to buffer surgery-related health declines, and the ability to avoid complications and rehabilitate early (50).

Summary

Multiple complication-reducing strategies can be implemented from the moment the patient gives their informed consent to surgery. These strategies consist of risk assessment and stratification, ERAS pathways, optimization of comorbidities, and multimodal prehabilitation. Risk assessment and stratification helps to subjectively define the relationship between patient resilience and surgical stress. That relationship guides decisions around how health care resources can be allocated to assist the patient along their recovery trajectory given the risks. The discrepancy between patient resilience and surgical stress can be diminished by using ERAS pathways that mitigate surgical stress and using MP to increase patient resilience. All aim to increase the likelihood of meaningful and good recovery from CRC surgery and increase its value to patients and society.

2.3 Multimodal Prehabilitation: State of the Evidence

Of the strategies discussed, MP is the newest intervention, but it has garnered increasing interest since its first description in medical literature in 2010 (101) because of accruing evidence of benefit, biologic plausibility, and coherence with clinical observations. Despite its associations with improved postoperative functional recovery and reduced complications, the evidence remains equivocal.

To evaluate the state of evidence for prehabilitation efficacy, McIsaac et al performed an umbrella review of systematic reviews summarizing the evidence on the extent to which prehabilitation (uni- or multimodal undertaken ≥ 7 days prior to surgery), compared to standard pre-operative care or other prehabilitation, affected patient experience, population health, and per capita cost associated with elective surgery. The overview included 55 systematic reviews published before 2020, representing 381 unique studies and 28363 patients (102). The population consisted of adult patients, 38% female, undergoing elective surgery. The prehabilitation interventions included in the reviews were 56% unimodal exercise, 22% mixed prehabilitation, with a minority (2%) specifically multimodal prehabilitation. Most reviews were graded as having low or critically low quality of evidence with high risks of bias among the studies. The health outcomes with sufficient evidence were postoperative complications, non-home discharge, functional recovery, and mortality. Among these outcomes, prehabilitation showed a benefit to complication rates among mixed surgical populations. Across the eleven systematic reviews evaluating complications, all showed a benefit for the prehabilitation groups, with relative risks ranging from 0.33 to 0.88. Six of the eleven reviews showed narrow confidence intervals, however, because of some biases attributed to the methods of the systematic reviews, the certainty of these conclusions remains low. Additionally, a positive effect on functional recovery among patients undergoing cancer surgery (+48 m in Six-minute Walk Distance (6MWD)) with a moderate level of certainty and non-home discharge (pooled OR: 0.51, 95%CI [0.28, 0.93]).

While this umbrella review offers robust and a rigorous analysis (103), it has limited external validity for MP interventions. Most of the reviews evaluated unimodal exercise prehabilitation and only 2% MP. Its main finding confirms previous knowledge that unimodal exercise prehabilitation is insufficient for conclusive benefits without the accompaniment of targeted nutritional support (37, 104) and strategies to foster self-efficacy (105). Nonetheless, this study highlights the need to use consensus-backed definitions of prehabilitation, study the core outcomes that capture the intended benefits of prehabilitation, and minimize bias in study design. These goals for future studies aim to build a foundation of strong evidence that can encourage prehabilitation uptake and development.

Since publication of the umbrella review, the results of three randomized controlled trials (RCT) of prehabilitation in elective colorectal surgery were published, two supporting the efficacy of MP and another refuting it. The positive trials targeted patients with significant comorbidities

(ASA II-III) undergoing elective colorectal surgery and demonstrated 40-50% reductions in postoperative complication rates for patients (27, 106). Conversely, the pragmatic PHYSSURG-C trial which prehabilitated predominantly healthy (ASA I-II) participants with exercise alone for a median duration of 15 days found no differences in postoperative recovery, complication burden, or unanticipated readmissions associated with their exercise-only intervention (107).

While each study makes valuable contributions to prehabilitation science, they also highlight the knowledge gaps apparent in the umbrella review. None of the trials used a common definition of prehabilitation: trials used different interventions (unimodal unsupervised exercise, bimodal supervised exercise program with nutritional counselling, multimodal supervised exercise program with nutritional and psychological counselling) of varying durations (2, 3, and 4 weeks). The trials also had differing primary outcomes including self-reported postoperative recovery, 30-day complication risk, and 30-day complication severity measured by CCI > 20. Moreover, two of the trials reported benefits contingent on complication etiology (medical vs surgical), but this distinction has only been loosely defined in the literature without consensus. The continued wide variation in studies obscures the potential effectiveness of MP, providing equivocal evidence for policymakers. These barriers to implementation decrease the adoption of a potentially beneficial intervention.

The problems with the current evidence base might also originate from the possibility that research methods that were used to evaluate MP efficacy are less suitable for studying a complex intervention. Currently-used study designs stem from pharmaceutical efficacy studies, where one therapy is compared to another or to a control group. However, a complex intervention is not a single focused intervention. It has multiple components that, together, produce a range of outcomes. It requires expertise and skills to deliver, and the desired outcome often involves transferring such expertise and skills to the patient. A complex intervention also may target multiple groups, be applied in multiple settings, and produce multiple levels of an outcome. Context also influences the intervention, and its components often require flexibility to adapt to its context (108). Applying pharmaceutical efficacy study designs to a therapy with this level of intricacy may not necessarily yield information that is useful or conclusive (7, 109). Indeed, MP exhibits all the characteristics of complex interventions, and the findings from the umbrella review starkly demonstrate the need for a paradigm shift. While for some complex intervention research problems, the RCT might still provide the best design for unbiased effect estimates. To address questions pertaining to implementation, upscaling, and application to differing localities and subgroups, methods that integrate studying the intervention *and* its context might be answered better with alternative designs and methodological innovations (108, 110, 111). Fletcher et al propose mixed-methods evidence synthesis, mixed-method case series research, and pragmatic process evaluations as methods that can identify how the effectiveness of a complex intervention may vary with changes in context (110). To address the abovementioned problems associated with complex interventions such as MP, experts exhort the research community to adopt "a bolder approach […] to include methods and perspectives where experience is still quite limited" to enable a shift from questioning whether the complex intervention is effective "to whether and how the intervention will be acceptable, implementable, cost effective, scalable, and transferable across contexts." (108). Adopting this broader and bolder approach in future research for MP would likely generate information that could clarify the question of MP efficacy and effectiveness.

2.3.1 Multimodal Prehabilitation Program Theory: How Does It Work?

Considering these recommendations, it is possible to use the complex intervention framework to describe the knowledge gaps in current MP research. Up until recently, the thrust of the last decade of MP research has been to demonstrate proof of concept and the viability of the intervention as a powerful tool for improving postoperative recovery. Now, investigators seek to refine the program theory for MP, represented by the question: "How does prehab work?." The program theory of a complex intervention describes how it is expected to work and under what conditions, the key components and their interactions, potential mechanisms for its effect, and how context influences its mechanisms and effects (108, 112). In addition to explaining how and where the complex intervention is effective, the program theory also provides a framework for its evaluation (113). To represent a program theory visually, logic models facilitate understanding of the multiple interacting elements. To refine and test these refinements to MP, these essential program theory elements must be defined.

Several potential program theory elements for MP have been identified, but no consensus has been reached. Refining the key elements of MP program theory requires answering the question: "What defines successful MP?" This principle of empirical scientific research emphasizes that to understand how something works, it is essential to study the examples of success. Analyzing the successes gives insights into the underlying mechanisms, principles, and processes that contribute to or explain their success. It also provides insight into areas to expand or improve. Identifying the characteristics of people undergoing MP who have better- than-average outcomes after surgery will aid in identifying MP targets and strategies to optimize these targets. Patients and clinicians embark on MP with the expectation that the patient will derive some benefit from improved health prior to surgery, but there are no defined or reproducible indicators of prehab response to substantiate or refute that expectation. Addressing this knowledge gap clearly has immediate applications and value as a significant improvement to MP.

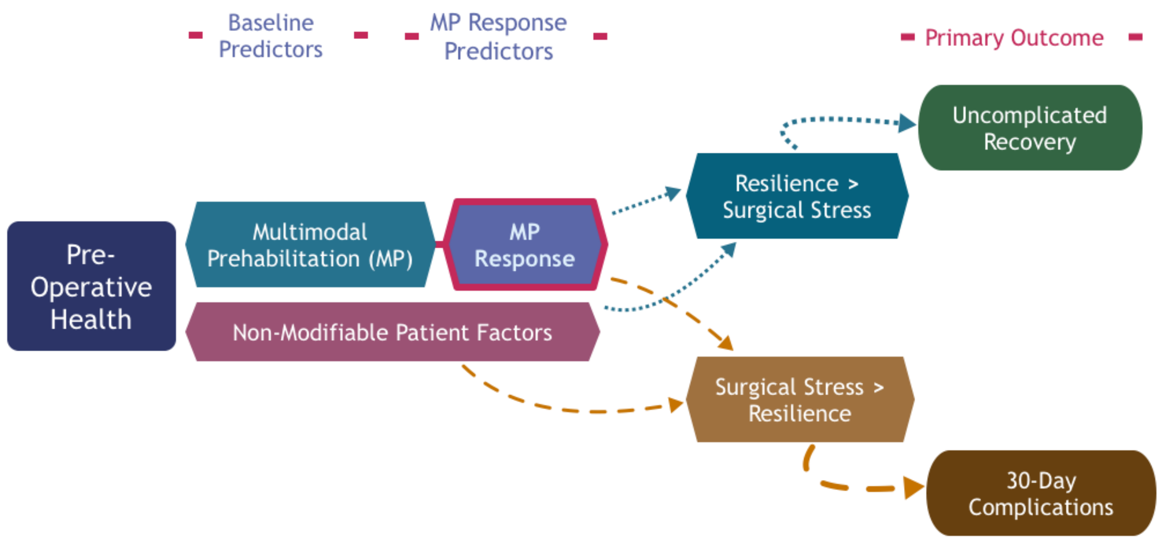
2.3.2 What is Successful Multimodal Prehabilitation?

There are a multitude of advantages associated with defining successful MP. It requires defining two components: first, the beneficial health outcome that is associated with success, and second, the characteristics of prehabilitated patients who are likely to receive this beneficial health outcome. In specifying these two components, we can rephrase the question “What is successful MP?” to “What characterizes a patient who has developed enough surgical resilience through MP such that they can undergo surgery with a high likelihood of having a specific beneficial health outcome?” However, based on the current prehabilitation literature, answering this question could be challenging because we do not know what fundamentally relevant and beneficial health outcomes are achievable through MP, nor are there MP response indicators that point to an increased probability of such beneficial outcomes.

The first component to define is which beneficial health outcome is sought through participation in MP. Since the initial series of MP trials which defined benefit as postoperative recovery of functional capacity (6MWT) (74, 114-116), the effect of prehabilitation on a panoply of additional health outcomes has been investigated. In a recent scoping review, Fleurent-Gregoire et al documented 184 different post-surgical health outcomes from 76 studies to characterize potential benefits from prehabilitation (117). The types of outcomes varied substantially, with 34% of studies using performance-based outcomes, 30% clinician-reported, and 15% patient-reported outcomes. To further complicate matters, a wide variety of different measures were used to assess similar outcomes, and the period for outcome measurement ranged from preoperative to > 90 days after surgery. Although only a third of their reviewed studies specifically delivered MP, this wide variation of studied health outcomes clouds understanding of what successful MP may imply. Indeed, experts emphasize the urgent need to focus future MP research on a core set of pertinent and standardized health outcomes to increase the validity and generalizability of findings (118). Nonetheless, outcomes pertinent to all stakeholders are likely to involve avoiding mortality, morbidity, and disability or demonstrating enhanced recovery of global functioning.

With the lack of clarity regarding which specific beneficial health outcomes could be ascribed to MP, describing the characteristics of MP participants who are likely to be successful has not yet been attempted. Conceptually, these characteristics could be classified by modifiability by MP (age and sex are non-modifiable, versus nutrition status and functional capacity which are modifiable) or by the point at which they were measured (before or after MP). These characteristics can serve as response indicators to MP, and those that demonstrate a strong positive association for favourable outcomes could become MP targets. These selected response indicators could then be considered potential key elements of the MP program theory, suggesting mechanisms for how MP might work and orienting future research and refinement efforts. They could also provide insight into what characteristics would indicate the presence of surgical resilience for elective CRC resection.

Figure 1: A Process Schematic Describing the Relationship Between Baseline Characteristics, Response Indicators, and Possible Outcomes in Multimodal Prehabilitation



2.4 Research Objective & Question

As such, the purpose of this study is to characterize, among patients receiving MP prior to undergoing elective colorectal surgery between 2012 and 2021 at an ERAS-compliant surgical center, the baseline and post-prehabilitation profiles of those who experienced an important reduction (≥10%) in 30-day complication risk. These profiles could provide a basis to describe patients with adequate resilience for elective colorectal surgery. The intent is to provide interpretable information that corresponds to observed phenomena in the clinical setting and to move away from focusing on the effects of individual risk factors.

2.4.1 Recursive Partitioning Algorithm Analysis

For this objective, I chose to do a classification and regression tree analysis using a recursive partitioning algorithm (RPA). A machine learning algorithm, RPA recursively tests each variable's ability to classify observations into subgroups with similar risk of outcome. Recursive testing means that the test result depends on or is influenced by a previous version of itself (119). The resulting model predicts each patient's group membership using a succession of rules that is associated with a predicted outcome (120). This succession of rules ranks partitioning variables into a hierarchy of importance and is often depicted as a tree branch originating from the 'trunk'-

-the undivided sample under study. The resulting diagram visually represents a hierarchy of variable influence. RPA is useful because it produces decision tree models that present complex variable interactions in an accessible format. The tree 'branches' are clear pathways or decision rules that describe the partitioning process in a readily understandable way. It is also a flexible algorithm that allows for variables to be weighted or ranked to create relevant models that reflect specific real-world applicability needs (121).

When evaluating a complex intervention such as MP where variables interact and may mutually modify effects, controlling for individual risk factors in a logistic regression model can generate estimates of effect that are not useful nor interpretable. The RPA modeling approach has precedence in multiple medical domains, and it has provided the framework for some widely-adopted clinical decision tools (122-126), and risk stratification models (127-130). This approach was also chosen in the spirit of Skivington et al's call to consider 'bolder' methods to answer questions of how a complex intervention such as MP can be "implementable, scalable, and transferable across contexts."

Creating the decision or classification tree involves applying the RPA to a set of variables containing one outcome variable and multiple predictor variables. The algorithm evaluates each variable's ability to partition into subgroups by calculating the variable's capacity to classify between those with and without the outcome. In essence, it constructs a 2x2 contingency table using a predictor and outcome variable, then assesses the quality of the split by calculating a quantity called the Gini Impurity index from the frequency of the outcome in the resulting subgroups. 'Purity' refers to the accuracy with which a partitioning predictor variable can classify those with and without the outcome. A completely pure split occurs when a predictor distinguishes with 100% accuracy those who had the outcome from those who did not, while a completely impure split occurs when the predictor partitions with 0% accuracy, resulting in a 50/50 distribution of the outcome between the subgroups as if by random chance. For a predictor to be retained as a partitioning variable, it must have the lowest Gini Impurity index among all potential partitioning variables for that split and must classify observations with the lowest misclassification rate. The RPA evaluates the partitioning ability of continuous variables as described above, with added recursive calculations that test each value of the continuous predictor in the data. The tree branching and partitioning continues until the algorithm reaches pre-specified limits.

The groups defined by splits are known as ‘nodes,’ and those that are split further are known as ‘split,’ ‘decision,’ or ‘internal’ nodes. Those nodes that are not split further are known as ‘leaf’ or ‘terminal’ nodes. Terminal nodes have the lowest Gini impurity indexes and are groups of observations with homogenous probabilities of outcome. The pathways leading to terminal nodes map a set of variables that interact and produce an aggregated effect on outcome probability (131).

Various RPA have different strategies for classifying observations that have missing data in the predictor variables. Some strategies used by RPA include assigning observations with missing data in the predictor variables to the largest subgroup or by the probability of outcome vs non-outcome, or even omitting them (132). The analysis software used in this study is the rpart package in R programming language. This package partitions observations with missing data elegantly by using ‘surrogate’ variables (132). Surrogate variables are other variables that help assign the observation with missing data to a subgroup that minimizes misclassification. These surrogates are identified using the same partitioning algorithm. To illustrate, a predictor variable, age > 40 years, is a strong partitioning variable for an outcome of mortality but it has observations with missing data. To assign these observations with missing values to age > 40 or < 40 years, the rpart package applies the impurity calculation algorithm, but replacing the outcome variable with the predictor variable age > 40 years. The algorithm then evaluates all potential ‘surrogate’ variables for their ability to classify age ≥ 40 or age < 40. Variables that can partition age > 40 years with low impurity are retained as a ‘surrogate,’ which suggests that the values of this surrogate predictor have a similar classification ability to ‘age > 40.’ Consequently, when data is missing in the variable age > 40, the values of the surrogate variable are then used as substitute information that determines into which subgroup this observation missing a value in the predictor ‘age > 40’ will be categorized. This powerful strategy likely minimizes the effects of missing data on the model’s performance.

As with most modeling procedures, a credible model must balance reliability (accuracy in prediction) and interpretability (explaining real associations between predictors). For decision trees, this balance is achieved by specifying the parameters that limit tree complexity or ‘growth.’ In rpart, the complexity parameter (cp) is the tuning parameter that limits tree growth and is analogous to the Akaike or Bayesian Information Criteria in regression analysis. It applies a ‘cost’ to adding variables and is scaled such that with a cp = 1, the tree model will have no splits and a cp = 0 will have split the sample into a highly complex tree with each observation in its own terminal node. Each possible tree configuration has an associated cp value, and rpart produces trees with increasing complexity until it produces a tree that has a smaller cp value than the user-defined minimum cp value. The rpart package cp default value is 0.01 (132). Another limit for tree complexity is specifying the minimum number of observations partitioned into nodes. Splitting does not occur if a group is smaller than a specified minimum number, or if partitioning results in groups smaller than a specified minimum number. These two strategies are used to find a model with the best balance between interpretability and reliability.

2.5 Summary

Using the recursive partitioning algorithm in the rpart package for R, the aim of this study is to obtain patient-centered rather than variable-centered information that characterizes participants who underwent successful MP. We hypothesize that the baseline and post-prehabilitation profiles that are associated with an important reduction (≥10%) in 30-day complication risk are those that could potentially characterize MP participants who demonstrate adequate resilience for elective colorectal surgery. The RPA approach is chosen to reflect the complex nature of the MP intervention and to provide interpretable information that corresponds to observed phenomena in the clinical setting. The following chapter contains a manuscript entitled “Successful Multimodal Prehabilitation Prior to Elective Colorectal Cancer Resection: A Recursive Partitioning Analysis of Pooled Trial Data” prepared as a result of this study.

3. Manuscript

Title: Successful Multimodal Prehabilitation Prior to Elective Colorectal Cancer Resection: A Recursive Partitioning Analysis of Pooled Trial Data

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Abbreviated Title: Successful Multimodal Prehabilitation Tree Models

Summary Statement: Among 231 participants receiving multimodal prehabilitation, classification trees have associated functional capacity, adequate red cell mass, absence of malnutrition, insulin sensitivity, and adequate exercise volume with lowered 30-day post-operative complication risk.

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Conflicts of Interest: The authors declare no competing interests.

3.1 Abstract

Background: Undergoing multimodal prehabilitation (MP) is associated with improved outcomes after elective colorectal surgery. However, the beneficiaries and the indicators of multimodal prehabilitation response that are associated with optimal preparation have yet to be defined. We sought to create preliminary descriptions of successful multimodal prehabilitation by defining characteristics of participants who avoided 30-day postoperative complications.

Methods: Using a pooled sample of participants randomized to the intervention arms of six trials, recursive partitioning classification tree models were generated to identify subgroups with reduced complication risk. Candidate predictors in these models were modifiable by prehabilitation and associated with surgical outcomes. Two tree models were generated: baseline and post-prehabilitation characteristics.

Results: Among a sample of 135 (58.4%) men and 96 (41.6%) women, 34.2% experienced 30-day postoperative complications. Of the four terminal nodes in the baseline tree model, those with the largest reductions in complication risk had a Six-Minute Walk Distance (6MWD) ≥519 m with a RAND Short Form 36-Item Physical Functioning Score (SF-36 PFI) ≥56 (14.9% complication risk; 95% CI: [8.3-25.3%]) or had a combination of SF-36 PFI ≥56, 6MWD 314-518 m, and Patient-Generated Subjective Global Assessment Score < 3 indicating low risk of malnutrition (6.2% risk; 95% CI [1.1-28.3%]). In the post-MP tree, the lowest 30-day complication risk was realized among patients who achieved a 6MWD ≥487 m at MP completion (22.2% risk; 95% CI [15.4-30.9%]). For those who could not reach this distance, ≥41 days of prehabilitation offset an otherwise elevated risk, reducing it from 46.4% to 31.8% (95% CI [19.5-45.7%]).

Conclusions: This study delineates several patient profiles with low postoperative complication risk as targets for successful multimodal prehabilitation programs. These profiles could be used as descriptors of successful prehabilitation in this population.

Keywords: multimodal prehabilitation, preoperative, colorectal, pre-surgery, Enhanced Recovery After Surgery, clinical outcomes

3.2 Introduction & Background

Colorectal cancer (CRC) represents 10.7% of the global cancer burden, and approximately 110,000 patients undergo elective colorectal surgery per year in the US and Canada (20, 21). Morbidity after colorectal surgery ranges from 22 to 28% percent (9, 10, 12), and this postoperative morbidity risk is increasingly attributed to patient characteristics. In a large cohort study of 15,755 patients, Bamdad et al demonstrated that 35% of the variance in complication risk after colorectal surgery was attributable to patient factors, compared to surgeon (2.4%) and hospital (1.8%) factors (13).

The advent of Enhanced Recovery After Surgery (ERAS) and multimodal prehabilitation (MP) programs has shown promise in reducing this complication burden. ERAS-compliant care can decrease the odds of complications after colorectal surgery by 27 to 40% (90-92). Similarly, multimodal prehabilitation (MP) programs have been associated with reductions in complications. A recent umbrella review of 55 systematic reviews on prehabilitation support benefit to complication rates among mixed surgical populations. Across the eleven systematic reviews looking at complications, all showed a benefit for the prehabilitation groups, with relative risks ranging from 0.33 to 0.88. Six of the eleven reviews showed narrow confidence intervals, but because of biases attributed to the methods of the systematic reviews, the certainty of these conclusions remains low (102). Furthermore, randomized controlled trials (RCT) of MP in patients with significant comorbidity burden (ASA II – III) showed 40-50% reductions in postoperative complication rates for patients undergoing elective colorectal (27, 106) and major abdominal surgeries (133). These results suggest that MP has the potential to reduce complication rates after colorectal and major abdominal surgery when offered to vulnerable patient groups.

Patients with low functional capacity and high comorbidity are likely to derive benefit from preoperative preparation and MP (134), but few specific criteria describe this population. Similarly, there are no specific descriptions of patients who have completed an MP program and subsequently benefitted from a reduction in postoperative complication risk. Essentially, who would benefit from MP and who has been sufficiently prehabilitated prior to elective colorectal surgery remains unknown. Because we have not defined potential target populations for MP nor potential endpoints that indicate successful MP, evaluating the effectiveness of such a complex intervention remains difficult. Moreover, successful MP has not been contingent upon the extent of patient optimization but rather on the waiting time prior to surgery, which ranged between 3-6 weeks (101) with most converging on a 4-week duration (114, 115, 133-142). Additionally, for many studies, successful recovery post-MP was associated with return to usual walking capacity rather than the avoidance of complications.

The purpose of this reanalysis was to begin addressing this knowledge gap by delineating patient profiles associated with a reduced risk of complications 30 days after surgery among multimodal prehabilitation participants undergoing elective colorectal surgery. Using baseline and post-prehabilitation characteristics, these profiles would constitute preliminary and hypothesis-generating definitions of successful multimodal prehabilitation

3.3 Methods

This is a reanalysis of pooled data from the intervention arms of 5 RCTs and one single-arm trial (27, 115, 138, 143-145) whose original aims were to estimate the effect of MP in patients undergoing elective colorectal cancer surgery. The trials were conducted between 2011 and 2021 at the Montreal General Hospital (McGill University Health Center, Montreal, Quebec). The Research Ethics Board of the McGill University Health Center approved each of the trials included in this study.

3.3.1 Patient Population

This secondary analysis included only those participants who underwent MP as per the intervention arms of the primary trials. Table 1 summarizes the inclusion and exclusion criteria from the primary trials. Excluded from the present analysis were participants who met an exclusion criterion after randomization (n = 1), did not receive any MP despite being randomized (n = 6), did not have surgery (n = 5), or had no available outcome data (n = 3).

3.3.2 Measurement

We considered three types of variables in this study to create profiles of patients undergoing successful MP: the outcome, potential predictors, and descriptive variables. The primary outcome was the presence of 30-day complications after elective colorectal surgery defined by the Clavien-Dindo Grading system (23, 25). Potential predictor variables are given and organized according to the rubrics of the Wilson-Cleary model in Supplementary Table 1 (52, 98). Biological & physiological predictor variables are listed first. Among these, the fat-free mass index (FFMI) was normalized to male sex by multiplying the values for women in the sample by a factor of 1.133 (17/15) so that the recursive partitioning algorithm (RPA) could identify a single cut-point for this variable. This factor is the ratio of gender-specific FFMI threshold values that indicate reduced muscle mass (men: ≤ 17 kg/m^2, women: ≤ 15 kg/m^2) (146). There were no variables under the 'Symptom' rubric as many of these are related to the underlying disease process or to anticipation of surgery and were expected to be resolved with completion of treatment. Under the physical functioning rubric are variables related to physical capacity and are explained in detail in Supplementary Table 1. Variables under the General Health Perception rubric were not under study in this investigation but were used to describe the sample.

From the potential predictor variables presented in Supplementary Table 1, risk factors modifiable through prehabilitation, known to influence post-colorectal surgical outcomes, and had ≤ 25% missing data were selected for this analysis. Table 2 presents this predefined set of influential predictor variables used in the classification tree modeling.

Data were extracted from the primary study databases, original study charts, electronic charts (OACIS, Telus Health), and archived paper hospital charts. Inconsistent data were checked against primary study charts, electronic hospital charts (OACIS, Telus Health), and archived hospital charts and updated in the study database.

3.3.3 Statistical Analysis

Distributional parameters were generated for all variables. Two classification tree models were generated: the first profiled the baseline characteristics of participants who avoided 30-day complications, and the second profiled post-MP (pre-surgery) characteristics associated with the same outcome.

To identify profiles of people who could benefit from prehabilitation, we used RPA analysis. This machine learning approach recursively tests each level of each variable to identify those that provide the best separation of the outcome into subgroups with similar values. To strike a balance between tree accuracy and simplicity, the rpart package for RPA in R allows users to tune the complexity of the tree by specifying a complexity parameter (cp). The cp can be interpreted as a 'cost' for adding additional splitting variables to the tree, such that the larger the cp, the fewer variables in the tree (132). A default cp value of 0.01 was used in this study. In addition to model parameters used to restrict the tree, we declared a node to be terminal when the sample size was ≤ 5% of the total cohort (n = 11), a minimum size for calculating an interpretable confidence interval (147), or when the split did not separate the groups by ≥10% (148). Missing data in the predictor variables were handled using "surrogates," where information from correlated variables was used to assign missing to a particular split value.

The profiles of successful MP are the predictor variables used to define terminal nodes with ≥10% absolute risk reduction in each of the final models (148). To provide further details to these profiles, the distributional statistics of select variables listed in Supplementary Table 2 (mean ± SD, median [Q1, Q3], and proportions) were generated for each important terminal node. These descriptive variables were selected for their known association with colorectal surgery outcomes (9, 13, 32, 149) and in the primary studies were not considered to be modifiable during an MP intervention (9, 13, 32, 149, 150). For each classification tree, the relative importance of each partitioning variable was also obtained. Ten-fold internal cross-validation was used to generate models with optimal classification performance.

As this is an analysis of existing data, the analysis plan for this study was established after data collection. All statistical analyses were performed with R version 4.2.3 using RStudio Version 2023.06.1+524 (Posit Software, PBC).

Table 1: Inclusion and Exclusion Criteria for Study Participation in the Pooled Primary Multimodal Prehabilitation Studies

Inclusion	Studies	Exclusion	Studies
Colorectal cancer, non-metastatic	(27, 115, 138, 143-145)	Language barrier or cognitive impairment impeding comprehension of MP	(27, 115, 138, 143-145)
Age > 18 years	(27, 115, 138, 143, 144)	Severe disease precluding exercise	(27, 115, 138, 143-145)
Age > 65	(145)	Metastatic disease	(27, 115, 138, 143-145)
Fried Frailty Phenotype Score ≥ 2	(145)	ASA Class ≥ 4	(27, 115, 138, 143, 144)
		Chronic Renal Failure	(27, 143, 144)
		Anemia < 100 g/L	(138, 143)
		Body Mass Index > 40 kg/m^2	(138, 143)
		Surgery within 4 weeks of MP start	(27)
		Abdominoperineal Resection	(27)

MP, multimodal prehabilitation; ASA, American Society of Anesthesiologists.

Table 2: Factors Included in the Recursive Partitioning Algorithm Classification Tree Analysis for Successful MP at Baseline and Post-MP

Construct	Variable	Model	
		Baseline	**Post-MP**
Serum biochemistry	Hemoglobin Concentration (g/L)	X	
	Glycated hemoglobin A1c (%)	X	
Nutritional Status	Patient-Generated Subjective Global Assessment	X	
	Body Mass Index (kg/m^2)	X	X
	Fat-Free Mass Index (kg/m^2)	X	X
	Grip strength (kg)	X	X
Functioning	30-second Sit-to-Stand Test (#)	X	X
	Six-Minute Walk Distance (m)	X	X
	SF-36 Physical Functioning Index	X	X
MP Components	Length of program (days)		X
	Supervised Exercise		X

3.4 Results

3.4.1 Pooled Cohort Characteristics

Data were available for 247 patients; 16 were excluded and analysis was performed on the 231 remaining patients. Ten patients did not return for post-MP evaluation, but outcome data were available for these patients. As a result, the baseline classification tree is based on 231 patients while the post-MP tree is based on 221 patients.

The details of the primary study protocols are provided in Table 3. The MP interventions consisted of exercise, nutrition, and stress management components with variations in the exercise component. Close to half of the patients (46.9%) received a combination of self-directed and supervised exercise training, 35.5% received supervised training only, and 17.5% self-directed only. All patients received nutrition counselling and supplementation targeted to achieve a protein intake of 1.2 to 1.5 g/kg/day. Multivitamin and vitamin D supplementation (400-800 IU daily) was given to 21% of the cohort. The psychological intervention was relatively homogeneous: all patients received recordings of guided stress reduction sessions and 92.3% had at least one in-person counseling session. The median duration of the MP program was 34 days (IQR 22, 45).

The characteristics of 96 women and 135 men who underwent MP prior to elective colorectal surgery are presented in Table 4 and 5. The cohort mean age was 69.1 years (SD: 12) with 70.2% of the cohort aged 60 to 79 years. Two-thirds of the cohort (67.6%) were classified as American Society of Anesthesiologists' (ASA) Class 2 or less. Twenty-four percent (n = 45) were frail according to Fried Frailty Criteria. Of the ten comorbidities reported, hypertension (43.9%), dyslipidemia (28.3%), and cardiovascular disease (20.0%) were the three most common. Half of the patients (51.3%) in this colorectal surgery population were anemic, as defined by the World Health Organization criteria of a serum hemoglobin concentration < 130 g/L (151) Seventeen percent were diagnosed with a Critical need for nutritional intervention. Minimally-invasive surgery was the most common approach (open approach, 9.7%), with patients undergoing right hemicolectomies (41.7%), low anterior resections (20.9%) and sigmoid resections (14.8%).

Characteristics of the cohort on tests and measures of physical function are presented in *Table* 5, with the sex-specific norms for individuals at the mean age of the cohort (69 years) provided for reference. Prior to starting MP, participants' physical functioning was generally slightly below the norm, and these test values generally increased after MP. Table 6 describes patient outcomes within the first 30 days after surgery. Over a third of the cohort had a postoperative complication (34.2%) with most occurring during the index hospitalization (26.4%). Of these complications, few were severe (Clavien-Dindo Class ≥ IIIa, 8.7%) and only 4.8% needed ICU admission. The median index hospital length of stay was 3 days (IQR 2, 5) with 55.0% of the cohort discharged in ≤ 3 days. After discharge, 8.7% (n = 20) of patients returned to the emergency department and 4.8% patients returned for unplanned hospital care.

Table 3: Study Design and Multimodal Prehabilitation Details of the Pooled Multimodal Prehabilitation Studies

Pooled Prehabilitation Studies	Frequency (%)
Gillis et al (2014)	40 (17.3%)
Bousquet-Dion et al (2018)	37 (16.0%)
Barrett-Bernstein et al (2019)	19 (8.2%)
Minnella et al (2020)	35 (15.2%)
Carli et al (2020)	51 (22.1%)
Molenaar et al (2023)	49 (21.2%)
Study Design	
Randomized Controlled Trial	212 (92.3%)
Single-Arm Trial	19 (8.2%)
Prehabilitation Intervention Components	
Exercise Mode (Sessions/week)	
Home-based (3) Only	40 (17.5%)
Home-based (2) & Supervised (1)	107 (46.9%)
Supervised (2 to 3) Only	81 (35.5%)
Nutrition Intervention	
Counselling with Supplementation:	231 (100%)
Protein Only	179 (78.5%)
Protein, Multivitamin, & Vitamin D	49 (21.5%)
Psychological Intervention	
In-Person Session & Recording	212 (92.3%)
Recording Only	19 (8.2%)
Program Duration (days), Median [Q1, Q3]	34 [22, 45]

Table 4: Baseline Demographic, Clinical & Surgical Characteristics of 231 Patients Who Underwent Multimodal Prehabilitation Prior to Elective Colorectal Surgery

Study Cohort (n = 231)	**Frequency (%)**
Demographic Characteristics	
Women	96 (41.6%)
Age, years	69.1 ± 12
Age Categories, years	
< 50	19 (8.2%)
50-59	30 (13.0%)
60-69	60 (26.0%)
70-79	72 (31.2%)
≥ 80	50 (21.6%)
Clinical Characteristics	
American Society of Anesthesiologists (ASA) Class	
1	20 (8.7%)
2	136 (58.9%)
≥3	75 (32.5%)
Comorbidities	
Hypertension	101 (43.9%)
Dyslipidemia	65 (28.3%)
Cardiovascular Disease	46 (20.0%)
Diabetes Mellitus	42 (18.3%)
Active Smoker	25 (10.9%)
Hypothyroidism	24 (10.5%)
Atrial Fibrillation	15 (7.0%)
Chronic Obstructive Pulmonary Disease (COPD)	16 (7.0%)
Obstructive Sleep Apnea	15 (6.5%)
Asthma	15 (6.5%)
Fried Frailty Score (n = 190)	
Robust (0)	68 (35.8%)
Pre-Frail (1-2)	77 (40.5%)
Frail (≥3)	45 (23.7%)
Prior Abdominal Surgery	91 (45.3%)
Biochemical & Nutritional Measures	
Hemoglobin concentration (g/L)	128 ± 20.9
Anemia (Hb ≤130 g/L)	117 (51.3%)
HbA1c (%), (n = 199)	5.8 [5.5, 6.2]
Albumin (g/L)	40.8 ± 3.9
C-Reactive Protein (mg/L), (n = 216)	2.8 [1.2, 6.8]
BMI (kg/m2)	26.1 [23.6, 30.6]
BMI ≥30	65 (28.1%)
PG-SGA, (n = 190)	4 [2.3, 7]
PG-SGA ≥9, n (%)	33 (17.4%)
SF-36 Physical Functioning Index, (n = 187)	75 [45, 100]
Surgical Characteristics	
Open Surgical Approach	22 (9.7%)
Surgical Procedure	
Right Hemicolectomy	96 (41.7%)
Low Anterior Resection of the Rectum	48 (20.9%)
Sigmoid or Anterior Resection	34 (14.8%)

Left Hemicolectomy	18 (7.8%)
Abdominoperineal Resection	9 (3.9%)
Total, Subtotal, or Transverse Colectomy	8 (3.5%)
Small Bowel and Ileocecal Resection	5 (3.1%)
Transanal Total Mesorectal Excision (TATME)	5 (2.2%)
Second-Stage Procedure	2 (0.9%)
Other	5 (2.2%)

Continuous variables are expressed as mean ± SD or as median [25th percentile, 75th percentile]. Categorical variables are expressed as numbers and percentages. Numbers of patients with available data are in brackets. Hb, hemoglobin; HbA1c, glycated hemoglobin A1c; BMI, body mass index; PG-SGA, Patient-Generated Subjective Global Assessment; SF-36, Medical Outcomes Study 36-Item Short Form Questionnaire.

Table 5: Functional Characteristics of 231 Participants Undergoing MP Prior to Elective Colorectal Cancer Resection

		Baseline			Post-MP		
Test	Norms (M/W)*	N	Mean ± SD	Median [Q1, Q3]	N	Mean ± SD	Median [Q1, Q3]
SF-36 Physical Functioning Index	78.6 / 73.3 (152)	187	67.7 ± 31.5	75 [45, 100]	172	76.6 ± 25.0	85 [64, 100]
Grip Strength (kg)	41.1 / 24.6 (153)	230	30 ± 11	30 [22, 38]	291	31 ± 11	30 [22, 39]
30-second Arm Curl Test (#)	17.2 / 14.8 (154)	150	19 ± 6	18 [15, 22]	141	21 ± 6	21 [18, 25]
30-second Sit-to-Stand Test (#)	14.0 / 13.7 (154)	188	14 ± 6	13 [10, 16]	173	15 ± 5	14 [12, 18]
Timed Up-and-Go (seconds)	7.3 / 8.1 (155)	191	7.8 ± 4.2	7 [6, 9]	179	7.2 ± 3.6	6 [5, 8]
Six-Minute Walk Distance (m)	475 / 447 (156)	231	452 ± 134	465 [382, 544]	221	475 ± 134	485 [407, 567]

Continuous variables are expressed as mean ± SD or as median [25^{th} percentile, 75^{th} percentile].
*The norms for physical function tests presented here are presented for men/women aged 69 years, the average age of the cohort.

Table 6: 30-Day Post-Operative Outcomes Among 231 Patients Who Underwent Multimodal Prehabilitation Prior To Elective Colorectal Surgery

Post-Operative Outcomes	Frequency (%)
Overall 30-day Complications	
Any Complication	79 (34.2%)
≥2 Complications	28 (12.2%)
Clavien-Dindo Grade ≥III	20 (8.7%)
CCI Score, median [IQR]	0 [0, 8.7]
CCI ≥20	38 (16.5%)
In-Hospital Complications	
Any Complication	61 (26.4%)
≥2 Complications	21 (9.1%)
Clavien Dindo Grade ≥III	20 (8.7%)
Admission to ICU	11 (4.8%)
Length of Index Hospital Stay	
Hospital Length of Stay (days), median [IQR]	3 [2, 5]
≤ 3 days	127 (55.0%)
Post-Discharge Complications	
Emergency Department Consultation	20 (8.7%)
Hospital Readmission	11 (4.8%)
Re-Operation	5 (2.2%)

CCI, Comprehensive Complications Index, ICU, Intensive Care Unit

3.4.2 Classification Trees and Descriptive Statistics of Patients Protected from Complications at Baseline and After Multimodal Prehabilitation

The classification tree using baseline predictors is shown in Figure 1. The first split occurred with a Six-Minute Walk Distance (6MWD) ≥314 m. This split divided the sample with an overall complication rate of 34.2% (risk 0.342) into two groups: one group comprising 86.6% (n = 149) of the sample with a complication rate of 29.5% (risk 0.295), and a second group comprising 13.4% (n = 31) of the sample with a 64.5% complication rate (risk 0.645). The first group (risk 0.295) was further split according to SF-36 PFI scores, with those scoring ≥56 (out of 100) having a complication risk of 0.248 and those scoring worse having a complication risk of 0.431.

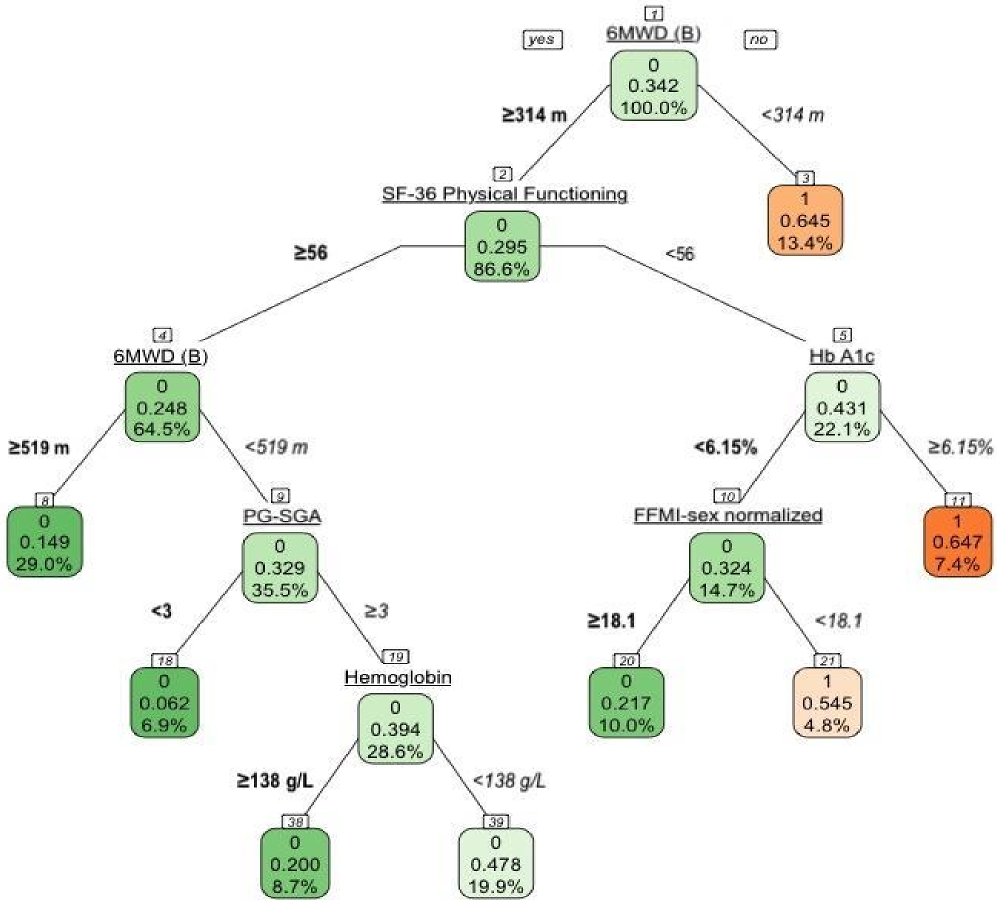
The baseline model yielded four important terminal nodes associated with lowered 30-day complication risk. In addition to the function variables SF-36 PFI and 6MWD, important splitting variables were nutritional (PG-SGA and FFMI) and biochemical (HbA1c and hemoglobin). In various combinations, these variables yield profiles associated with avoiding 30-day complications. The first important profile (Profile 1) describes MP participants who had good physical functioning at baseline, scoring ≥56 on the SF-36 PFI and walking ≥519 m. Participants with profile 1 had a 0.149 risk of 30-day postoperative complications. Similarly, profile 2 describes MP participants who had SF-36 PFI ≥56, walked 314-518 m, and had a PG-SGA score < 3, with a risk of 0.062. The four profiles associated with lowered 30-day complication risk are summarized in Table 7, and the relative importance of the partitioning variables used in this tree are presented in *Supplementary Table* 2. In the tree, the 6MWD and FFMI discriminated most accurately between participants with or without the outcome, while BMI, grip strength and 30-second sit-to-stand test were not influential partitioning variables.

Additional factors associated with these four profiles are presented in Table 7 where the distribution of selected descriptive and classifying variables among the four profiles is shown. Among patients with these decreased risk profiles, few had atrial fibrillation or COPD, and all had above average cohort grip strength at baseline. While the four profiles showed similar distributions of these additional factors, profile 3 describes a subgroup consisting of 85% men, 40% of whom were ASA Class ≥3.

The classification tree using post-MP classifiers also yielded 4 terminal nodes associated with a ≥10% absolute reduction in 30-day complication risk (Figure 2). The post-MP 6MWD was once again the first splitting variable partitioning participants walking ≥ 487 m (49.1%, n = 108) after MP into a lowered risk group (0.222 risk). Those who could not attain this distance (50.2%, n = 112) doubled their risk (0.464). Subsequent splits identified three additional groups protected from excess risk: MP program duration ≥41 days, 6MWD ≥ 255 m, and the type of exercise supervision. The profiles defined in this post-MP tree model are presented in Table 9. Among participants walking < 487 m, the criteria associated with clinically-relevant decreases in complication risk included participation in MP for ≥ 41 days with any post-MP 6MWD, or 30-40 days of MP provided maintaining a minimal post-MP 6MWD > 255 m. Accordingly, in this tree the 6MWD and MP duration were the variables that discriminated most accurately between participants who avoided 30-day complications and those who did not. The relative variable importance for this tree is also presented in Supplementary Table 2.

The additional descriptions of participants who grouped into profiles 5 to 8 and avoided 30-day complications are presented in Table 8. In three profiles describing those who walked < 487 m, ≥ 50% were women classified as ASA 3. Of these, profile 7 consisted of 60% women without atrial fibrillation who participated in MP with an exclusively self-directed exercise component for the shortest mean duration (22 ± 6 days) and avoided 30-day complications (0.300). Participants in terminal node 59 (Figure 3) who had the same MP duration (n = 25, mean age 76 ± 9.6, women 48%, 22 ± 6.2 days) but had supervised exercise fared poorly (risk 0.72).

Figure 1: Classification Tree Model for the Risk of Developing Complications Within 30-days of Elective Colorectal Surgery Using Baseline Predictor Variables of 231 MP Participants



6MWD-B, Six-Minute Walk Distance at Baseline; SF-36 PFI, Rand Medical Outcomes Study 36-Item Short Form Quality of Life Questionnaire, Physical Functioning Index; HbA1c, glycated hemoglobin; PG-SGA, Patient-Generated Subjective Global Assessment; FFMI, fat-free mass index.

Within each node, three numbers from top to bottom indicate the most common outcome, the risk of 30-day complications, and the percentage of the cohort contained within the node is shown. "0" indicates the absence of 30-day complications, and "1", the presence of complications.

Table 7: Profiles of Baseline Classifiers Associated with Lowered 30-day Complication Risk Among 231 Prehabilitated Patients Undergoing Elective Colorectal Resection

		Baseline Classifiers						30-D CR	95% CI	n	% cohort
Overall								0.342	[0.284, 0.405]	231	
		6MWD-B (m)	SF-36 PFI	PG-SGA	Hb (g/L)	HbA1c (%)	FFMI (kg/m²)				
Profile	**1**	≥519	≥ 56					0.149	[0.083, 0.253]	67	29.0%
	2	314-518	≥ 56	< 3				0.062	[0.011, 0.283]	16	6.9%
	3	314-518	≥ 56	≥3	≥138			0.200	[0.081, 0.416]	20	8.7%
	4	314-518	< 56			< 6.15	≥18.1 M ≥16.0 W	0.217	[0.097, 0.419]	23	10.0%

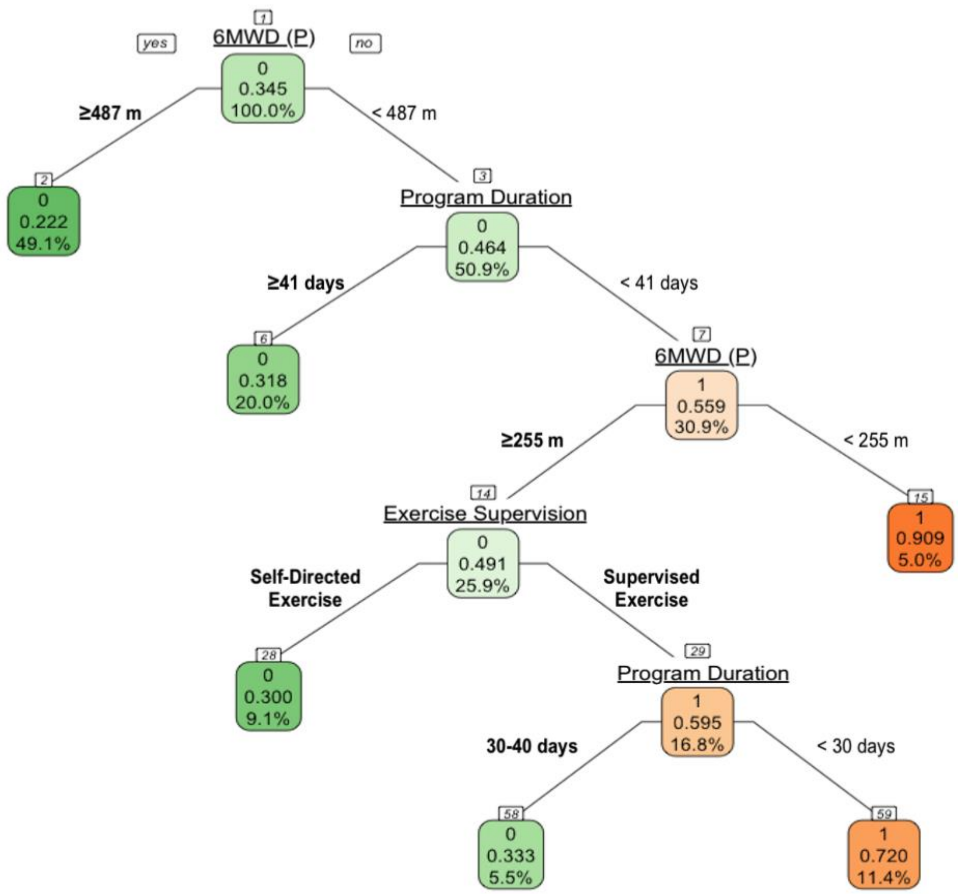
30-D CR, 30-day Complication Risk; CI, confidence interval; 6MWD-B, Six-Minute Walk Distance at Baseline; SF-36 PFI, Rand Medical Outcomes Study 36-Item Short Form Quality of Life Questionnaire, Physical Functioning Index; PG-SGA, Patient-Generated Subjective Global Assessment; Hb, serum hemoglobin concentration; HbA1c, glycated hemoglobin; FFMI: fat-free mass index; M, men; W, women.

Table 8: Selected Characteristics of MP Participants with Profiles 1 to 4 Associated with Lowered 30-Day Complication Risk After Elective Colorectal Surgery

	Cohort	Baseline Pathways			
		1	**2**	**3**	**4**
Profile Description		6MWD ≥519 m	6MWD 314-518 m	6MWD 314-518 m	6MWD ≥315 m
		SF-36 PFI ≥56	SF-36 PFI ≥56	SF-36 PFI ≥56	SF-36 PFI < 56
			PG-SGA < 3	PG-SGA ≥3	HbA1c < 6.15%
				Hb ≥138 g/L	FFMI ≥18.1 (M) ≥16.0 kg/m^2 (W)
Number of Participants	231	67	16	20	23
30-Day Complication Risk	0.342	0.149	0.062	0.200	0.217
Descriptive Characteristics					
Age	69 ± 12	61 ± 11	71 ± 11	72 ± 7.1	66 ± 12
Women	96 (41.6%)	25 (37%)	6 (38%)	3 (15%)	9 (39%)
Active Smoker	25 (10.9%)	7 (10%)	0 (0%)	2 (10%)	2 (9%)
Atrial Fibrillation	15 (7.0%)	0 (0%)	1 (8%)	1 (5%)	1 (5%)
COPD	16 (7.0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Diabetes Mellitus	42 (18.3%)	4 (6%)	2 (12%)	3 (15%)	2 (9%)
ASA Class ≥3	75 (32.8%)	6 (9%)	4 (25%)	8 (40%)	6 (26%)
Classifying Variables					
Hb Concentration (g/L)	128 ± 21	135 ± 19	140 ± 16	145 ± 4.4	124 ± 21
HbA1c (%)	6.0 ± 0.85	5.7 ± 0.43	5.8 ± 0.67	5.9 ± 0.6	5.7 ± 0.28
Nutritional Characteristics at Baseline					
BMI (kg/m^2),	27.2 ± 5.4	26 ± 4.4	28 ± 4.1	27 ± 5	29 ± 6
FFMI (kg/m^2)	18 ± 2.7	20 ± 2.4	19 ± 1.9	19 ± 2.6	20 ± 2
PG-SGA	5.2 ± 3.4	3.9 ± 2.6	1.8 ± 0.44	5.3 ± 2.4	5.4 ± 3.8
Functional Testing at Baseline					
SF-36 PFI	68 ± 32	93 ± 10	88 ± 10	81 ± 15	32 ± 20
6MWD (m)	465 [382, 544]	587 [548, 626]	480 [452, 495]	453 [425, 495]	408 [350, 474]
Grip Strength (kg)	30.2 ± 10.9	35 ± 11	31 ± 10	32 ± 10	32 ± 10
30-second Sit-to-Stand Test (#)	13.5 ± 5.6	18 ± 5	14 ± 3	12 ± 4	9.6 ± 4

Continuous variables are expressed as mean ± SD or as median [25th percentile, 75th percentile]. Categorical variables are expressed as numbers and percentages.
COPD, Chronic Obstructive Pulmonary Disease; ASA, American Society of Anesthesiologists; Hb, hemoglobin; HbA1c, glycated hemoglobin A1c; BMI, body mass index; FFMI, fat-free mass index; PG-SGA, Patient-Generated Subjective Global Assessment; SF-36 PFI, Rand Medical Outcomes Study 36-Item Short Form Quality of Life Questionnaire, Physical Functioning Index; 6MWD Six-Minute Walk Distance; M, men; W, women.

Figure 2: Classification Tree Model for the Risk of Developing Complications Within 30-days of Elective Colorectal Surgery Using Post-MP Predictor Variables of 221 MP Participants



Abbreviations: 6MWD(P), Post-Prehabilitation Six-Minute Walk Distance.
Within each node, three numbers from top to bottom indicate the most common outcome, the risk of 30-day complications, and the percentage of cohort contained within the node is shown. "0" indicates the absence of 30-day complications, and "1", the presence of complications.

Table 9: Profiles of Post-MP Classifiers Associated with Lowered 30-day Complication Risk Among 221 Prehabilitated Patients Undergoing Elective Colorectal Resection

		Post-MP Classifiers			**30-D CR**	**95% CI**	**n**	**% cohort**
Overall					0.344	[0.284, 0.409]	221	
6MWD < 487 m					0.460	[0.371, 0.552]	113	51.1%
		6MWD-P (m)	Prehab Duration (days)	Exercise Supervision				
Profile	**5**	≥487			0.222	[0.154, 0.309]	108	48.9%
	6	255-486	≥41		0.311	[0.195, 0.457]	45	20.4%
	7	255-486	< 41	No	0.300	[0.145, 0.519]	20	9.0%
	8	255-486	30-40	Yes	0.333	[0.138, 0.609]	12	5.4%

30-D CR, 30-day Complication Risk; CI, confidence interval; 6MWD-P, Six-Minute Walk Distance After MP.

Table 10: Selected Characteristics of MP Participants with Profiles 5 to 8 Associated with Lowered 30-Day Complication Risk After Elective Colorectal Surgery

		Post-MP Pathways			
	Cohort	**5**	**6**	**7**	**8**
Profile Descriptions		6MWD-P ≥ 487 m	6MWD-P < 487 m MP Duration ≥41 days	6MWD-P 255-486 m MP Duration < 41 days Self-Directed Exercise	6MWD-P 255-486 m Duration 30-40 days Supervised Exercise
Number of Participants	221	108	45	20	12
30-Day Complication Risk	0.345	0.222	0.311	0.300	0.333
Personal Characteristics					
Age	69 ± 12	64 ± 11	76 ± 8.2	67 ± 15	76 ± 9.2
Women	96 (41.6%)	34 (31%)	22 (49%)	12 (60%)	6 (50%)
Active Smoker	25 (10.9%)	12 (11%)	5 (11%)	1 (5%)	0 (0%)
Atrial Fibrillation	15 (7.0%)	1 (1%)	4 (9%)	0 (0%)	2 (17%)
COPD	16 (7.0%)	0 (0%)	5 (11%)	2 (10%)	1 (8%)
Diabetes Mellitus	42 (18.3%)	12 (11%)	11 (24%)	4 (20%)	5 (42%)
ASA Class 3	75 (32.8%)	15 (14%)	23 (51%)	6 (30%)	6 (50%)
Classifying Variables					
Hb Concentration (g/L)	128 ± 21	136 ± 18	123 ± 20	124 ± 17	115 ± 14
HbA1c (%)	6.0 ± 0.85	5.8 ± 0.52	6.1 ± 0.7	6.4 ± 2.1	6.5 ± 1.2
Nutritional Characteristics					
BMI post-MP	27.2 ± 5.2	27 ± 4.3	27 ± 5.5	27 ± 5.6	29 ± 7.8
FFMI post-MP	19.4 ± 2.3	20 ± 1.9	19 ± 2.1	19 ± 2.4	20 ± 3.2
Functional Testing					
SF-36 PFI post-MP	77 ± 25	90 ± 17	68 ± 24	70 ± 22	59 ± 19
6MWD post-MP (m)	485 [407, 567]	572 [522, 625]	395 [339, 451]	436 [384, 478]	432 [378, 444]
Grip Strength post-MP (kg)	31 ± 11	36 ± 10	26 ± 10	30 ± 10	29 ± 15
30-second Sit-to-Stand Test post-MP (#)	15 ± 5.4	18 ± 5	13 ± 4	13 ± 0	12 ± 2
MP Program Characteristics					
Length of program (days)	40 ± 35	39 ± 31	64 ± 56	22 ± 6	37 ± 3
Supervised Exercise	172 (74.5%)	82 (76.0%)	38 (84.0%)	0 (0.0%)	12 (100.0%)

Continuous variables are expressed as mean ± SD or as median [25th percentile, 75th percentile]. Categorical variables are expressed as numbers and percentages.

COPD, Chronic Obstructive Pulmonary Disease; ASA, American Society of Anesthesiologists; Hb, hemoglobin; HbA1c, hemoglobin A1c; BMI, body mass index; FFMI, fat-free mass index; PG-SGA, Patient-Generated Subjective Global Assessment; SF-36 PFI, Rand Medical Outcomes Study 36-Item Short Form Quality of Life Questionnaire, Physical Functioning Index; 6MWD Six-Minute Walk Distance.

3.5 Discussion

This study profiled the baseline and post-prehabilitation characteristics of multimodal prehabilitation participants who showed a lower-than-average 30-day complication rate after colorectal resection and associated this outcome with 'success'. Eight profiles were proposed as preliminary descriptions of successful multimodal prehabilitation (Tables 7 and 9). We found that functional capacity measures were the most important discriminators for success, both before and after multimodal prehabilitation, then the ancillary discriminators differed depending on timing. Before starting multimodal prehabilitation, ancillary partitioning variables were nutrition status, red cell mass, insulin sensitivity, and muscle mass; whereas after, they were program duration and the presence of exercise supervision. To further describe the people in each profile, non-modifiable personal characteristics were examined for each (Table 8 and Table 10).

While people profiled as the most functional both at the start and end of multimodal prehabilitation unsurprisingly partitioned into groups with lowered complication rates, others with significant functional limitations and comorbidity also partitioned into lowered risk subgroups. As such, our study findings present multiple options for avoiding 30-day complications by combining and prioritizing various factors affecting post-surgery outcomes, suggesting relevant thresholds for these factors, and by linking each profile with quantitative risk estimates. They offer several pathways towards favourable post-surgical outcomes and a multi-faceted understanding of successful multimodal prehabilitation.

This study differs from previous investigations by using a classification tree approach that identifies groupings rather than independent variables. We believe that this approach is better suited for generating useful information about a complex intervention such as multimodal prehabilitation. By ranking multiple variables iteratively, recursive partitioning highlights potential key components and significant associations that can explain multimodal prehabilitation's beneficial effects. This information then also elucidates the conditions in which it can work optimally (108). This patient-profiling approach has been used in developing risk stratification models (122-126, 129) and in describing successful aging (127, 128). To our knowledge, this method has not been applied to prehabilitation cohorts, so these study findings represent novel and preliminary descriptions of participants who either likely have the potential to reach or have already reached targets associated with lowered 30-day complication risk. This information could be valuable as the basis for specific, measurable, relevant, and time-bound (SMART) goals for patients and professionals (157, 158) in the preoperative preparation for colorectal cancer resection.

The baseline classification tree identified two functional capacity predictors (6MWD and SF-36 PFI) as the most important discriminators for successful multimodal prehabilitation. The 6MWD is a performance-based measure of functional capacity and the SF-36 PFI is a measure of patient-reported behavioural limitations in performing everyday physical activities (159). Low scores in these assessments have been associated with increased risk of post-operative complications. Patients with a 6MWD < 400 meters are likely to have poor post-operative outcomes after lung resection and lung transplant (160, 161). Likewise, Rumsfeld et al found that every 10-point decrease in the preoperative SF-36 physical component summary (which includes the PFI) was associated with increased odds (odds ratio (OR) 1.39, 95%CI: 1.11-1.77) of all-cause mortality six months after coronary artery bypass graft surgery (162). The functional capacity threshold values identified in this tree may also define a minimum level of physical functioning that is amenable to multimodal prehabilitation. For reference, the 6MWD threshold (519 m) is between the 25th and 50th percentiles of adults 50-80 years old (163) and has in the range of an abnormally low 6MWD (164). Similarly, the threshold SF-36 PFI value of 56 is below the mean score for Canadians aged ≥ 75 (59.1) (152) and below the mean value of adults aged > 65 years with a positive fall history (63.3) (165).

The baseline classification tree also suggests several avenues by which patients with reduced physical functioning (6MWD < 519 m) can still be successfully prehabilitated, provided they have either adequate nutritional status, adequate serum hemoglobin (Hb), or insulin sensitivity with a FFMI consistent with normal muscle mass. Since poor nutrition is a known risk factor for increased 30-day mortality risk after colorectal and gastric cancer surgery (166), participants with intermediate walking distance and less critical need for nutritional support (PG-SGA < 3) were protected from excess risk in this cohort. Similarly, anemia is a risk factor that positively correlates with post-operative morbidity and mortality (167-171) and those in this cohort whose serum hemoglobin ≥ 138 g/L also benefited from lowered 30-day complication risk. This hemoglobin threshold aligns with current recommendations citing ≥130 g/L as an optimal pre-operative hemoglobin level (172). Finally, insulin resistance increases the risk of complications after major surgery (173-175), and reduced skeletal muscle indicated by reduced FFMI negatively influences surgical outcomes (73, 176). As a result, in those with a SF-36 PFI < 56, insulin sensitivity with a normal FFMI may provide an optimizable milieu resulting in successful multimodal prehabilitation. Notably, this preliminary FFMI threshold identified in this study (men ≥ 18.1 kg/m^2, women ≥ 16.0 kg/m^2) is higher than the consensus definitions for reduced muscle mass (females: < 15 kg/m^2, males: < 17 kg/m^2) (146). This disparity may suggest that more FFM may be necessary for success than merely avoiding sarcopenia definitions.

Like the baseline tree, the post-multimodal prehabilitation tree model identified functional capacity (6MWD) as the most important partitioning predictor associated with successful multimodal prehabilitation. The threshold value of ≥487 m compares to other values linked to favourable post-operative outcomes, albeit in non-prehabilitated patients. A secondary analysis of the METS trial identified > 477 m as a threshold for mild or no post-operative complications (177). Similarly, Sinclair et al identified 427 and 563 meters (average 495 m) as indicative of an oxygen consumption among non-prehabilitated patients at anaerobic threshold (AT VO_2) < 11 and ≥ 11 $ml/kg^{-1}\ min^{-1}$, respectively (178).

Differing from the baseline tree, the ancillary partitioning variables related less to biologic factors and more to program characteristics, as measured by days in multimodal prehabilitation and the type of supervision during exercise. Exercise volume quantifies an exercise stimulus by taking the product of energy expenditure (metabolic equivalents) and time spent performing the given exercise (in minutes) (179). As such, those patients not attaining the requisite physical function could still achieve lower risk by participating in multimodal prehabilitation ≥41 days or by maintaining a minimum 6MWD > 255 m while having a shorter (30-40 days) program duration. This 7-week duration threshold aligns with kinesiology study durations assessing the efficacy of aerobic (180-182) and resistance training in general and suggests that this period may be more effective for developing the resilience needed to protect against complications. In those with shorter program durations (30-40 days), several meta-analyses of studies comparing supervised and unsupervised exercise among elderly patients showed that supervised training results in greater physical gains (increased mean walking distances, balance, and gait speed), but self-directed training was associated with greater program adherence (183-185). The effect of exercise volume on outcomes may be modified by age and physiologic reserve, as demonstrated by the marked difference in operative risk between participants with profile 7 and terminal node 59.

Finally, both trees identified comparable critical minimal functional capacity under which multimodal prehabilitation is unsuccessful: 6MWD < 314 or < 255 m. These distances compare with a < 269 m lower bound corresponding to a VO_2 AT < 8 ml/ kg^{-1} min^{-1}, indicating prohibitive risks of post-operative complications (178).

Our study's main limitation is its small sample size that likely affects the prediction accuracy, precision, and stability of the tree models. Other research groups could replicate the process demonstrated here and collectively provide robust data to derive prehabilitation targets to optimize multimodal prehabilitation programs. In addition, we were limited to variables included in our historical data set, had missing data on variables that proved to be important for the partitioning process, and had variability in the data collection process over the time spans of the six original trials. Having a consistent and parsimonious set of important predictors could reduce response burden and missing data (117). In this study, a surrogate variable approach built into the rpart package to assign missing mitigates the possibility of misclassification bias. Finally, the single-center experience represented in this study may limit the generalisability of our results.

3.6 Conclusions

Among patients undergoing multimodal prehabilitation in preparation for elective colorectal cancer resection, our study proposes several multi-faceted, patient-centered profiles that may be used to define successful multimodal prehabilitation. By combining and ranking key variables associated with favourable outcome and specifying thresholds, patients and clinicians may have additional tools to improve intervention effectiveness. Patient experience can equally be improved by the specific, measurable, attainable, relevant, and time-bound goals proposed in these profiles. Patients who have potential to benefit from multimodal prehabilitation are described by measures of physical functioning, metabolism, and oxygen transport, while those who have received enough multimodal prehabilitation are described by physical functioning and exercise volume targets. These patient profiles can also further prehabilitation science by offering additional insights into the fundamental questions about for whom it is likely to be most beneficial, what are its core components associated with success, and how these components might work together to improve its effectiveness.

Supplementary Table 1: Variables and Associated Constructs Considered for Analysis Organized Within the Wilson-Cleary Framework of Health Outcomes Adapted for Prehabilitation

Variables	Baseline	Post-MP	Definitions	References
Biological & Physiological Factors				
Demographics				
Age (y)	X			
Sex	X			
Active Smoker	X		Risk factor associated with postoperative complications	Myles 2002
Anthropomorphic Measures				
Height (m)	X			
Weight (kg)	X	X		Cederholm 2019
Body Mass Index (kg/m²)	X	X	Weight indexed to body surface area	Cederholm 2019
Comorbidities				
Atrial Fibrillation	X		Risk factor associated with postoperative complications after colorectal surgery	Flynn 2020
Chronic Obstructive Pulmonary Disease (COPD)	X		Risk factor associated with postoperative complications after colorectal surgery	Flynn 2020
Diabetes Mellitus	X		Insulin resistance or insufficiency leading to chronic hyperglycemia and associated pathophysiology including increased postoperative complications	
Hypertension	X		Risk factor associated with postoperative complications after colonic surgery	Fawcett 1996
Serum biochemistry				
Albumin (g/L)	X		Negative acute phase reactant indicating extent of systemic inflammation	McMillan 2013
C-reactive protein (CRP) (mg/L)	X		Acute phase reactant indicating extent of systemic inflammation	McMillan 2013
Creatinine (mmol/L)	X		Indicator of kidney function	
Glycated hemoglobin (HbA1c), (%)	X		Indicator of glycemic control over prior 2-3 months	Koenig 1976
Hemoglobin concentration (g/L)	X		Hemoglobin < 130 g/L associated with increased risk of adverse postoperative outcomes	Elhenawy 2021
Nutrition phenotype				
Fat-Free Mass (kg)	X	X	Measured by bioelectrical impedance analysis to assess malnutrition and cachexia	Cederholm 2019
Fat-Free Mass Index (kg/m²)	X	X	Indexed to body surface area by dividing fat-free mass by the square of height in meters. Assesses adequacy of muscle mass.	Cederholm 2019
Patient-Generated Subjective Global Assessment	X		Validated tool for diagnosing malnutrition and triaging need for nutritional support	Ottery 1996
Grip strength (kg)	X	X	Measures muscle function via hand grip dynamometer to assess malnutrition and cachexia. Best value retained from bilateral testing.	Cederholm 2019
Functioning				
30-second Arm Curl Test (#)	X	X	Upper body strength measured by number of bicep curls in 30 seconds holding a hand weight (women 5 lbs, men 8 lbs). Best value retained from bilateral testing.	Rikli 1999
30-second Sit-to-Stand Test (#)	X	X	Lower body strength measured number of full stands in 30 seconds with arms folded across the chest	Rikli 1999

Variables	Baseline	Post-MP	Definitions	References
Six-Minute Walk Distance (m)	X	X	Physical endurance (ability to maintain submaximal aerobic exercise) measured by maximal distance walked in six minutes	Rikli 1999
Timed Up-and-Go (s)	X	X	Core musculature strength and balance measured by the time taken to rise from seated to standing position, walk 3 meters, turn, return, and sit down.	Bohannon 2006
VO2 peak (mL/kg^{-1} min^{-1})	X	X	Maximal cardiovascular fitness measured by oxygen consumption at peak effort during cycle ergometer CPET testing with predictive capacity for postoperative morbidity and mortality	Older 2017
VO2 Anaerobic Threshold (mL/kg^{-1}min^{-1})	X	X	Cardiovascular fitness measured by oxygen consumption at anaerobic threshold during cycle ergometer CPET testing with < 11 ml/kg^{-1}min^{-1} associated with postoperative cardiac events	Older 1993
SF-36 Physical Functioning Index	X	X	Measures the patient-reported performance of physical activities normal for people in good physical health (walking, climbing stairs, carrying objects)	Haley 1994
General Health Perceptions & Overall Quality of Life				
Health-Related Quality of Life				
SF-36 Bodily Pain Scale	X	X	Measures patient-reported ability to live without limitations due to pain	Ware 1993
SF-36 General Health Perceptions Scale	X	X	Measures patient self-assessment of general health and impact of symptoms	Ware 1993
SF-36 Mental Health Scale	X	X	Measures patient self-assessment of anxiety, depression, loss of behavioural/emotional control, and psychological well-being	Ware 1993
SF-36 Vitality Scale	X	X	Measures patient self-assessment of subjective well-being and impact of disease	Ware 1993
Mood Disorder Screening				
Hospital Anxiety Depression Scale	X	X	Screening test for psychiatric disorder among non-psychiatric hospital patients	Zigmond 1983
Generalized Anxiety Disorder 7-item	X		Screening test for generalized anxiety disorder for general population	Spitzer 2006
Multimodal Prehabilitation Program Details				
Length of program (days)		X	Number of days between baseline and post-prehabilitation assessments	
Overall Program Participation (%)		X	Weighted average of percent completed exercise and nutrition components	
Exercise Supervision (Y/N)		X	Exercise Intensity may affect efficacy of MP	Mayo 2011

Supplementary Table 2: *Selected Additional Clinical Characteristics of MP Participants Partitioned into Terminal Nodes with Lowered 30-Day Complications Post-Colorectal Surgery*

Descriptive Characteristics

- Mean age (149)
- Female Sex (13)
- Atrial fibrillation (32)
- Chronic obstructive pulmonary disease (COPD) (32)
- Diabetes (32)
- Active smoker
- American Society of Anesthesiologists Class ≥ 3 (9, 150)
- Open surgery (13)

Classifying Variables

- Hemoglobin Concentration (g/L)
- Hemoglobin A1c (%)
- Nutritional Characteristics at Baseline
    - Body Mass Index (kg/m^2),
    - Fat-Free Mass Index (kg/m^2)
    - Patient-Generated-Subjective Global Assessment Score
- Functional Testing at Baseline
    - SF-36 Physical Functioning Index
    - 6-Minute Walk Distance (m)
    - Grip Strength (kg)
    - 30-second Sit-to-Stand Test (#)

Supplementary Table 3: The Relative Importance of Variables Partitioning MP Participants into Groups with Lowered Risk of 30-Day Complications After Elective Colorectal Surgery

Variables	**Relative Importance**
Baseline	
Six-Minute Walk Distance (m)	34
Fat-Free Mass Index (kg/m^2)	14
Serum Hemoglobin (g/L)	11
SF-36 Physical Functioning Index	10
HbA1c (%)	9
Patient-Generated-Subjective Global Assessment Score	7
Body Mass Index (kg/m^2)	7
Grip Strength (kg)	7
30-second Sit-to-Stand Test	1
Post-Multimodal Prehabilitation	
Six-Minute Walk Distance (m)	40
Prehabilitation Duration (days)	24
Grip Strength (kg)	13
Exercise Supervision	9
Fat-Free Mass Index (kg/m^2)	6
SF-36 Physical Functioning Index	6
Body Mass Index (kg/m^2)	1

4. Discussion

As presented in the manuscript, I sought to generate preliminary definitions of patients who have been successfully prehabilitated prior to elective colorectal surgery. The two classification trees yielded eight patient profiles associated with avoiding 30-day postoperative complications. To my knowledge, no similar profiles describing successful MP exist. These profiles are valuable since influencing variables are ranked by importance, assigned cut-points, linked with other influencing variables, and associated with quantitative risk estimates for the primary outcome.

By assessing which variables partition the most effectively between groups with and without the outcome, RPA also generates a relative variable importance score that ranks the model variables by their partitioning ability. This importance value also accounts for a variable that yields multiple partitioning threshold values, such as the 6MWD in my tree models. Such variables will be assigned a higher relative importance because they differentiate groups in multiple circumstances (132). Thus, the variables with the highest relative variable importance are likely to be closely linked to the occurrence of 30-day complications (Supplemental Table 2) and, consequently factors that have particular value in defining successful MP. Moreover, the cutpoints for these important variables are biologically-plausible and consistent with known threshold values associated with risks of post-operative complications following colorectal surgery (170, 178).

In addition to indicating variable importance, these patient profiles also associate risk estimates to a set of variables instead of to individual ones. In doing so, they present multiple and varied pathways towards favorable post-operative outcomes. While these profiles remain exploratory and hypothesis-generating, they could still be used as a starting point for defining successful MP prior to elective colorectal surgery. They could also offer clinically-relevant and actionable information to guide optimisation efforts since they emphasize factors that are modifiable during a course of MP.

4.1 Potentially Important Constructs of Successful Multimodal Prehabilitation

Within these profiles, five important constructs with a significant discriminatory capability were identified: functional capacity, nutritional status, oxygen transport, adequate milieu for insulin sensitivity, and patient adherence to the MP program. I will discuss how findings from these two classification tree models compare with current knowledge and how they may contribute to defining successful MP for colorectal surgery.

4.1.1 Functional Capacity

In both baseline and post-MP classification trees, functional capacity has been identified as a fundamental construct that differentiates those with 30-day complication risk from those without. Specifically, the 6MWD and the SF-36 PFI, indicators of functional capacity, were the most important differentiating factors in these models and lend support to functional capacity as a fundamental element in surgical resilience and a key construct associated with successful MP (186). High functional capacity is critical in maintaining long-term physical independence and avoiding subsequent disability (187-190). Increased functional capacity implies being able to adapt and to reestablish homeostasis after exposure to a wide range of stressors including surgical stress (15). As such, it is biologically plausible that high functional capacity could protect against 30-day complications after elective colorectal cancer resection. Previous MP studies have demonstrated the critical importance of functional capacity in influencing the quality of surgical recovery and suggested it as a marker of surgical resilience (50). In these early studies, improvement in 6MWD was a marker for recovery of walking capacity 8-weeks after surgery (27, 37, 114, 115, 138, 141, 145, 191-193). In addition to improved post-surgical functional recovery, this study links functional capacity to decreased 30-day complication risk, adding another dimension to this association.

The threshold values for the variables identified in this study are comparable with other threshold values associated with good functional performance and lowered complication risks. In this study, 6MWD of ≥519 m and ≥487 m were the values associated with avoiding complications. Among METS trial participants who had mild or no postoperative complications, the mean 6MWD was 477 meters (177). These values fall between the upper and lower estimates of 6MWD that correlate with AT ≥ 11 ml/kg^{-1} min^{-1} and VO_2 peak ≥ 15 ml/kg^{-1} min^{-1} (178).

The thresholds are also greater than the 6MWD > 432 m that is needed to cross a four-lane intersection during a green light (gait speed of 1.2 m/s) (194), implying that necessary resilience towards the stress of colorectal surgery is likely to be greater than the level of physical fitness allowing one to easily cross a major intersection. Similarly, this study suggests that targeting a > 400-meter threshold to avoid increased postoperative complications among non-prehabilitated (160, 161, 186) and frail patients who underwent MP (186) may not be sufficient. This disparity emphasizes that avoiding high-risk criteria does not necessarily equate to better outcomes, and that a higher level of physical functioning may be more indicative of the resilience needed to tolerate the stress of colorectal cancer surgery.

Of note, this study also identified two minimal 6MWD thresholds: < 314 m and < 255 m, below which participants had very high risks of 30-day complications. These distances are comparable to threshold values in other studies that indicate high operative risk. For reference, a 6MWD value of 288 m corresponds with a minimal gait speed of 0.8 m/s necessary to cross a two-lane intersection during a green light (194). A 6MWD < 269 m is the lower bound of the range found to correspond to a VO_2 AT < 8 ml/ kg^{-1} min^{-1}, indicating very high risk of postoperative complications (178). For these participants with significantly reduced functional capacity, achieving successful MP is likely to require modified or alternative interventions than those described in this study.

4.1.2 Adequate Nutritional State

In addition to functional capacity, adequate nutritional state is another construct likely to be a foundation for successful MP. In this study, a PG-SGA < 3 at baseline partitioned patients into a subgroup with a significantly lowered risk of 30-day complications (6.2%) (95% CI [1.1%, 28.3%]). This suggests that well-nourished participants are more likely to undergo successful MP since malnutrition is known to modify both MP-associated walking capacity gains and surgical outcomes (104). Gillis et al observed that MP participants with a PG-SGA ≥ 9 (critical need for nutritional intervention) experienced functional impairments that impeded MP exercise component adherence despite improvements in their mood and perceptions of general health. These impairments resulted in lower self-reported physical activity levels, weight loss, and muscle mass losses during MP (104). Nutritional status is also an independent factor protective against major 30-day complications among non-prehabilitated patients undergoing gastrointestinal cancer resections. A recent prospective, international cohort study (n = 5709, colorectal (80.5%) and gastric (19.5%)) showed severe malnutrition increased the odds of 30-day postoperative mortality (166). In sum, adequate nutritional state is likely to be fundamental to successful MP since metabolic reserves are critical both for resilience to the anabolic exercise stressors during MP and the catabolic stressor of surgery.

4.1.3 Adequate Oxygen Transport

The construct of oxygen transport, which is measured in this study with serum hemoglobin concentrations, also emerged as an important classifier. The threshold value > 138 g/L associated with successful MP is also consistent with published definitions of optimal pre-operative hemoglobin concentrations. Anemia is a well-known independent risk factor not only associated with increased 30-day mortality and morbidity (167, 170-172, 195), but also compromises physical functioning. Penninx et al found that the higher the serum Hb above WHO anemia criteria the better the hand-grip strength and physical functioning test scores. In addition, a negative correlation was seen with decreasing serum Hb below the threshold for anemia among 1008 community-dwelling adults aged ≥ 65 years (196). Anemia symptoms have been observed to impede effective participation in MP, with exertional dyspnea and fatigue decreasing physical activity and exercise tolerance. Fatigue and oral iron supplementation also impact oral intake by suppressing appetite, increasing nausea and constipation. Thus, a hemoglobin-replete state is likely to be a significant contributing element to successful MP that can build increased surgical resilience.

4.1.4 Adequate Milieu for Insulin Sensitivity

Evidence of insulin sensitivity (HbA1c ≤ 6.15%) in the presence of adequate muscle mass at baseline emerged as ancillary components of successful MP, suggesting that these predictors together may provide a milieu supporting anabolic stimuli and enabling gains during MP. However, this HbA1c threshold is exploratory since it is not clear whether it could represent a suitable target for optimisation in the pre-operative period. Unfortunately, the optimal pre-operative HbA1c targets for surgical cohorts are unknown (197), and the HbA1c threshold identified in this study is lower than recommended treatment targets. The 6.15% threshold value found in this study may have been influenced by the lower prevalence of long-standing diabetes in the study sample (18.3%), compared to an estimated 20.8-33.6% prevalence among various surgical populations (130, 198, 199). As such, the threshold associated with successful MP requires further examination, especially for patients with type 2 diabetes in whom lower HbA1c targets may be associated with harm. For example, the ACCORD randomized control trial found that a target HbA1c < 6.0% was associated with increased all-cause mortality within 5 years (Hazard Ratio (HR) 1.22; 95% CI, 1.01-1.46) (200). In contrast, an earlier trial similar in size and follow-up period showed benefit with an HbA1c < 6.4% (HR 0.9; 95% CI, 0.82-0.98) (201). While a lower bound of HbA1c has yet to be determined in surgical populations, an HbA1c > 8.0% has been associated with increased risk of mortality in both surgical (202) and non-surgical patients (200, 203) and could represent an upper limit to the range of possible HbA1c targets for MP interventions. Regardless of the exact HbA1c threshold value, this study suggests that insulin sensitivity is among protective factors against 30-day complications after colorectal surgery.

Adequate muscle mass allows for greater insulin-mediated glucose disposal and decreases postoperative complication risk, (73) thereby also contributing to successful MP. Since muscle mass contains the body's amino acid "reserves," a sufficient basal quantity suggested by an FFMI ≥ 18.1 kg/m^2 in men and ≥ 16.0 kg/m^2 in women is likely to be a pre-condition for effective MP. As Gillis et al observed with severely malnourished (PG-SGA ≥ 9) patients, an MP program, which was primarily aerobic exercise-based, may exceed available physiologic reserves and result in deterioration (104). Similarly, in the postoperative period, insufficient skeletal muscle negatively impacts physical function (204) and malnutrition decreases wound healing and immune function (205, 206), impairing necessary repair processes in the postoperative period. The lack of muscle mass also exacerbates postoperative catabolism by contributing to perioperative insulin resistance (71, 207). As such, successful MP is likely to require more fat-free mass than the Global Leadership Initiative on Malnutrition consensus definitions for reduced muscle mass in the context of diagnosing malnutrition (females: < 15 kg/m^2, males: < 17 kg/m^2) (63, 146). This once again highlights that thresholds for success during MP are likely to be higher than those required for avoiding high risk of adverse outcomes.

4.1.5 Adequate Program Adherence

Finally, this study suggests that patient adherence is likely to be among the significant determinants of successful MP and proposes revised target durations for MP prior to elective CRC resections. Instead of a 4-week minimal duration, the post-MP tree proposes an optimal ≥41-

day MP program length and alternative shorter durations (30-40 days, 22 ± 6 days) depending on the type of exercise supervision.

This longer duration may be preferable since it may increase resilience to a level associated with avoiding complications rather than recovery of walking capacity. The 7-week duration also aligns with kinesiology literature describing significant gains from aerobic exercise (beginning at 4 weeks and peaking at 6 to 8 weeks) (180-182) and resistance training (8 weeks) (208). Prior MP studies based their program durations on the time in which participants increased their physical activity levels (137). This duration was adopted in several subsequent MP studies (106, 133, 144). Guidelines for pre-operative exercise training also recommend a minimum of 4 weeks, but with an unclear rationale (209).

This study also proposes that shorter MP durations may also be associated with success provided adequate patient adherence. Unsupervised exercise with a shorter duration (22 ± 6 days) and supervised exercise for 30-40 days both offered the possibility of lowered 30-day complication risks among those with moderately decreased physical functioning at MP completion. In both scenarios, patients may have attained an adequate exercise volume to avoid complications. Exercise volume is the product of the physical activity intensity measured in terms of metabolic equivalents of task ("METs") and the time spent performing the activity in minutes (179). This validated measure of exercise stimulus has been studied as a risk factor for metabolic, oncologic, and cardiovascular disease (210, 211), and provides a means to compare the intensity of various physical activities. In the case of the self-directed exercise group, exercise volume (intensity x time) could have been achieved through increased time at the expense of intensity. Notably, the detailed activity log that participants kept and shared with study investigators may have motivated increased adherence to their programs. Conversely, the supervised exercise group may have exercised with sufficient intensity over a shorter time span. These participants received 1 to 3 sessions of supervised moderate to high-intensity exercise per week according to study protocols, with unclear volumes of unmonitored exercise or rest between sessions.

In this manner, the construct of exercise volume could be used to explain how both approaches ultimately resulted in lowered 30-day postoperative complication risk and could be associated with successful MP. A meta-analysis comparing the efficacy of supervised and unsupervised exercise among the elderly found that in general, supervised training results in greater physical gains (increased mean walking distances, balance, and gait speed), while unsupervised exercise is associated with increased program participation and adherence (183-185), supporting the idea that both intensity and time are critical aspects for MP success.

4.2 An Analogy Representing Surgical Recovery

In the process of exploring how prehabilitation may contribute to avoiding postoperative complications in this thesis, I discovered multiple exciting areas of research that investigate the relationship between patient factors, postoperative recovery, and risk of complications. I present an analogy illustrating how insufficient patient resilience for a given surgical stress may underlie the development of postoperative complications. In this analogy, the patient is represented as a wire spring while the surgery is represented by an ice block. When the ice block is dropped on the spring, the block compresses and stresses the spring. This situation is analogous to a patient who receives a surgical insult and whose overall health is reduced by the physiological stress induced by surgery. Over time, the ice block melts and its impact on the spring attenuates, allowing the spring to regain its original configuration. Similarly, the impact of the surgical insult diminishes as the patient heals, allowing the patient to resume their original level of functioning and health. The interaction of the ice block and the spring is dynamic and is context-sensitive, analogous to a given patient's recovery trajectory after a given surgery.

4.2.1 The Wire Spring: Patient Resilience to Surgery

The first element of this analogy is the spring which represents patient resilience to surgery. Surgical resilience is a dynamic construct that addresses a patient's ability to withstand, adapt, and ultimately restore a new steady state when challenged by a negative or adverse stressor such as surgery (44, 51). Similarly, a wire spring is dynamic and has its ability to withstand, adapt, and arrive at a new steady state when loaded. A wire spring is a complex entity with at least 11 specifications influencing its rebound ability under stress. Likewise, a patient is also a complex entity with physiologic factors such as functional capacity, oxygen transport, metabolic reserve/flexibility, mental resilience/flexibility, immune system regulation (pro- vs anti-inflammation), endocrine system (HPA) regulation, and socioeconomic and environmental determinants. These 'specifications' likely influence a patient's ability to 'rebound' after surgery.

Thus, the spring can be an apt representation of a patient undergoing surgery since both spring and patient performance under stress is a function of multiple factors interacting in a complex manner.

4.2.2 The Ice Block: Surgical Insult and Response

The second element in this system is an ice block, a representation of the surgical insult and stress response. An ice block can place a significant and dynamic load on a wire spring, just as surgery will be a significant stressor for a patient. The size of the ice block represents the expected magnitude of surgical stress, enlarging with greater tissue perturbation and surgical risks (40). In the same way that a larger ice block melts away over a longer period, the more complex and extensive the surgical procedure, the longer the expected recovery time. Moreover, the behaviour of the ice block is context-sensitive. For example, the melting rate for the ice block can be modified through factors external to the ice-block-and-wire-spring system, in the same way that surgical stress can be intensified or mitigated by contextual factors. For example, ambient heat applied to the ice block accelerates the spring's recovery to baseline by making the ice block melt away faster, in the same way enhanced recovery pathways 'melt' away surgical stressors by preventing hypercatabolic processes. Conversely, added insulation around the ice block prevents melting and prolongs the stress applied to the spring just as prolonged fasting or inadequate analgesia impede recovery by exacerbating surgical stress.

4.2.3 Dynamic Interaction

When a patient undergoes surgery, their initial health decline is most pronounced in the same way that a spring reaches its minimal height from the ice block compression. The subsequent behaviour after the initial loading represents the various recovery trajectories described after surgery (14, 212, 213). When the spring rebounds quickly to its original height because it had enough structural integrity to support the load or because the ice block was small or melted rapidly, it describes a patient experiencing an uncomplicated and complete recovery trajectory. In contrast, when the spring breaks on initial loading, postoperative mortality has occurred. Intermediate scenarios include where the spring rebounds slowly or partially, with residual deformations that weaken the spring and increase its risk of failure on subsequent loadings. The ice block might also not melt away, becoming a constant stressor which permanently compresses the spring into a new, weaker configuration. All these intermediate scenarios represent postoperative morbidity, disability, and dependency.

When conceptualized in this way, the figures that have been drawn to describe a surgical recovery trajectory look like a graph of a spring's height over time after being loaded:

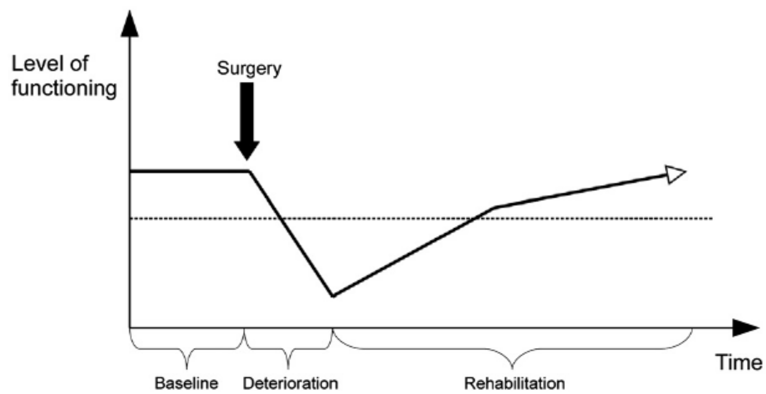
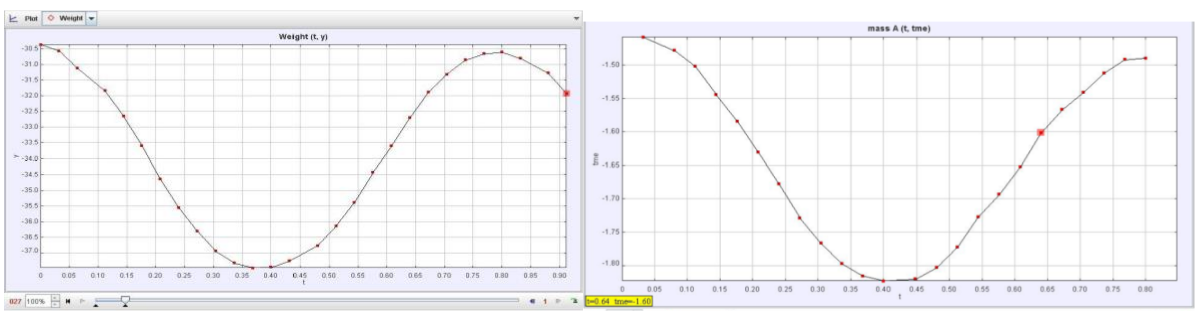


Fig 1. Expected trajectory of recovery. The *dotted line* represents the minimum level of functioning.

Expected Trajectory of Surgical Recovery from Lee et al. (214)



Variation of a Spring's Vertical Position (Left) and Total Mechanical Energy (Right) over Time During Loading (215)

4.2.4 Beyond Resilience: Hormesis and Anti-Fragility

In this analogy, MP could be represented by a conditioning or tempering process which strengthens the spring with cyclic applications. When a system demonstrates an adaptive response to a disruption in homeostasis that simultaneously enhances its ability to adapt and withstand a more severe disruption, the system is described as exhibiting 'hormesis' (216) or 'antifragility' (217). Both these terms describe a dynamic process where a system not only becomes more resistant to shocks but also exhibits growth and adaptation to *increase resilience* itself (217). While antifragility is a younger concept, first coined in 2012 (218), 'hormesis' has been described and investigate in biological systems since 1943 (219). Indeed, hormesis has been described in multiple diverse fields (220-222) and is also defined by a biphasic dose-response relationship to a given stressor, where low doses are likely to have beneficial or stimulatory effects and high doses, detrimental or inhibitory effects (223). In this study, a potentially hormetic dose-response to MP was suggested by the post-MP classification tree where patients with insufficient or excessive exercise volume were both associated with increased risk of adverse outcomes.

Studying MP as a hormetic and antifragile process may be advantageous because this approach may guide the design or identification of metrics that measure dynamic constructs such as resilience and recovery. Critical information such as the optimal dosing of each component or measures of recovery after stress could be useful response indicators for MP participants that could be used to predict potential patient recovery trajectories during surgical stress. Among the various approaches used to assess these constructs, stress testing and tracking performance metrics over time may be applicable in prehabilitation. Perioperative physicians may already be assessing hormesis and antifragility in patients by stress testing—CPET—to stratify patients for postoperative complication risk. By applying an incremental stress, the dynamic changes in system performance or recovery capacity are quantified. The second approach, measuring rates of change, growth, progression, or recovery in response to a testing stressor, may also capture hormesis or antifragility of a patient undergoing MP. Instead of using thresholds of linear measures such as distance or time, thresholds of dynamic measures such as rates could prove more useful and relevant for assessing the capacity for recovery or decline after surgery. An MP participant is a complex and dynamic system that demonstrates hormetic and antifragile characteristics. Future research could explore how these constructs could be adapted for the perioperative context and could yield new metrics for evaluating success in multimodal prehabilitation.

4.3 Study Strengths and Unique Features

This study's unique strengths are its choice of outcome, analysis, and relevance to prehabilitated patients undergoing surgery. The chosen outcome associated with 'successful' MP in this study is the avoidance of 30-day complications, which contrasts with previous perioperative literature that identified factors linked to increased risk of complications after elective colorectal surgery (32). This study's results are a preliminary attempt to describe desirable, rather than undesirable, profiles of MP participants and to propose optimisation targets that may lower 30-day complication risk rather than identify merely the opposite of high-risk features.

In addition to choosing a positive outcome, an analysis that clustered variables was deemed more appropriate for addressing the complexity in the MP intervention (98). Identifying important combinations of variables is 'patient-centered' instead of 'variable-centered', and reflects real-world situations where variables are not observed to occur in isolation. This approach has been used in 'successful aging' literature, (127, 128) in which Rowe and Kahn defined successful aging as "multidimensional, encompassing the avoidance of disease and disability, the maintenance of high physical and cognitive function, and sustained engagement in social and productive activities" (224). My definition of successful MP was inspired by this definition of successful aging, since the same elements are also found in definitions of successful surgical recovery in surgical outcomes literature (214, 225). Additional strength of this study is the selection of actionable predictor variables for inclusion in these models. Instead of identifying red-flag features that are unlikely to be modified by MP, my analysis provides information that orients optimization efforts towards areas that can be improved.

Finally, our study sample consists exclusively of MP participants, which makes our findings specifically relevant to populations undergoing this intervention. As demonstrated by recent reviews of prehabilitation literature (96, 102), pooling the effects of all prehabilitation trials, both uni- and multimodal, generates information that may not be applicable to populations specifically undergoing MP. Most importantly, the profiles obtained in this study can be seen as preliminary and valid guidance for MP, contributing to a sounder basis for clinical decisions than applying analogous information derived from non-prehabilitated or non-surgical populations.

4.4 Study Limitations and Improvements

In this study, the validity of our findings is limited by potential information bias, tree instability, sampling bias, and limited generalisability due to data from a single center. First, the information bias in my study, as defined by the Center for Evidence Based Medicine Catalogue of

Bias (226), arises from heterogeneous data collection, handling, and recording methods in the primary trials. Key definitions of MP exposures and the measures for these exposures varied and introduced missing data. As a result, the effects of certain constructs could not be assessed in my analysis since the measurement variables were not standardized across all studies. I was also limited by the variables selected for use in the primary studies, which may have introduced imprecision in measuring the key constructs explored in my study. For example, assessing muscle mass in this study used the proxy of BIA-determined fat-free mass instead of using the gold-standard method of computed tomography. This information bias results in inaccurate estimations of effect, which may explain the wide 95% confidence intervals around some estimates of 30-day complication risk. To avoid information bias, a follow-up study should define a priori the key exposures and outcomes to study, the measurement strategies for these variables, and the methods to reduce missing such as multiple imputation by chained equations.

Second, a limitation of the RPA analysis is the instability of classification trees. Instability refers to changes in the splitting variables and the position of the cut points that results if changes occur in the distribution of observations from one sample to another (227). Ensemble learning methods such as random forest methodology can be a solution for such instability, thus increasing the reliability and internal validity of tree models. Random forest methods generate multiple trees and use them to produce an 'averaged' tree to improve accuracy and produce models that are more robust against noise (228).

Third, sampling bias (229) may be present in my study since participants who were enrolled in these research studies may differ systematically from the population of patients awaiting elective colorectal surgery, impacting the generalizability of my findings. Patients who volunteered to participate in these trials may already be predisposed to benefit from MP. In fact, the belief that exercise could positively influence post-colorectal surgical outcomes has been found to increase the likelihood of recovering walking capacity (37). As a result, validation of the findings of my tree models would require a more pragmatic recruitment process that includes MP participants who were asked to participate in MP as a pre-requisite for surgery.

The external validity of my findings is also limited because it represents a single-center experience administering one concept of MP. The MP delivered in the primary studies is specialist-tier MP–hospital-based, specialist-delivered, and developed specifically in the McGill concept of MP. Three levels of MP, 'universal', 'targeted', and 'specialist' (212), are organized along a pyramidal framework adapted from the Health Impact Pyramid for public health interventions (230), widely adopted in other disciplines. In this framework, the base of the pyramid represents MP requiring the least individualized resources to deliver and reaching the broadest segments of society with the greatest impact on public health, hence 'universal'. The intermediate level of the pyramid is 'targeted' MP, a level requiring increased resources to address specific optimisation issues such as diabetes or coronary artery disease. The apex, or 'specialized' MP, targets those with complex and severe acute conditions that significantly impair functional capacity and impact surgical recovery (212, 231), requiring specialized expertise.

Since this type of MP may not necessarily be feasible in other contexts, the generalizability of my findings should be limited to this model of MP. Because MP is a complex intervention with multiple components, precisely defining prehabilitation interventions in future studies is critical for future research and for applicability of study findings to specific MP tiers. Moreover, since recovery after surgery is hypothesized to be determined not only by patient resilience but also by the magnitude of the surgical stress, this definition of 'successful MP' is relevant only to elective colorectal surgery and could change depending on the type of surgery.

4.5 Study Implications and Impact

As the eminent statistician Dr. George Box states in his paper about robustness in scientific model building, "All models are wrong, but some are useful" (232). My objective in this study was to offer a probably wrong, but useful and stimulating exploratory model of what characterizes successful MP for elective colorectal surgery. It is important to highlight that these patient profiles and their associated risks of postoperative complications do not provide information on the magnitude of the prehabilitation effect. These patient profiles are, foremost, descriptions of MP participants who are likely to have favourable surgical recoveries, not subgroups in which prehabilitation has the greatest impact. This study was not designed to determine effect sizes associated with MP, but estimating effect size and treatment effect heterogeneity would be important future directions for MP research. As such, the profiles have the greatest value as signposts or benchmarks for progress or for stratifying the level of MP intervention. They also contribute to the Triple Aims for improved health care by enhancing patient experience and population health while increasing value for per capita cost (233).

4.5.1 Improved Patient Experience

These profiles contribute to improving patient experience during MP by presenting clusters of patient characteristics that are associated with lowered risk of post-operative complications. Each profile is also associated with quantified risk estimates that can be compared to the cohort average or any other relevant profile in the tree model. Given that some patients perceive MP as an added burden during a time of illness, these criteria may provide a rationale and manageable goals that can increase patient understanding and motivation during the program (234). The profiles from this study can also be used to structure MP program goals along the SMART goal-setting framework for personal development. This framework suggests that enumerating specific, measurable, actionable, relevant, and time-bound elements in a goal can increase the likelihood of reaching it (157, 158). With precise targets, personalized MP can be more effective. Finally, this study's profiles can be used to flag patients who have completed successful MP to surgical teams, prioritizing those who are ready to undergo colorectal resection with a high likelihood of avoiding 30-day complications. These definitions of successful MP place uncomplicated and meaningful patient recovery after colorectal surgery at the forefront for the patient and MP care team.

4.5.2 Improved Population Health

In general, MP can positively impact population health by reducing the significant disease burden from postoperative complications and empowering patients towards harm reduction during the salient health moment prior to surgery. More specifically, the profiles of successful MP presented in this study contribute to achieving this aim by proposing criteria that may facilitate triaging patients to the different tiers of MP intervention, thereby increasing efficient resource allocation and access to MP. Given that postoperative complications are the third leading cause of mortality globally, increasing access to MP could be an effective public health measure to decrease this burden of disease (235). By triaging patients to different levels of MP based on objective profiles of need, resource allocation for each level can be improved.

Currently, suggestions for criteria that triage to levels of nutrition prehabilitation exist for patients undergoing oncologic surgery (231), but none have been proposed for MP levels in preparation for elective colorectal surgery. As a result, the profiles in this study could be a basis for creating such preliminary triage criteria. For example, universal MP could be offered to patients with low risk profile 1 (SF-36 PFI ≥ 56 and 6MWD ≥ 519 m). Alternatively, patients with high-risk profiles could use this information in their shared decision-making process for surgery.

Finally, increasing access to MP may have a wider impact on population health by providing an opportunity to adopt harm-reducing health behaviours during a salient health moment. Given that every year, 4% of the world's population is expected to undergo surgery (235), these MP-enabled harm reduction behaviours could eventually diffuse into the larger population and improve public health. Ultimately, defining triage criteria for MP levels improves population health by matching patient needs to MP resources and increasing its overall positive impact in society.

4.5.3 Increased Per Capita Value

Defining successful MP also increases the value of surgical care by investing in the best outcomes for the patient. Value in health care is defined as the costs incurred to produce the best health outcomes for the patient (236). Knowing when a patient has successfully undergone MP increases the likelihood of desirable surgical outcomes and decreases costs related to postoperative complications and unplanned health care utilisation. Conceptually, when a patient fits a profile for successful MP, harmonizing the date for surgery with the occurrence of optimal patient resilience would make an ideal scenario for minimizing costs of surgical complications. In so doing, the preoperative investment of resources and energy during MP would be most likely to yield favourable returns in the postoperative period. This harmonization could minimize costs to the patient such as time off work, lost productivity, and loss of quality of life. This reasoning aligns with cost calculation across an entire trajectory of care rather than per intervention (236), a key concept underlying value-based, high-quality health interventions.

Furthermore, with definitions of successful MP, it would be possible to investigate the costs of performing elective non-oncologic surgery in patients who do not meet such criteria for surgical 'readiness'. Doing so could potentially decrease wastage and increase efficiency in the surgical care trajectory. For oncologic surgery, clear criteria for successful MP could enhance the shared decision-making process for surgical interventions, helping patients consider the value of surgery within the context of their global care trajectory.

Overall, the information contained within the profiles from this study can increase the value of colorectal surgery for all stakeholders. By incorporating patient-defined readiness criteria into the decision-making process for surgery, surgical teams can augment the likelihood of best outcomes.

4.6 Future Directions

With increasing numbers of patients receiving MP, I envision that refining proposed definitions of successful MP, examining MP treatment effect heterogeneity, and clarifying the economic value of MP are three very pertinent and exciting directions for future research.

A prospective study that refines and validates these preliminary definitions of successful MP for CRC must be done. A classification tree analysis on a larger cohort of MP participants with pre-defined, consistent measures and predictors to improve data quality, will likely generate more robust and stable tree models. The resultant profiles could then form the basis for subsequent development of a surgical resilience score to quantify readiness for elective colorectal surgery among prehabilitated patients. This surgical resilience score may yield more precise risk estimates, greater resolution, and personalization of priorities for MP optimisation prior to colorectal surgery. With this process defined, successful MP for other surgical specialties, such as lung cancer, could also be conceived. With definitions of successful MP available for several populations, a subsequent study could examine which influential components are universal or surgery-specific. By honing in on the fundamental components of successful MP, our understanding of this complex intervention improves and facilitates implementation for all stakeholders in a broader range of settings.

Second, performing studies that examine treatment effect variations are critical for personalizing MP interventions and facilitating broader implementation across varying contexts, ultimately improving MP effectiveness and accessibility. The profiles described in this study could inform a priori subgroup definitions for primary and secondary analyses in future RCTs. With the presence of a control group and defined subgroup analyses, the magnitude of heterogenous treatment effects associated with MP can be investigated with the modeling approaches proposed in the Predictive Approaches to Treatment effect Heterogeneity (PATH) Statement (237).

Finally, studies examining the economic value of MP are urgently needed to help decision-makers invest resources to upscale MP programs. At this early stage, integrating economic questions into MP research is timely and advantageous (108). Specifically, a priority is to define the units of value and cost for the MP context that is consistent with value-based principles. Instead of evaluating the value of MP with current fragmented paradigms, newer and broader evaluation methods such as cost-benefit or cost-consequence analysis are recommended (108). These approaches are likely to yield more accurate information on the true value of MP and align with Porter and Teisberg's concept of value-based health care (236, 238). The collaboration and expertise of health economists will be invaluable at this early stage to ensure that MP can evolve along value-based health care principles, making it an intervention that is economically-viable, sustainable, and beneficial on a large scale.

5. Conclusion

My objective was to delineate, at two points of the multimodal prehabilitation trajectory, profiles of patients who underwent MP and benefitted from an important reduction in 30-day complication risk following elective colorectal surgery performed at the Montreal General Hospital, an ERAS-compliant surgical center, between 2012 and 2021. The eight profiles described in this thesis represent groups that were successful in lowering their 30-day complication risk ≥10% and proposes key elements for this definition of successful MP. These key constructs include functional capacity, oxygen transport, metabolic milieu favouring anabolism, and program adherence and exercise volume. The two classification tree models also rank these key constructs by importance, propose associations between them, assign quantitative risk estimates, and describe multiple avenues for avoiding 30-day complications. While preliminary, these findings are also biologically-plausible, consistent with observations, novel, and stimulate further research.

This study was also conducted using approaches that consider multimodal prehabilitation as a complex intervention, so that it could generate useful information applicable to the human at the center of it all, the patient. Since MP is a complex intervention, the choice to use classification trees reflects an intent to move beyond variable-centered methodology towards a patient-centered one. Studying MP using frameworks for complex interventions will require shifts in study design and analysis paradigms that may be unfamiliar. Nonetheless, in their guidance document for complex intervention research, Skivington et al exhorted the research community to "include methods and perspectives where experience is still quite limited, but [...] there is an urgent need to make progress. This endeavour will involve mainstreaming new methods that are not yet widely used, as well as undertaking methodological innovation and development" (108).

For me, this thesis represents the pinnacle of my professional career, a journey that has stimulated not only my growth as an academic, but also as an anesthesiologist and as a person. To finish this masters' thesis, I learned not only about prehabilitation science and the skills to conduct high-quality research, but also to analyze data in R, and to juggle the needs of my family, of my patients, and of my well-being. This thesis has instilled a profound respect for the systematic research methods that are critical for meaningful inquiry. It has laid a sound foundation and kindled a desire to continue academic research. Most of all, it has inspired a deep gratitude for the work of the research community that is universally imbued with a desire to serve science with excellence, to collaborate with curiosity and openness, and to drive towards disruptive progress in hopes of making the world a better place.

This journey has strengthened my conviction that multimodal prehabilitation has the potential to transform surgical care. By increasing resilience to surgical stress through MP, we may contribute to lowering the risks of morbidity and mortality after major elective surgery for many. I dare to believe that in 1962, if Sir Ronald A. Fisher had undergone MP, his outcome after CRC resection would have been different.

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