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Is preoperative physical function testing predictive of length of stay in patients with colorectal cancer? A Retrospective study

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Is preoperative physical function testing predictive of length of stay in patients with colorectal cancer? A Retrospective study

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Résumé

La chirurgie est le traitement principal du cancer colorectal (CCR). Une durée d'hospitalisation prolongée peut augmenter le risque de complications et d'inactivité physique, entraînant un déclin de la fonction physique. L'objectif de cette étude est de déterminer si la celle-ci peut prédire l'hospitalisation prolongée chez les patients atteints de CCR.

Un total de 459 patients provenant de 7 cohortes a été analysé. Une régression logistique a été utilisée pour déterminer le risque d'hospitalisation prolongée (>3 jours) et une courbe ROC a été tracée pour établir la sensibilité/spécificité. Les variables sélectionnées comprenaient l'âge, le sexe, l'IMC, la présence de comorbidités, le statut ASA, le site tumoral, l'approche chirurgicale, la force de préhension, le test Timed-Up and Go, le test assis-debout de 30 secondes, le test de flexion des coudes de 30 secondes, le test de marche de 6 minutes (6MWT), le questionnaire CHAMPS et le SF-36.

Les résultats démontrent que les patients atteints d'une tumeur rectale ont un risque 2,7 fois plus élevé d'appartenir au groupe d'hospitalisation prolongée que ceux atteints d'une tumeur du côlon (O.R. 2,7 ; C.I. 1,3-5,7, p=0,01). Pour chaque augmentation de 20 mètres dans le 6MWT, il y a une diminution de 9% du risque d'être dans le groupe d'hospitalisation prolongée (C.I. 1.03-1.17, p=0.00). Un seuil de 431 m peut prédire 70% des patients dans le groupe d'hospitalisation prolongée (AUC 0,71, C.I. 0,63-0,78, p=0,00). L'utilisation du 6MWT comme outil de dépistage de l'hospitalisation prolongée devrait être intégrée dans le parcours chirurgical préopératoire.
Mots-clés : fonction physique, cancer colorectal, durée de séjour prolongée

Abstract

Surgery is the primary treatment for colorectal cancer. A prolonged Length of Stay (pLOS) can increase risk of complications and physical inactivity, leading to a decline in physical function. While promising results were seen from preoperative exercise training and post-operative functional recovery, the predictive potential of preoperative physical function has not yet been investigated. The objective of this study is to determine if preoperative physical function can predict pLOS in patients with for colorectal cancer.

A total of 459 patients from 7 cohorts were analyzed. Logistic regression was used to determine risk of pLOS (>3 days), and ROC curve was plotted to establish sensitivity/specificity. Selected variables included age, sex, BMI, comorbidity, ASA status, tumor site, surgical approach, handgrip strength, Timed-Up and Go, 30-second Sit-to-Stand, 30-second Arm Curl Test, 6-Minute-Walking Test (6MWT), CHAMPS Physical Activity Questionnaire for Older Adult and 36-Item Short Form Survey.

The results showed that patients with rectal tumor are 2.7x more at risk to be in the pLOS group compared to those with colon tumor (O.R. 2.7; C.I. 1.3-5.7, *p=0.01*). For every increment of 20 meters in 6MWT, there is a decreased risk of 9% of being in pLOS group (C.I. 1.03-1.17, *p=0.00*). A cut-off of 431m can predict 70% of patients in pLOS group (AUC 0.71 C.I 0.63-0.78, *p=0.00*). Tumor site (rectal) and 6MWT were significant predictors of pLOS. Using the 6MWT as a screening tool for pLOS with cut-off of 431 m should be implemented in the preoperative surgical pathway.
Keywords: physical function, colorectal cancer, prolonged length of stay

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Abbreviations

6MWD 6-minute walking test distance
6MWT 6-minute walking test
ACT 30-second arm curl test
ASA American Society of Anesthesiologists
ASHT American Society of Hand Therapists
ATS American Thoracic Society
CDC Center of Disease Prevention
CHAMPS Community Healthy Activities Model Program for Seniors
CPET Cardiopulmonary exercise test
CRC Colorectal cancer
ERAS Enhanced Recovery After Surgery
ERP Enhanced recovery programs
HGS Hand grip strength
HIIT High Intensity Interval Training
iLOS Ideal length of stay
IQR Interquartile range
JGH Jewish General Hospital
LOS Length of stay
MGH Montreal General Hospital
MICT Moderate Intensity Continuous Training
MP Multimodal Prehabilitation
NCI National Cancer Institute
OACIS Open Architecture Clinical Information System
OR Odds ratio
pLOS Prolonged length of stay
Prehab Prehabilitation
QOL Quality of Life
ROC Receiver Operating Characteristic
SD Standard deviation
SF-36 36-Item Short Form Survey
STS 30-second sit-to-stand
TNM Classification for Malignant Tumors
TUG Timed-up-and-Go
UICC Union for International Cancer Control
VO_2peak Maximum rate of oxygen consumption measured during incremental exercise

Chapter 1: Introduction

The following section will cover the epidemiology of colorectal cancer as well an overview of its diagnosis, tumor staging, and treatment. Prolonged length of stay and its predictors reported in literature will then be discussed. In order to understand the nature of physical function testing, a description of each test included in this study will be presented. The objectives of this study will also be described.

1.1. Colorectal cancer

This section will discuss : 1) the epidemiological data of colorectal cancer, 2) details on diagnosis and Cancer Staging, 3) the treatment and 4) length of stay following colorectal cancer surgery.

1.1.2. Epidemiology

Colorectal cancer (CRC) is leading as the second most common cancer in Canada (Brenner et al., 2019). Higher incidence rates have been seen in developed countries, notably in Northern Europe, Australia, North America and East-Asia, while lower rates were observed in most developing countries in Africa and South-East Asia (Bray et al., 2018). This phenomenon can be attributed by a country's socioeconomic development as incidence rates increase concomitantly with rising Human Development Index (Bray & Soerjomataram, 2015). Currently, CRC is a prevalent cause of cancer-related mortality in Western countries (Kuipers et al., 2015). While a decreased prevalence of CRC diagnoses in older adults has been observed, recent studies have shown an increasing incidence in Canadian adults under 50 years old (Brenner et al., 2017). Despite having improved screening and diagnosing practices, clinicians are concerned about the likelihood of poor lifestyle factors being at the root of the heightened risk in this younger age group (Arnold et al., 2017). Sedentarism is a significant modifiable risk factor of CRC. Studies have shown a protective association between physical activity and CRC (Shaw et al., 2018), while physical inactivity increased the risk of disease development by 50% (Rawla, Sunkara, & Barsouk, 2019). Insufficient exercise can lead to obesity, which can disrupt the gut microbiome causing irritation and inflammation of the lining of the large intestine (Jahani-Sherafat, Alebouyeh, Moghim, Ahmadi Amoli, & Ghasemian-Safaei, 2018; Watson & Collins, 2011). With adipose tissue being the most inflammatory tissue of the body, obesity can be a contributor to other types of cancer for its tumor-promoting cytokine production and metabolic disturbance (Lengyel, Makowski, DiGiovanni, & Kolonin, 2018). A poor diet is also a strong contributor to obesity, exacerbating carcinogenesis. Irrespective of obesity, studies have shown the influence of nutrition on CRC. A high consumption of red and processed meat increases risk of its development (Chan et al., 2011). Evidence show increased incidence in patients with low intake of fiber, whole grains and calcium. Adequate consumption of these substances are believed to improve gut motility and microbiota, thereby reducing intestinal exposure to carcinogens (Holscher, 2017). Additionally, alcohol consumption has been seen to be associated with CRC. A moderate to elevated intake increases risk of CRC development by 20% for individuals drinking 2-3 servings per day and 40% for three servings and more (Bagnardi et al., 2015; Rawla et al., 2019). Active and former smokers also are at heightened risk of CRC incidence and mortality. More specifically, there is a significant association between smoking duration and rectal cancer

(Liang, Chen, & Giovannucci, 2009). While modifiable factors are known to be associated with CRC diagnosis , many non-modifiable variables can largely contribute to individual risk. Increasing age poses higher risk, with 90% of cases and deaths occurring after the age of 50 years old (Keum & Giovannucci, 2019). Most medical screenings for the disease generally occur at that age. With the emerging shift in the prevalence of CRC in a younger age group, improved screening tools should be in place. Family history is a well-known contributor to the disease and is estimated to be involved in 30% of all cases (Lichtenstein et al., 2000). Males are 1.5 times more at risk of CRC compared to females and have a higher mortality rate (Bray et al., 2018; White et al., 2018). The proportion of male CRC diagnoses is especially higher after the age of 50 (Keum & Giovannucci, 2019). There are sex-specific differences in the development of this type of cancer, which warrants different clinical screening pathways. There is some evidence that races and ethnicities are associated with higher risk and prevalence. The Center of Disease Prevention (CDC) and the National Cancer Institute (NCI) showed a greater incidence in the black community and lower incidence in communities with Asian or Pacific Islander backgrounds. The same trends were seen with death rates (Centers for Disease Control and Prevention, 2017). It has been speculated that genetic factors could be involved in this racial disparity. While different patterns of incidence have been seen through ethnic and racial groups, a Canadian study shows poor accessibility to proper healthcare in ethnic and racial minority groups compared to their non-minority counterparts, which can lead to an untimely cancer screening. This study therefore highlights the social implication of risk of disease development (S. & Shahid, 2012)

1.1.3. Diagnosis and Cancer Staging

Well-known symptoms of CRC include disruption in bowel habits, bowel obstruction, and bloody stools (Kuipers et al., 2015). Whether the patient presents with symptoms or not, screening for CRC in Quebec begins at 50 years old, which corresponds to the recommended target age by the Canadian Task force on Preventative Health Care (Canadian Task Force on Preventative Health Care, 2016; Health Quebec, 2017). Asymptomatic patients are considered at low risk of CRC. Screening is performed through the immunochemical fecal occult blood test (iFOBT), a laboratory test to detect blood in a stool sample. As it does not indicate the presence of cancer, a physician can perform a colonoscopy to examine the large intestine and search for potential anomalies. Colonoscopies are the gold standard for diagnosis and are recommended for individuals presenting with active symptoms.

The Classification for Malignant Tumors (TNM) is globally used by oncology health care professionals to categorize extent of cancer development. Established by the Union for International Cancer Control (UICC), the TNM refers to the tumor (T), lymph node (N), and metastasis (M) (Brierley, 2016). Each category is further classified into subcategories. T describes extent of tumor invasion in the colorectal tissue. T1 indicates tumor location in the lamina propria, the innermost layer of the bowel. T2 indicates a tumor invasion in the following layer, the muscularis propria. T3 describes a tumor growth through the muscularis propria, into the surrounding tissues. There are two stages in T4, where T4a describes tumor penetration to the surface of the visceral peritoneum, and T4b indicates growth through the bowel wall, into organs in situ (National Collaborating Centre for Cancer, 2011). The N category refers to the involvement of regional lymph nodes in the cancer. N0 means there is no lymph involvement. N1a means one regional lymph node is affected by the cancer. N1b means two or three nearby lymph nodes are affected by the cancer. N1c indicates presence of non-cancerous tumor deposits in the subserosa, or the mesentery. N2 is divided into 2 stages. N2a indicates invasion of four or more regional lymph nodes, and N2b indicates invasion in seven or more. The M category describes whether the cancer has metastasized. M0 indicates no metastasis. M1 is indicative of distant metastasis (invasion of distant organs such as the lung or liver). M1a is used to describe metastasis to one distant site or organ. M1b means the cancer has spread to 2 or more distant sites or organs or the peritoneum (Obrocea, Sajin, Marinescu, & Stoica, 2011). Prognosis and survival vary depending on the individual, with tumor staging being the strongest prognostic factor. Earlier detection of the disease and lower staging are indicative of a better outcome for the patient.

1.1.4. Treatment

CRC treatment is dependent on tumor stage. Non-metastatic CRC is mainly treated through surgery, during which the malignant section of the bowel is resected. In the past three decades, remarkable strides in research and technology has led to the development of minimally invasive surgical techniques (Abu Gazala & Wexner, 2017). Approaches such as laparoscopic resection has been proven to be equal or better than traditional open surgery. In patients with more advanced cancer stage, other options including chemotherapy, radiotherapy and neo-adjuvant therapy can be suggested by the oncological team. In order to optimize treatment outcome, research has shown the importance of action plans based on the assessment of the physiological age, the patient's life expectancy, and tolerance to treatment (Millan et al., 2015). With surgery being the primary course of treatment for CRC (Millan et al., 2015), enhanced recovery programs (ERP) are implemented to optimize perioperative care with the objective to facilitate patient recovery after surgery. Also known as fast-track surgery pathways, ERPs focus on patient-centered care by providing specific interventions to minimize perioperative physiological stress (Lohsiriwat, 2014). The Enhanced Recovery After Surgery (ERAS) society is an organization that aims to develop ERPs for various types of surgery through the implementation of evidence-based practices. Founded in 1999, more than 100 institutions in 20 countries are implementing the ERAS guidelines, with the Montreal General Hospital of the McGill University Health Center being one of the few centers of excellence in the world (Enhanced Recovery after Surgery). The first ERAS guidelines pertaining to colorectal cancer was published in 2012 and has been updated over time to follow current evidence-based practices. The pre-admission recommendations include patient education and counselling, optimization (comorbidity assessment, smoking cessation, avoiding alcohol abuse), prehabilitation (multimodal optimization of functional capacity), malnutrition screening, and anemia management (Gustafsson et al., 2019). The ERAS guidelines suggest pre-operative recommendations pertaining to vomiting and nausea prevention, premedication, prophylactic antibiotics, bowel preparation, fluid and electrolyte therapy, and carbohydrate loading. Intraoperative recommendations related to anesthetic protocol, fluid and electrolyte therapy, hypothermia prevention, minimally invasive surgery, and drainage of peritoneal cavity and pelvis are addressed. Finally, post-operative recommendations include details on nasogastric intubation, analgesia, thromboprophylaxis, fluid and electrolyte therapy, management of urinary output and drainage, hyperglycemia prevention, prevention of ileus and proper nutrition, and early mobilization. The aforementioned recommendations accelerate recovery by minimizing perioperative physiological stress, maintain postoperative physical function and decrease hospital length of stay (LOS) (Gustafsson et al., 2019).

1.1.5. Length of Stay in CRC

LOS is a surgical outcome that is an indicator of efficiency of health care. A prolonged LOS can lead to an increased mental and socio-economic burden on patient, in addition to raising costs of healthcare resources (Leung, Gibbons, & Vu, 2009). Identifying patients who are at risk of a prolonged LOS (pLOS) is imperative to determine the variables that might need to be preoperatively adjusted and optimized. Studies have been conducted to identify predictors of a delayed discharge. Some socio-demographic factors have been reported as significant predictors. Evidence shows increasing risk of pLOS with increasing age (Faiz et al., 2011; Feroci et al., 2013; Kelly, Sharp, Dwane, Kelleher, & Comber, 2012). Other studies show that the male sex appears to be at increased risk compared to the female sex. Vlug et al., (2012) found that LOS could be reduced by 15% if the patient was female (Vlug et al., 2012). A greater body mass index (BMI) has been reported to be a greater risk factor. According to Poelemeijer et al., (2018), a BMI higher than 30 kg/m^2 is predictive of a LOS of over 14 days (Poelemeijer et al., 2018). Some studies highlighted the social factors, such as marital status and social deprivation, as important predictors. Compared to patients who were married, non-married individuals were at higher risk of pLOS (Faiz et al., 2011; Kelly et al., 2012). Some factors on patient preoperative status were also reported. Presence of comorbidities is an important risk factor of pLOS (Dekker et al., 2012; Faiz et al., 2011; Keller, Bankwitz, Nobel, & Delaney, 2014; Kelly et al., 2012; Leung et al., 2009). Leung et al., (2009) identified the presence of coronary artery disease to be a predictor of pLOS in CRC surgery. A high American Society of Anesthesiologist (ASA) physical status grade has also been seen to predict pLOS. The ASA is a 5-point classification system to evaluate patient general fitness for surgery, with a score of 1 representing a healthy patient, and 6 being declared brain-dead. A lower ASA grade could have protective effects to pLOS (Ahmed, Lim, Khan, McNaught, & Macfie, 2010; Dekker et al., 2012; Feroci et al., 2013). Some studies identified oncological surgery variables as predictors. Faiz and collaborators identified tumor pathology as a predictor. A patient with a malignant tumor increases risk of pLOS compared to a benign tumor (Faiz et al., 2011). Tumor site was also found to be a significant predictor, where rectal tumors were seen to be associated with pLOS compared to colon tumors (Aravani et al., 2016; Faiz et al., 2011; Hendry et al., 2009; Kelly et al., 2012). The surgical approach can influence the outcome of the surgery thereby increasing LOS. The laparoscopic technique is a minimally invasive technique that seems to decrease pLOS. Studies have shown that the open approach is a significant risk factor (Faiz et al., 2011; Vlug et al., 2012). Other surgical variables including resection site (distal vs. proximal) (Faiz et al., 2011), surgical duration (Chand et al., 2016; Keller et al., 2014), and ileostomy creation (Feroci et al., 2013) have been identified as risk factors for LOS. A study by Galas and colleagues revealed that a preoperative inflammatory diet is a predictor of pLOS (Galas, Kulig, & Kulig, 2014). Finally, a brief use of epidurals and an avoidance of oral opiates (Ahmed et al., 2010) have been seen to predict pLOS as well.

A prolonged hospital stay increases risk of complications and the consequences of physical inactivity. Post-operative hospitalization is usually characterized by extended periods of bed rest and sedentarity, leading to a loss of muscle mass and physical function (Meesters, Conijn, Vermeulen, & Vliet Vlieland, 2019). Increased physical activity was found to decrease LOS (Abeles, Kwasnicki, Pettengell, Murphy, & Darzi, 2017). Due to these risk factors, studies have stressed the importance of targeting colorectal cancer patients for multimodal prehabilitation (MP) (Carli & Scheede-Bergdahl, 2015). There is a growing interest in MP, aims to increase functional capacity in patients awaiting for surgery by focusing on the optimization of modifiable risk factors (Carli et al., 2010). Its main components include exercise conditioning, nutritional counselling, and relaxation therapy. A prehabilitation assessment serves to identify impairments in order to tailor multimodal interventions to the patient to build up a physiological reserve to sustain the stress of surgery and to enhance recovery (Figure 1) . While promising results were seen from research on preoperative exercise training and post-operative functional recovery (Li et al., 2013), the predictive potential of physical function testing has not yet been investigated. Additional research is warranted to determine preoperative strategies to estimate LOS in patients waiting for CRC surgery. Physical function testing is time efficient, inexpensive and reliable methods to assess patient fitness but have not yet been studied as potential predictors of LOS.

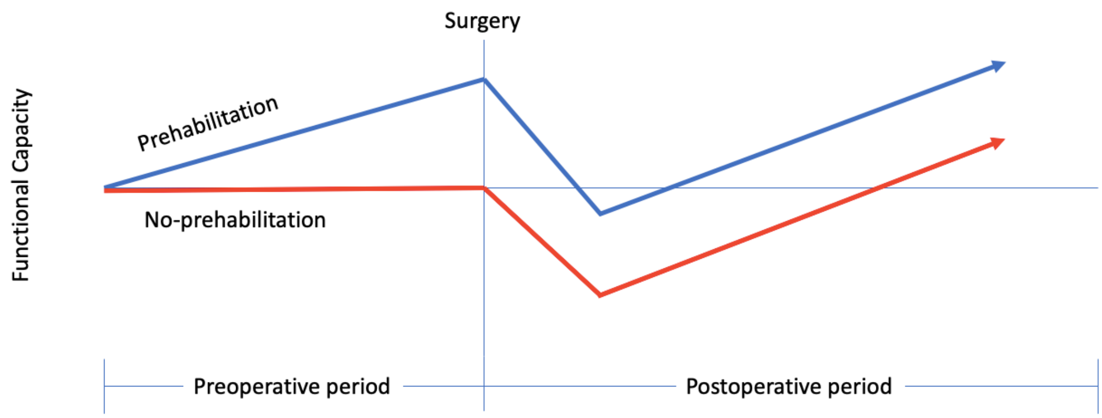


Figure 1. - Concept of prehabilitation (Carli & Zavorsky, 2005)

1.2. Physical function tests

The following section will present information pertaining to physical function tests and their validity and reliability. The discussed tests include the 6-minute walking test, the 30-second arm curl test, the 30-second sit-to-stand test, the hang grip strength test, the Community Healthy Activities Model Program for Seniors questionnaire, and the 36-Item Short-Form Health Survey.

1.2.1. The 6-Minute Walking Test

Designed to evaluate specific areas of function and performance, many physical function tests have been developed and validated in the field of exercise science. Test selection is to the discretion of the clinician. Developed by the American Thoracic Society (ATS), the 6-Minute Walking Test (6MWT) is a submaximal self-paced test that evaluates functional capacity while providing an objective measurement of performance (American Thoracics Society, 2002).

Despite having been developed for patients with respiratory impairments, it has been seen to be clinically valid and reliable across different populations. A hallway of 30 meters is required and the distance delimitated by two cones. The patient is instructed to walk back and forth as fast as they can around the cones for 6 minutes. The result is recorded by calculating the total distance (m) that a patient can briskly walk in a period of 6 minutes, during which they can dictate when to slow down or stop during the test, if needed. In order to ensure test reliability, the ATS strongly recommends that clinicians use the standardized patient instruction script and encouragements that was published to standardize the test (American Thoracics Society, 2002). Other words of encouragements are discouraged. The 6MWT is a validated exercise test to assess functional capacity. Studies have shown construct validity through correlations between 6MWT distance (6MWD) and peak oxygen uptake (VO_2peak) in different populations. In patients with CRC, a higher 6MWD correlated with a higher VO_2peak (r=0.67; 0.70) (Schmidt, Vogt, Thiel, Jäger, & Banzer, 2013). Another study supports the validity of the 6MWT as a measure of post-operative surgical recovery in CRC (Moriello, Mayo, Feldman, & Carli, 2008). A reliability analysis conducted by Rikli and Jones (1998) showed high correlation between three trials in older adults (r=0.88;0.97) (Rikli & Jones, 1998). The 6MWT showed excellent test-retest reliability (ICC 0.97, 95% CI 0.94–0.98) in patients with pulmonary fibrosis (Bloem et al., 2017).

1.2.2. The Timed-up and Go

The Timed-up and Go (TUG) is a balance, speed and agility test developed to be conducted in the geriatric population. The set up consists of placing a chair and a cone 3 meters apart. With the patient starting in a seated position, they are instructed to stand up from the chair, walk 3 meters, turn around the cone, return to the chair, and sit down (Podsiadlo & Richardson, 1991). This sequence is timed, with a shorter time representing a better functional performance. Construct validity has been evaluated by testing TUG scores against different components of balance, speed and agility, where correlation was found to be strong (gait speed [r=-0.61], Barthel Index [r=−.78], Berg Balance scale [r=-0.81]) (Podsiadlo & Richardson, 1991). Excellent inter- and intra-rater reliability was reported (ICC 0.98, ICC 0.99 respectively) (Podsiadlo & Richardson, 1991). Test-retest reliability in older adults has been reported to be high (ICC 0.96 [CI 95%, 0.91–0.98]) (Mangione et al., 2010).

1.2.3. The 30-second Arm Curl Test

The 30-second Arm Curl Test (ACT) is an assessment of upper extremity strength. While holding a dumbbell from a seated position, the patient is to perform as many bicep curls as possible during 30 seconds. The proper technique is instructed. The test is scored by counting the number of repetitions performed during the assigned time while maintaining proper form. Inadequately performed bicep curls are not counted (Rikli & Jones, 1999). Construct validity was tested by analyzing correlation between ACT and upper extremity strength (1RM bicep curl, chest press, seated row) where a moderate to good correlation was seen (r=0.81 in men, r=0.78 in women) (Rikli & Jones, 1999). Good test-retest reliability has been reported (ICC 0.78, CI 95% -3.1-2.8) (Boneth et al., 2012).

1.2.4. The 30-second Sit-to-Stand Test

The 30-second Sit-to-Stand Test (STS) is an assessment of lower limb strength. From a seated position with the knees positioned at 90 degrees, the patient is asked to perform as many stands as possible during 30 seconds. The score is the total amount of repetitions performed during the assigned time. The clinician is to ensure that the test is performed with proper form. Inadequate stands are not counted (Rikli & Jones, 1999). Construct validity was tested by conducting correlation analysis between STS score and leg-press performance. A correlation of 0.78 has been observed for men and 0.71 in women. This supports that the STS is a valid assessment for lower body strength (Rikli & Jones, 1999). Test-retest reliability for this test is good (ICC= 0,78 [CI 95% -3,8-3,2] (Boneth et al., 2012).

1.2.5. The Hand Grip Strength Test

The hand grip strength Test (HGS) measures maximal isometric force generation of the forearm and is widely used to assess overall strength (G. F. Hamilton, McDonald, & Chenier, 1992). Studies have shown that lower HGS is associated with a higher prevalence of physical disability and frailty (Syddall, Cooper, Martin, Briggs, & Aihie Sayer, 2003). HGS is assessed by using a hand dynamometer, a device that is adjustable for different hand sizes. The Jamar Hydraulic hand dynamometer is most commonly used in clinical settings as it is recommended by the American Society for Surgery of the Hand and the American Society of Hand Therapists (ASHT). The device's hand spacings must be adjusted at the appropriate size as per recommended standardized ASHT positioning. The seated patient is instructed to position the elbow at a flexion of 90 degrees and to squeeze the dynamometer as hard as they can (G. F. Hamilton et al., 1992). It is recommended to perform the test three times and to use the mean score as the final result (A. Hamilton, Balnave, & Adams, 1994). HGS is correlated with muscle mass (r =0.60) (Kallman, Plato, & Tobin, 1990) and total muscle strength (r=0.70-0.90) (Wind, Takken, Helders, & Engelbert, 2010). It is important to note that once adjusted for bodyweight, correlation significantly decreased (r=0.50-0.60). The Jamar hand dynamometer was found to be highly reliable (ICC [0.98) and valid (ICC 0.99) for measuring hand grip strength (Bellace, Healy, Besser, Byron, & Hohman, 2000). Excellent intra- and interrater reliability (r>0.80) and test-retest reliability (ICC > 0.9) have been reported (Gerodimos, 2012; A. Hamilton et al., 1994; Wind et al., 2010). Evidence shows that HGS outperforms chronological age as a marker of frailty, although its validity is to be tested.

1.2.6. The Community Healthy Activities Model Program for Seniors Questionnaire

The Community Healthy Activities Model Program for Seniors (CHAMPS) is a self-reported questionnaire assessing weekly frequency and duration of physical activity (PA). This 41-item questionnaire covers different activities at different intensities (light, moderate and vigorous) and estimates total caloric expenditure per kilogram per week. (Stewart et al., 2001). A total weekly caloric expenditure can be analyzed by observing total PA or by PA intensities (Stewart et al., 2001). Evidence shows that the CHAMPS was able to identify participants who were inactive, somewhat active, and active ($p = 0.001$), thereby showing good group discrimination validity. Construct validity was tested in a study by Harada et. al. (2001). A correlation’s analysis was performed with the CHAMPS, lower extremity function and endurance tests and the Mini-

Logger activity monitor data from ankle and waist sensors. Correlation scores with the CHAMPS varied between 0.44 to 0.68 for the physical tests and 0.36-0.59 for the ankle sensors and 0.42-0.61 at the waist sensors (Harada, Chiu, King, & Stewart, 2001). Higher validity coefficients were found for in older men (65-74 years old) which suggests that the CHAMPS may have greater validity in the older adult population. Evidence shows that this self-reported questionnaire provides adequate test-retest reliability in older adults (ICC 0.56-0.70), but suggests that potential overestimation of some CHAMPS items poses a bias in this assessment tool (Hekler et al., 2012).

1.2.7. The Medical Outcomes Study36-Item Short-Form Health Survey

The Medical Outcomes Study (MOS) 36-Item Short-Form Health Survey (SF36) is a self-reported questionnaire assessing quality of life (QOL) measures (Stewart, Hays, & Ware, 1988). Consisting of 36 questions, it covers eight subscales of health: physical functioning, role of limitations due to physical impairments, role of limitations due to emotional impairments, vitality, emotional well-being, social functioning, pain and general health (Ware & Sherbourne, 1992). Each of these sub-categories are assessed on a 0 to 100 scale. Two total scores summarize the physical and mental components of the questionnaire. A high score in any of the subscales or total scores is indicative of a better QOL. Correlation's analysis of health measures in the short-form and long-form measures from previous research was performed. All correlations were statistically significant and were greater than 0.80 (Stewart et al., 1988). The questionnaire produced good internal consistency reliability (Cronbach alpha = 0.87) (Ware & Sherbourne, 1992). Validity of the physical function score of the SF36 was seen through significant correlations between other physical function performance tests including single limb stance time (r = 0.42), TUG (r = −0.70), and gait speed (r = 0.75) (Bohannon & DePasquale, 2010).

1.3. Objectives

While these tests are normally conducted to determine physical performance, it is not known whether they can be a predictive parameter of LOS in CRC.

The objective of this study is to determine if preoperative physical function can predict pLOS patients with CRC. For each significant predictor, a cut-off value is to be established to identify patients with increasing risk of a pLOS.

Chapter 2: Methods

In the following section, the surgical subjects will be described, from their diagnosis and recruitment to their surgery. Details pertaining to the different cohorts included in this study will be discussed. The study design and statistical analyses will then be presented.

2.1. Subjects

A reanalysis of the data extracted from one cohort study and six randomized controlled trials (including one that is undergoing) from 2011 to 2020 was performed. Approval was obtained for all trials from the Research Ethics Board of the McGill University Health Centre, Montreal, Quebec, Canada, and study procedures were executed in accordance with ethical standards. Data was retrospectively collected from studies conducted at the Peri-Operative Program's prehabilitation clinic of the Montreal General Hospital. Adult patients undergoing non-metastatic elective colorectal cancer surgery were included. Patients with linguistic barrier to English or French and/or who had medical conditions that contraindicated exercise were excluded.

2.2. Pathway: From diagnosis to surgery

Following an initial clinical visit with a surgeon, newly diagnosed CRC patients were referred to the Peri Operative Program for enrollment in a multimodal cancer prehabilitation study. This patient-centered preoperative approach that can yield significant functional benefits in the CRC population including improved functional capacity (Chen et al., 2017), nutritional status (Gillis et al., 2018), mental status (Barrett-Bernstein et al., 2019), and improved QOL (Carli & Scheede-Bergdahl, 2015; Li et al., 2013).

Once consent was obtained in eligible patients, an intervention began with participants randomized into the prehabilitation (prehab) or no prehab groups until their surgery date. Patients assigned to the no-prehab group received standard of care. The prehab group received preoperative MP interventions of aerobic and resistance exercises, nutritional counseling with protein supplementation, and anxiety-reducing strategies. Some of the trials differentiate in the exercise component of the design. The studies included in this re-analysis are summarized below (Table 1). The Gillis et al. (2014) and Bousquet-Dion et al. (2018) studies included 77 and 80 participants respectively, randomized with a ratio of 1:1. The prehab group received a home-based intervention of moderate aerobic and resistance exercises in addition to the nutritional counseling and anxiety-reducing strategies. Exercise training was performed 3x/week from home (Bousquet-Dion et al., 2018; Gillis et al., 2014). All 20 patients from the Barrett-Bernstein (2019) study received the same MP intervention (Barrett-Bernstein et al., 2019), this time with 1x/week supervised training and 2x/week home-based training. In the Schram et al. (2019) study, all 20 participants did not receive MP (Schram et al., 2019). This cohort received a no-prehab intervention for early mobilization post-surgery. The Minnella et al.(2020) study followed the same previously described MP model, with modifications in the exercise program. The 42 participants were randomized in the high-intensity interval training (HIIT) group, or moderate intensity continuous training (MICT) group with a 1:1 ratio. Patients were required to attend 2x/week supervised training, during which they would follow their respective aerobic trainings and complete a standardized moderate resistance program. Aerobic intensity was prescribed by performing a Cardiopulmonary Exercise Test (CPET) to assess their anaerobic threshold (VO_2at) and maximal oxygen consumption (VO_2peak). The HIIT group performed 4 bouts of 2 minutes at 80-90% of their VO_2peak while the MICT group at 80-90% of their VO_2at (Minnella et al., 2020). The Carli et al., (2020) study included 120 patients randomized with a 1:1 ratio. The prehab group received 1x/week supervised training, 2x/week home-based training in addition to the standard nutrition supplementation and anxiety-strategies (Carli et al., 2020). The van Rooijen et al. (ongoing) study followed an exercise regimen of 3x/week supervised HIIT training, defined at 4 bouts of 3 minutes at 80-90% of VO_2peak. Prehab patients also received nutritional counselling with protein supplementation and anxiety-reducing therapy (van Rooijen et al., 2019). The 6MWT, HGS, STS, ACT, TUG, CHAMPS, and the SF36 were conducted in every trial, with the exception of the STS, ACT and TUG in the Gillis et al. (2014) study, and the ACT and SF36 in the Bousquet-Dion et al. (2018) study. As per the institutional protocol, all patients were treated within the standardized Enhanced Recovery After Surgery (ERAS) care pathway implemented at the Montreal General Hospital (MGH) since 2008 and at the Sir Mortimer B. Davis Jewish General Hospital (JGH) since 2015. This enhanced recovery pathway includes multimodal perioperative techniques to decrease physiological stress, minimize loss of postoperative physical function and reduce rates of prolonged LOS and morbidity related to colorectal surgery (Gustafsson et al., 2019).

Table 1. - Prehabilitation Trials included in reanalysis.

							Intervention			Assessment tests						
							Aerobic		Resistance							
	Author and year	**n**	**Title**	**Objective**	**Inclusion Criteria**	**Prehab: No Prehab**	**HIIT**	**MICT**	**Moderate**	**6MWT**	**HGS**	**STS**	**ACT**	**TUG**	**CHAMPS**	**SF36**
1.	Gillis et al. (2014)	77	Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer.	To quantify the effect of a 4-week trimodal prehabilitation on pre- and postoperative functional walking capacity	Inclusion: adult patients with awaiting elective surgery for non-metastatic CRC. Exclusion: (1) illiteracy in English or French (2) presence of premorbid conditions contraindicating exercise.	1:1		x	x	x	x				x	x
2.	Bousquet-Dion et al. (2018)	80	Evaluation of supervised multimodal prehabilitation program in cancer patients undergoing colorectal resection: a randomized control trial.	To determine whether a weekly supervised exercise session could provide further benefit to currently implemented prehabilitation program, when comparing to standard post-surgical rehabilitation.		1:1		x	x	x	x	x		x	x	
3.	Schram et al (2019)	20	In-hospital resistance training to encourage early mobilization for enhanced recovery programs after colorectal cancer surgery: A feasibility study.	To investigate the feasibility of initiating resistance exercise to promote early mobilization in colorectal cancer patients during the in-hospital period.		0:1				x	x	x	x	x	x	x
4.	Barret-Bernstein et al (2019)	20	Depression and functional status in colorectal cancer patients awaiting surgery: Impact of a multimodal prehabilitation program.	To assess differences in physical performance (self-reported) and functional capacity (performance-based) and explore the impact of prehabilitation on functional capacity in individuals with depressive symptoms versus those without.		1:0		x	x	x	x	x	x	x	x	x
5.	Minnella et al. (2020)	44	Effect of two different pre-operative exercise training regimens before colorectal surgery on functional capacity: A randomized controlled trial	To compare peri-operative functional trajectory in response to two different exercise training protocols within a 4-week, supervised, multimodal prehabilitation program.		1:0	x	x	x	x	x	x	x	x	x	x
6.	Carli et al. (2020)	110	Effect of Multimodal Prehabilitation vs Postoperative Rehabilitation on 30-Day Postoperative Complications for Frail Patients Undergoing Resection of Colorectal Cancer: A Randomized Clinical Trial.	To assess the extent to which a prehabilitation program affects 30-day postoperative complications in frail patients undergoing colorectal cancer resection compared with postoperative rehabilitation.	Inclusion: frail adult patients with awaiting elective surgery for non-metastatic CRC. Exclusion: (1) a Fried Frailty Index score of 1, (2) illiteracy in English or French (3) presence of premorbid conditions contraindicating exercise.	1:1		x	x	x	x	x	x	x	x	x
7.	Van Rooijen et al. (undergoing)	120	Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and reduce postoperative complications: The first international randomized controlled trial for multimodal prehabilitation	To determine the impact of multimodal prehabilitation on patients' functional capacity and postoperative complications.	Inclusion: adult patients with awaiting elective surgery for non-metastatic CRC. Exclusion: (1) chronic renal failure (dialysis or creatinine > 250 mmol) (2) ASA score 4 or higher (3) illiteracy in English or French (4) presence of premorbid conditions contraindicating exercise	1:1	x		x	x	x	x	x	x	x	x

2.3. Data collection and management

Individual databases from the trials summarized in Table 1 were merged into a master database. Data selection included patient demographics, medical history, surgical data, baseline physical performance test and questionnaire scores, and duration of post-operative LOS. All data of patients with metastatic cancer, benign polyps, or who dropped out from the studies were deleted as they did not meet the inclusion criteria. Data cleaning was performed to remove incorrectly formatted datapoints and to delete duplicates. Missing data was corrected by consulting the original physical copies of patient files or by referring to the electronic patient file through the Open Architecture Clinical Information System (OACIS), the medical data system used at the MGH and the JGH. If the missing data was not found, it was left blank.

2.4. Study Design

To enable us to determine predictors for a prolonged LOS, median LOS was calculated. Patients with a LOS above the median were classified into the prolonged LOS (pLOS) group, while those with a length of stay equal or below the median were classified into the ideal length of stay group (iLOS). Independent variables to predict pLOS were firstly selected based on a prior literature review and data availability. These variables included age (Faiz et al., 2011; Feroci et al., 2013; Kelly et al., 2012), sex (Vlug et al., 2012), BMI (Poelemeijer et al., 2018), comorbidity (Charlson Comorbidity score) (Dekker et al., 2012; Faiz et al., 2011; Keller et al., 2014; Kelly et al., 2012; Leung et al., 2009), ASA status (Dekker et al., 2012; Feroci et al., 2013; S. & Shahid, 2012), tumor site (colon or rectal) and surgical approach (open or laparoscopic surgery) (Ahmed et al., 2010; Faiz et al., 2011; Kelly et al., 2012; Leung et al., 2009; Orive et al., 2019; Poelemeijer et al., 2018; Vlug et al., 2012). Several physical function tests and questionnaires performed at the Peri Operative Program upon first visit were also analyzed: hand grip strength (proxy of overall strength), Timed-Up and Go (TUG was previously defined) (evaluation of balance and agility), 30 second Sit-To-Stand (measurement of lower extremity strength), 30 second Arm Curl Test (measurement of upper extremity strength), 6-minute-walking test (evaluation of functional capacity), CHAMPS Physical Activity Questionnaire for Older Adult (measurement of physical activity frequency and caloric expenditure) and 36-Item Short Form Survey (self-perceived QOL). These tests are recognized for their validity and reliability and can be easily performed with minimal equipment and proper training (American Thoracics Society, 2002; G. F. Hamilton et al., 1992; Jones, Rikli, & Beam, 1999; Podsiadlo & Richardson, 1991; Rikli & Jones, 1999; Stewart et al., 2001; Ware & Sherbourne, 1992). The intervention of prehabilitation was additionally included as a variable for its potential effect on LOS.

2.5. Statistical analyses

A statistician from Université de Montréal was consulted to determine the appropriate statistical methodology for the purpose of this study. Descriptive statistics were calculated for the demographic variables and compared between the pLOS and iLOS groups. Analysis of physical function tests was also conducted to compare performance between the pLOS and iLOS groups. Normality of data was testing by using the Shapiro-Wilk test. Continuous data with normal distribution were reported as mean ± standard deviation (SD) and compared using independent Student t-test. Continuous data with non-normal distribution were reported as median (interquartile range [IQR]) and compared using Mann-Whitney U test. Categorical variables were reported as frequency (%) and compared using the Chi-squared test.

A binary logistic regression was performed to determine if the known predictors from literature and the physical test variables were predictors of pLOS. Odd ratios (OR) were interpreted to determine the risk factor of each identified predictor. Statistical significance was defined as p-value less than 0.05. For each identified predictor, the prediction model was validated by plotting a Receiver Operating Characteristic (ROC) curve analysis. The Area Under the Curve (AUC) was calculated to summarize the performance of a screening test and its predictive accuracy. The AUC ranges between 0 and 1, where 0.5 is equivalent no discrimination (or a discrimination equal to chance) and 1 is a perfect discrimination (Hanley & McNeil, 1982). Therefore, the larger the AUC, the stronger its discrimination capacity. Cut-off point predicting pLOS were identified. The sensitivity and specificity for the latter were presented. All data were analyzed using IBM® SPSS® Statistics 26.0.

Chapter 3: Results

The present section will compare iLOS and pLOS demographic data. Our sample consisted of 459 adult patients with non-metastatic colorectal cancer awaiting for surgery. For any missing data point from the variables included in the analysis, the entire list-wise case was entirely excluded from the model. A total of 183 patients were therefore included in the analysis. Data on patient physical testing performance in both groups will also be presented. Results from the statistical analyses pertaining to predictors of pLOS and cut-off values will be discussed.

3.1. Patient Demographics

A total of 459 adult patients with non-metastatic colorectal cancer awaiting for surgery were included in this database. Median LOS was 3 days (IQR 3). All patients were divided into one of two groups, where the iLOS group included subjects with a LOS equal or below 3 days and the pLOS group included those with a LOS of equal or above 4 days. Baseline characteristics are presented in Table 2. Median LOS between groups were significantly different, with the iLOS group at 3(IQR 1) days and the pLOS group at 6 (IQR 5) days (*p=0.00*). Sex and BMI were similar in both groups *(p=0.57*). Patients in the pLOS group were three years older (iLOS 72 [IQR 18]; pLOS 75 [IQR 15], *p=0.03*) and presented with a higher Charlson Comorbidity score, indicative of more comorbidities (iLOS 2 [IQR 1]; pLOS 3 [IQR 2], *p= 0.01*). The pLOS group also had a lower physical status as indicated by an ASA score of greater than 3 (iLOS 32.3%, pLOS 58.3%, *p= 0.00*). In both groups, there was a larger proportion of patients with a colon tumor (iLOS 76.1%, pLOS 61.8%, *p*=0.01). However, the pLOS group presented with a higher incidence of patients awaiting rectal tumor (iLOS 17.2%; pLOS 35.7%, *p=0.01*). Additionally, while the prevalence of laparoscopic surgery was greater than 80% in both groups, there were significantly more patients undergoing open surgery in the pLOS group (*p=0.00).* There were no significant differences in the interventions between groups (*p=0.52*).

Table 2. - Baseline Characteristics of the iLOS and pLOS groups**.**

	iLOS		pLOS		
	N	Data	N	Data	p value
LOS, median (IQR[a])	247	3(1)	212	6(5)	0.00
Age, median (IQR)	247	72 (16)	212	75 (14)	0.03
Male Sex, N (%)	247	140 (56.7)	212	120 (56.6)	0.98
BMI, median (IQR)	246	26.2 (7)	210	27 (7)	0.57
Charlson Comorbidity Index, median (IQR)	163	2 (1)	119	3 (2)	0.01
ASA status, N (%)					
ASA < 3	236	175 (74.2)	211	115 (54.8)	0.00
ASA ≥ 3	236	61 (25.8)		95 (45.2)	
Tumor site, N (%)					
Colon	247	188 (76.1)	212	131 (61.8)	0.01
Rectal	247	59 (23.9)		81 (38.2)	
Surgical Approach, N (%)					
Laparoscopic	245	239 (97.6)	209	172 (82.3)	0.00
Open	245	6 (2.4)		37 (17.7)	
Intervention, N (%)					
Prehabilitation	247	129 (52.2)	212	117 (55.2)	0.52
No prehabilitation	247	118 (47.8)		95 (44.8)	

[a] inter-quartile range

3.2. Physical testing performance

Table 3 compares physical testing performance of patients in iLOS and pLOS groups at their initial visit. Most assessment test results show a significantly greater performance in the iLOS group. More specifically, the 6MWT distance was significantly different between the two groups, with the patients in iLOS having walked a distance of 496 m (IQR 163) while the pLOS group walked less distance with 418 m (IQR 201) (p=0.00). Results show that iLOS patients better executed the TUG with a median time of 6.8 seconds (IQR 2) compared to 11 seconds (IQR 4) in the pLOS group (p=0.02). The ACT showed significantly greater performance in the iLOS group, with 19 executed repetitions (IQR 7) compared to 16 (IQR 7) in the pLOS group (p=0.00). The STS showed similar outcome with 13 repetitions (IQR 6) in the iLOS group and 11 (IQR 5) in the pLOS group (p=0.00). Caloric expenditure per week from physical activity was higher in the iLOS group, resulting in a median of 48.4 (IQR 67) compared to 46 (IQR 77) in the pLOS group (p=0.05). Total SF36 scores we also higher in the iLOS group (76.8 [IQR 26]) compared to the pLOS group (65.5 [IQR 35]) (p= 0.00). In both mental and physical components of the SF36, the iLOS group had significantly better scores than the pLOS group, indicating better mental and physical health (iLOS mental 70.5 (IQR 34) vs pLOS mental 55 (IQR 33), p=0.00 ; iLOS physical 70 (IQR 33), pLOS physical 54.4 (IQR 31), p=0.00). The assessment of HGS was the only test that was not significantly different between the two groups.

3.3. Predictors of pLOS

Binary logistic regression was performed to determine factors predicting pLOS, defined by a LOS greater than 3 days. For any missing data point from the variables included in the analysis, the entire list-wise case was entirely excluded from the model. A total of 183 patients were included in the analysis. Demographic data of this sub-group was similar to the total cohort, as seen in Table 4. Table 5 shows odd ratios (OR) from all the analyses. From the 14 variables included in the model, only two of these were significant predictors of pLOS: the tumor site (rectal) and the 6MWT. The results showed that patients with rectal tumor are 2.7x more at risk to be in the pLOS group compared to those with colon tumor (O.R. 2.69; C.I. 1.27-5.70, p=0.01). As for the 6MWT, it results show that for every increment of 20 meters in the distance walked, there is a decreased risk of 10% of being in pLOS group (C.I. 1.03-1.16, p=0.00). The 6MWT was therefore the only physical function test that can predict pLOS.

Table 3: Median (IQR) Physical Testing Performance of iLOS and pLOS groups at initial visit.

	iLOS	pLOS	p-value
6-Minute Walking Test (meters)	497 (163)	418 (201)	0.00
Timed-up and Go (seconds)	6.8 (2)	11 (4)	0.02
30s Arm Curl test (repetitions)	19 (7)	16 (7)	0.00
30s Sit-to-Stand (repetitions)	13 (6)	11 (5)	0.00
Hand Grip Strength (kg/F)	26.0 (16)	26.2 (13)	0.41
CHAMPS questionnaire (caloric expenditure/week)	48.4 (67)	46 (77)	0.05
SF36 questionnaire (/100)	76.8 (26)	65.5 (35)	0.00
Mental Score	70.5 (34)	55 (33)	0.00
Physical Score	70 (33)	54.4 (31)	0.00

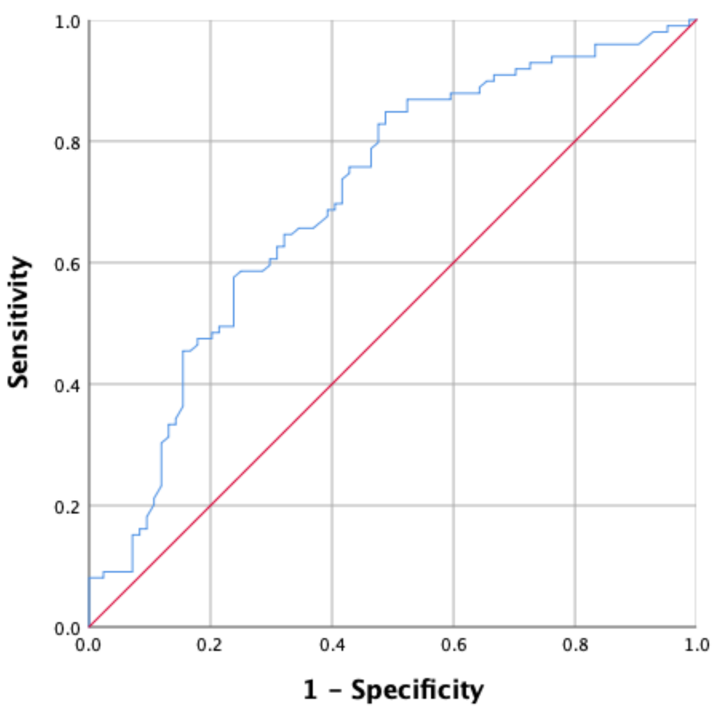
Table 4. - Baseline Characteristics of the sub-cohort of iLOS and pLOS groups					
	iLOS		pLOS		
	N	Data	N	Data	p value
LOS, median (IQR [a])	99	3(1)	84	6(5)	0.00
Age, median (IQR)	99	72 (18)	84	75 (15)	0.03
Male Sex, N (%)	99	51 (51.5)	84	45 (53.6)	0.88
BMI, median (IQR)	99	26 (7)	84	27 (9)	0.71
Charlson Comorbidity Index, median (IQR)	99	2 (1)	84	3 (2)	0.01
ASA status, N (%)					0.00
ASA < 3	99	67 (67.7)	84	35 (41.7)	
ASA ≥ 3	99	32 (32.3)	84	49 (58.3)	
Tumor site, N (%)					0.01
Colon	99	82 (82.8)	84	54 (64.3)	
Rectal	99	17 (17.2)	84	30 (35.7)	
Surgical Approach, N (%)					0.00
Laparoscopic	99	96 (97)	84	69 (82.1)	
Open	99	3 (3)	84	15 (17.9)	
Intervention, N (%)					
Prehabilitation	99	53 (53.5)	84	38 (45.2)	0.30
No prehabilitation	99	46 (46.5)	84	46 (54.8)	

Table 5: Binary Logistic Regression analysis for the prediction of pLOS		
	OR (95% CI)	p-value
Rectal tumor	2.69 (1.27 - 5.70)	0.01
6MWT	1.10 (1.03 - 1.16)	0.00

3.4. Determination of cut-off score for pLOS prediction

In order to determine a cut-off value in the 6MWT, a ROC curve was plotted. Figure 2 shows that the area under the ROC curve (AUC) was 0.71, and the 95% confidence interval (CI) was 0.63–0.78, indicating that the model could effectively identify 71% of patients with pLOS. A cut-off point of the predicted probability of prolonged LOS was identified as 431 m. At this optimal cut-off point, the sensitivity of the ROC classifier was 0.70, and the specificity was 0.61. This shows that a cut-off of 431 m can predict 7 patients on 10 in pLOS.

Figure 2. - Receiver operating characteristic (ROC) curve to evaluate the discrimination of the prediction model.



Area under ROC curve (AUC) = 0.71, (95% CI 0.63–0.78)

Chapter 4: Discussion

The purpose of this thesis was to determine if preoperative physical function tests could predict pLOS in patients with CRC. Patients with a LOS above the median were classified into pLOS group while those patients with a LOS below the median were classified into iLOS group. The overall median LOS was 3 days. Our results showed that tumor site (rectal) and the 6MWT are significant predictors of pLOS. Patients with rectal tumor are predisposed to higher risk of having a pLOS compared to those with colon tumor. This confirms literature findings affirming that patients undergoing rectal cancer surgery are hospitalized for a longer than patients with colon cancer (Aravani et al., 2016; Faiz et al., 2011; Hendry et al., 2009; Kelly et al., 2012). The 6MWT was found to be the only physical function test that demonstrated predictive value, with a lower walking distance indicating increased risk of pLOS. A cut-off of 431 m can be used to effectively identify 71% of patients with pLOS.

In this section, a review on length of stay in CRC surgery in other countries will be compared to our results. Then, all physical function tests included in the prediction model will be discussed to further examine why the 6MWT appeared to be the only significant predictor. Threshold selection of the latter test will also be justified. The pLOS predictors reported in literature will also be addressed to support the possible reasons why all variables were rejected except tumor site (rectal). Finally, the prehabilitation intervention will be discussed to understand why it did not appear to be a predictor of pLOS.

4.1. Length of Stay in other countries

Our literature review show variation in the selected LOS cut-offs from one study to another. While some chose to use the median LOS to define ideal and prolonged LOS groups, others chose the upper limit of the interquartile range. In general, the median LOS in our study appeared to be shorter than what has been reported in literature. With the inclusion criteria being adult patients undergoing non-metastatic elective CRC surgery, the median LOS in our study was 3 days (IQR 3). The implementation of the ERAS perioperative protocols influences the early recovery of patients in our institutions. According to Pecorelli et al. (2017), a high adherence to the ERAS protocols is associated with a LOS of 3 days and less, which further justifies the use of this cut-off in our study (Pecorelli et al., 2017).

Kelly et al. (2012) conducted a similar study in Irish CRC surgery patients. The overall median LOS was 16 days (IQR 14) and included elective and emergent surgeries (Kelly et al., 2012). Median LOS of elective admissions was of 14 days (IQR 9) and 21 days (IQR 18) for emergency admissions. Ireland has a mixed public and private healthcare system and does not have a national standardized system in place to optimize patient outcome. Patients included in their analysis were treated in different public and private institutions, which could have been a source of bias. It is unknown whether or not enhanced recovery programs were implemented in these different hospitals. Compared to our 3-day cut-off in a nation with free access to public healthcare, patient care discrepancy and lack of institutionalized protocols in Ireland might explain why the median LOS was higher compared to our 3-day cut-off.

Another analysis on predictors of LOS performed in the United States found a median LOS of 8 days (IQR 2-71) (Leung et al., 2009). The USA is one of the only developed countries who do not offer universal healthcare to their citizens. Therefore, CRC screening and treatment is not easily accessible to those who do not possess the socioeconomic resources to afford care. This analysis also included both elective and emergent admissions. Emergency resections are known to increase LOS compared to elective procedures. Seeing as low socio-economic individuals are at twice as likely of urgent emergency department visits (Tang, Stein, Hsia, Maselli, & Gonzales, 2010), it is probable that the median LOS in the Leung et al. (2009) study was higher than our study due to the amount of patients undergoing emergency resection.

Some studies reported median LOS in CRC surgical patients from NHS institutions of the United Kingdom. Results from a study by Ahmed et al. (2010) from the Scarborough NHS presented with an overall median LOS of 6 days (IQR 4) in CRC elective surgery. The patients included in this retrospective analysis were treated within the ERAS guidelines (Ahmed et al., 2010). Only those undergoing elective open surgery were included. Compared to the laparoscopic approach, open surgery is known to increase risk of pLOS and other post-operative complications (Faiz et al., 2011; Vlug et al., 2012). This explains why their median is twice as long as the one found in our study. Faiz et al. (2011) conducted a retrospective study across different English NHS Trusts in the last 10 years undergoing elective colorectal surgery. They presented LOS range post-CRC surgery by tumor site: a range 11-14 days for colon procedures and 13-15 for rectal procedures. There was no mention of the implementation of ERAS or any enhanced recovery program in the treatment of the patients. The discrepancy between our study and the Faiz et al. (2011) is likely due to the differences in perioperative management across different centers.

We observed a shorter postoperative LOS (median of 3 days) compared to studies with a similar methodology in other countries. This is likely due to adherence to ERAS protocols and the high incidence of laparoscopic surgery compared to open surgery.

4.2. Physical Function tests: why the 6MWT was the only predictor of pLOS

The 6MWT appeared to be the only physical function test that could significantly predict PLOS. This might be explained by its encompassing systemic response to submaximal exercise while the other tests (Timed-up and go, 30s Arm Curl Test, 30s Sit-to-Stand, Hand Grip Strength, CHAMPS and SF36) evaluate localized components of fitness. Assessment of functional capacity was formerly conducted by asking a patient how many flights of stairs they could climb. This subjective measurement could yield biased results through the inaccurate estimation of patient's self-reported performance (American Thoracics Society, 2002). The 6MWT provides an objective measurement of functional capacity and aerobic fitness. It evaluates the multi-system response to submaximal exercise. As opposed to maximal exercise testing such as the CPET, the 6MWT is a self-paced test that allows participants to slow down and even stop if they need to. While it does not provide precise aerobic capacity variables such as oxygen consumption, it offers a functional performance score that represents a global systemic response to exercise (American Thoracics Society, 2002). This test is considered to encompass pulmonary, cardiovascular, skeletal, and neural response to exercise. The American Thoracic Society affirms this being a feature that best reflects daily physical activity intensity, which makes the 6MWT a more functional test.

The Timed-up and Go (TUG) measures balance, speed and agility by asking a seated patient to walk 3 meters, turn around, and return to seated position. This sequence is timed, with a shorter time representing a better functional performance (Podsiadlo & Richardson, 1991). Research shows that the TUG also strongly correlates with gait speed (Pearson's r = 0.61). In a study conducted by Huisman et al. (2016), the TUG was seen to effectively predict patient risk of post-operative complications in onco-geriatric patients using a cut-off of 20 seconds (OR 3.43; 95% CI 1.14–10.35) (Huisman et al., 2014). The 30-second sit-to-stand (STS) evaluates lower extremity strength by asking a seated patient to perform as many stands as possible during 30 seconds with the score being the total amount of repetitions performed during the assigned time (Rikli & Jones, 1999). Both the TUG and the STS are more localized assessments of fitness compared to the 6MWT, which evaluates global function. However, it is important to note that components of fitness evaluated by the TUG and STS are needed for greater performance in the 6MWT. Both the 6MWT and the TUG assess ambulation. As for the STS, the 6MWT was found to show a positive relationship between lower extremity muscle strength, demonstrating that lower limb strength is implicated functional performance (Rausch-Osthoff, Kohler, Sievi, Clarenbach, & van Gestel, 2014; Swisher, Baer, Moffett, & Yeater, 2005). In order to further investigate the relationship between these tests and the 6MWT, we performed a Pearson correlation analysis, where $p<0.05$ was considered significant. Our analysis showed significant correlations between the TUG and the 6MWT (Pearson's r = −0.73, *p*=0.00) and the STS and the 6MWT (Pearson's r = 0.69, *p*=0.00). These strong correlations indicate that patient who scored shorter TUG times and who performed more STS repetitions had a greater 6MWT distance. TUG and STS also correlated strongly between each other (Pearson's r = −0.65, *p*=0.00). It is plausible the 6MWT performance encompasses the fitness components of the TUG and STS, thereby explaining why they were rejected as predictors of pLOS.

The 30-second Arm Curl Test (ACT) is an assessment of upper extremity strength, where a patient is instructed to perform as many seated unilateral biceps curls as possible during 30 seconds while maintaining proper technique. The test is scored by counting the number of performed repetitions. The Hand Grip Strength test (HGS) evaluates maximal isometric force of the forearm by using an adjustable hand dynamometer. Its result is widely used as a proxy overall strength (G. F. Hamilton et al., 1992). However, evidence have shown that using it for the latter purpose this might not be accurate. A cross-sectional study by Felicio et al. (2014) showed no correlation between knee flexor peak torque and average power, and knee extensor peak torque and total work (Spearman $\rho < 0.30$). They advise cautious use of HGS as a measurement of overall strength (Felicio et al., 2014). Sanderson et al. (2016) suggest the combination of another lower body strength test might improve indication of overall strength in clinical settings (Sanderson, Scherbov, Weber, & Bordone, 2016). The ACT and the HGS are localized fitness tests that were rejected from the prediction model. These tests had a low to moderate correlation with the 6MWT (ACT: Pearson's r = 0.53, *p*=0.00; HGS Pearson's r = 0.48, *p*=0.00) and with each other (Pearson's r = 0.52, *p*=0.00). The common factor between the ACT and the HGS is that they are both measurements of strength only and do not account for aerobic fitness and ambulation. Therefore, we believe this could have been a reason for their rejection from the model.

The Community Healthy Activities Model Program (CHAMPS) for Seniors is a 41-item self-reported questionnaire assessing weekly frequency and duration of physical activity at different intensities (light, moderate and vigorous). It provides an estimation of caloric expenditure per kilogram per week by asking numeral based questions, where patients are asked to recall how many hours of an activity they performed in the previous week (Stewart et al., 2001). The CHAMPS was rejected as a predictor of pLOS. We suspect that this might due to its many limitations. Studies reported incidence of overestimation of weekly exercise frequency, due to misunderstanding of the physical activity intensity (Hekler et al., 2012). Some cognitive biases can also occur such as the need to respond in a socially desirable manner (Sallis & Saelens, 2000). The correlation score with the 6MWT was weak (CHAMPS: Pearson's r = 0.24, p=0.00).

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF36) is a self-reported questionnaire assessing QOL covering eight spheres of health: physical functioning, role of limitations due to physical impairments, role of limitations due to emotional impairments, vitality, emotional well-being, social functioning, pain and general health (Stewart et al., 1988; Ware & Sherbourne, 1992). Each of the latter components are scored on a 0 to 100 scale, with two summary scores evaluating physical and mental components. The total score, which is a mean of both, did not appear to be a significant predictor of pLOS. Compared to all of the other physical function tests, the total SF36 score was the only variable that accounted for the mental component of QOL, which could have biased the result. Its correlation score with the 6MWT was weak (Pearson's r = 0.47, *p*=0.00). In order to eliminate the bias from the mental component in the SF36 questionnaire, we performed a correlation analysis on the 6MWT physical component of the SF36 to see if there would be a stronger association. Our results show moderate correlation (Pearson's r=0.51, *p*=0.00).

4.2.1. 6MWT Cut-off Threshold Selection

In this section, the process of selecting the cut-off will be discussed and justified. A ROC curve was performed to determine a cut-off value of the 6MWT to discriminate patients in pLOS vs. iLOS. The ROC curve is the gold standard for evaluating the discriminative value of a diagnostic test and prediction models for binary outcomes (Zou, O'Malley, & Mauri, 2007). A perfect classifying test would be represented by an AUC of 1. An AUC of 0.5 is equal to the discrimination ability of chance (Hosmer, Lemeshow, & Sturdivant, 2013). It is visually represented by a 45-degree diagonal. With improved diagnostic test accuracy, the AUC will increase to approach a value of 1. According to Hosmer et al. (2013), a value between 0.7 and 0.8 suggests acceptable discrimination. A value between 0.8 and 0.9 is considered excellent, and a value greater than 0.9 is considered to be outstanding (Hosmer et al., 2013). Results from the plotted ROC curve show an AUC of 0.71 (95%0.63–0.78), which is indicative of an acceptable prediction.

The cut-off selection was then conducted by analyzing data points. A distance of 431 m was selected, where sensitivity was 0.70 and specificity 0.61. Therefore, this cut-off can identify 7 patients out of 10 in pLOS. This cut-off could be used in a pre-admission surgical setting to determine if a patient is at risk of late post-operative discharge. Many 6MWT cut-offs have been reported to describe several outcomes in different populations. Our selected cut-off corroborates with a study conducted by Sinclair et al. (2012). The latter aimed to evaluate the ability of the 6MWT to discriminate between low and high anaerobic threshold (AT) in patients awaiting major non-cardiac surgery (Sinclair, Batterham, Davies, Cawthorn, & Danjoux, 2012). With increasing oxygen consumption during exercise, the AT describes the moment at which anaerobic mechanisms begin to produce energy, thereby producing lactate and metabolic acidosis. A poor oxygen consumption at AT is indicative of a lower volume and diminished oxygen flow during exercise (Wasserman, 1986). The authors of this study used a cut-off of 11 ml O_2 kg^{-1} min^{-1} to discriminate between low and high AT. In order to measure AT, a cardiopulmonary exercise test (CPET) was performed. A CPET evaluates the integrative systemic response to physical activity. The mechanistic interaction between the cardiovascular, respiratory, and skeletal muscular systems is assessed in response to physiological stress of the incremental exercise (K. Wasserman, Hansen, Sue, Stringer, & Whipp, 2005). Since the 1990s, it has been widely integrated in preoperative assessments to evaluate physical function (Older, 2013). Their analysis demonstrated that a 6MWT cut-off of 427m could identify patients with an AT of less than 11 ml O_2 kg^{-1} min^{-1} (AUC 0.85, 95% CI 0.77–0.91, sensitivity 0.64, specificity 0.96) (Sinclair et al., 2012). In the context of surgery, Antonescu et al. (2014) considered a 20-meter as the minimal clinically important difference (MCID) (Antonescu, Scott, Tran, Mayo, & Feldman, 2014), therefore, our established 6MWT cut-off can be considered similar to that of Sinclair et al (2012).

Other studies have investigated walking tests cut-offs and poor functional capacity. The LIFE Study Randomized Clinical Trial by Pahor et al. (2014) defined major mobility disability by a patient's inability to walk 400m within 15 minutes without sitting or external help (Pahor et al., 2014). Research has also been conducted in the surgical population. Lee (2012) studied the use of 6MWT to predict post-operative outcomes after major abdominal surgery. A ROC curve determined a cut-off score of 392m for predicting cardiopulmonary morbidity (AUC=0.75, 95% CI 0.64-0.86, sensitivity=74%, specificity=72%) (L. Lee, 2012). A study by Brunelli et al. (2013) have stressed the use of a cut-off of 400 m to identify patients at low/high risk during lung resection surgery (Brunelli, Kim, Berger, & Addrizzo-Harris, 2013). In a study by Sathyaprasad et al. (2020) pertaining to patients awaiting major oncological surgeries, a cut-off of 390m was chosen as it represented the median of their sample. It was seen to correlate with longer LOS and ICU stay (p=0.001). Additionally, a 6MWT performance below this cut-off was significantly associated with post-operative pulmonary complications (6MWT<390m 76.3%, 6MWT>390 26.2%, p=0.001) (Sathyaprasad, Thomas, Philip, & Krishna, 2020). While 6MWT thresholds are population and outcome-specific, cut-offs appear to be similar and close in value.

4.3. Predictors of pLOS reported in literature

4.3.1 Surgical approach

A laparoscopic surgical approach is a minimally invasive technique has been shown to influence LOS. Studies have shown that the open approach vs laparoscopic can predict pLOS (Faiz et al., 2011; Vlug et al., 2012). However, in this study, this variable did not appear to reflect those findings. This could be explained by the unequal distribution of patients undergoing open and laparoscopic surgery in our sample. In the iLOS group, 93 patients underwent laparoscopic surgery while only 3 patients underwent open surgery. In the pLOS group, 69 patients received laparoscopic resection while 15 patients received the open approach. The prevalence of patients undergoing laparoscopic surgery was greater than those undergoing open surgery in both groups, with iLOS at 97.5% of patients and pLOS at 82.3%. The pLOS group had a significantly larger proportion of patients undergoing open surgery (iLOS 2.4%, pLOS 17.7%, $p=0.00$). The following section will address the benefits of the laparoscopic approach based on perioperative surgical outcomes compared to the open approach. ERAS evidence supporting the use of laparoscopic resections will also be discussed.

Minimally invasive surgical approaches for cancer patients were initially considered in the 1990s as a viable alternative to open surgery. A systematic review on laparoscopic vs. open surgery for colorectal cancer in geriatric patients was conducted by Fujii et al. (2016). Patients undergoing laparoscopic surgery experienced significantly less blood loss ($p< 0.0001$), decreased overall morbidity ($p< 0.0001$), decreased surgical site infection ($p< 0.014$), lower incidence of bowel obstruction and ileus ($p < 0.0044$), and decreased post-operative cardiovascular complications ($p < 0.0062$) with similar survival rates in both approaches. Some studies have shown enhanced post-operative recovery in the laparoscopic group defined by earlier discharge (LOS laparoscopic 5 days, LOS open 6 days, $p < 0.001$) (Nelson et al., 2004). Laparoscopic resections are proven to be superior in short-term post-operative outcomes and improve patient QOL. It can also lead to a reduction in resources and expenses. A cost-effectiveness study conducted by Jensen et al (2012) was performed to determine cost per quality-adjusted life-year in patients undergoing CRC surgery. Results show laparoscopic resection cost savings of 4283 USD compared to open resections (Jensen, Prasad, & Abcarian, 2012). For the benefit of patient care and cost-effectiveness, implementation of enhanced recovery protocols are strongly advised.

A systematic review with meta-analysis performed by Spanjersberg et al. (2015) aimed to study surgical outcomes from laparoscopic versus open colon surgery with or without an ERAS program. The ERAS guidelines provide innovative evidence-based techniques with the goal of minimizing physiologic stress and accelerating patient recovery. Results demonstrate reduced LOS and morbidity when laparoscopic resection was performed and ERAS guidelines were followed (Spanjersberg, van Sambeeck, Bremers, Rosman, & van Laarhoven, 2015). ERAS guidelines suggest practice of minimally invasive approach over open surgery in CRC for its strong benefits on post-operative recovery (Gustafsson et al., 2019). Since hospitals participating in our study are following ERAS guidelines, open surgery is performed less frequently compared to the laparoscopic procedure, which explains the disproportionate distribution of surgical approaches in our sample. We speculate that the latter could explain why this variable was rejected from our prediction model.

4.3.2. Tumor site

The site of the tumor appears to be the most prominent predictor out of all variables in the analysis. A rectal tumor increases the risk of pLOS compared to a colon tumor in patients awaiting cancer surgery (Aravani et al., 2016; Faiz et al., 2011; Hendry et al., 2009; Kelly et al., 2012). Post-operative complications are also known to be predictors of LOS (Chand et al., 2016; B. L. Johnson, 3rd, Davis, Rafferty, & Paquette, 2015; C. M. Johnson et al., 2013; Leung et al., 2009; Orive et al., 2019). As our study aimed to evaluate preoperative predictors of pLOS, post-operative items were not included in the analysis. However, it is important to note that patients with rectal tumors have a higher risk of post-operative complications, which in turn could have been associated with pLOS. As reported by Konoshi et al. (2006), rates of incisional surgical site infection in colon (n = 339) and rectal (n = 217) resections were 9.4% and 18.0%, respectively (P = 0.0033) (Konishi, Watanabe, Kishimoto, & Nagawa, 2006). According to Lipska et al. (2006), rectal cancer at ≤12 cm from the anal verge was seen to increase risk of anastomotic leakage (Lipska, Bissett, Parry, & Merrie, 2006). Readmission after CRC surgery is a marker surgical success and quality. Faiz et al. (2011) reported higher 28-day readmission rates in rectal surgery compared to colon surgery (7.7% to 8.6% vs 8.8% to 11.9%, respectively) (Faiz et al., 2011). This might explain why a rectal tumor was such a strong predictor of pLOS in our study.

While comparing LOS in colon and rectal cancer patients, Faiz et al. (2011) reported a range of 11-14 days for colectomy procedures and 13-15 for rectal procedures (Faiz et al., 2011). Within our analysis, median LOS of colon cancer patients was 3 days (IQR 3) compared to was 4 days (IQR 6) in rectal cancer patients. The latter diagnosis represented 26% (n=47) of our total sample, which is reflective of the incidence of rectal cancer in large bowel cancers in Western countries (Y. C. Lee, Lee, Chuang, & Lee, 2013). A retrospective epidemiological analysis conducted by Lee et al. (2013) studied the differences between colon and rectal cancers. This population-based study determined that rectal cancer patients were mostly males and younger at diagnosis, which was reflected in our sample. Males represented 60% of rectal cancers (n=28). Median age for rectal cancer patients was 72 (IQR 17) while colon cancer patients was 74 (IQR 16). Within our model, tumor site appeared to be a stronger predictor of pLOS than sex and age. It is plausible that it is because statistics related to rectal cancer considers the effects of sex and age.

The use of minimally invasive surgery techniques such as the laparoscopic approach has been on the rise for its improvement in patient post-operative outcome in rectal surgery. Studies have been conducted to compare the latter approach to open surgery to determine its noninferiority. The ACOSOG Z6051 (2015) and ALaCart (2015) RCTs were both unable to establish noninferiority of the laparoscopic compared with open surgery for successful rectal cancer resection (Fleshman et al., 2015; Stevenson et al., 2015). While most of the patients in our study received laparoscopic surgery, a larger proportion of open surgeries were performed on rectal patients. Twenty-four percent of patients with a rectal tumor received the open approach (n=9) compared to seven percent (n=9) in colon cancer patients. Chand et al. (2012) addressed the issue of high surgical complexity in rectal resection related to operating within the pelvis and that surgeons should perform a cautious patient risk assessment to ensure optimal safety (Chand, Bhoday, Brown, Moran, & Parvaiz, 2012). As previously mentioned, laparoscopic surgery is superior to open surgery due to its improvements in blood loss, overall morbidity, surgical site infection, incidence of bowel obstruction and ileus, and incidence in other post-operative complications. Tumor site was superior to surgical approach as a predictor of pLOS. It is possible that because there is a higher incidence of open surgeries in rectal tumor patients, the effect of the surgical approach is already considered.

4.3.3. Age

While age has been seen to be an effective predictor of pLOS , this variable was rejected from the prediction model despite being a prominent predictor in previous studies (Faiz et al., 2011; Feroci et al., 2013; Kelly et al., 2012). Some studies have been conducted to investigate the effect of age on surgical outcomes in CRC patients. More recently, Park et al. (2021) aimed to compare post-operative outcomes following CRC surgery in patients below and over 80 years of age. All patients were treated within the ERAS pathway. Results indicate similar post-operative outcomes between the younger and older groups. There was no statistical significant difference between LOS, with the older group at 14 days (4-70) and the younger group 12 days (4–69) (p= 0.21). Additionally, there was comparable rate of major complications, including mortality, in both groups (80>:8.9%; 80<: 8.9%, p=0.67). While literature shows increased risk of CRC in the geriatric population, they seem to have similar surgical outcomes when compared to their younger counterparts (H. Park, Parys, Tan, Entriken, & Hodder, 2021). Park et al. (2021) states that these results might be due to the implementation of the ERAS protocol, which favors patient-centered preoperative optimization. This recent study supports that age might not be the most determinant variable influencing LOS, which could explain why it was not a predictor of pLOS.

Since chronological age does not always appear to be predictive of poor post-operative outcomes, some studies sought to determine which perioperative practices was most appropriate in this surgical population. In a study pertaining to the importance of multidisciplinary and patient-centered care in rectal cancer, Montroni et al., (2018) states that fit patients should be treated within the same standard of care as younger patients. The aim of their study was to determine how to optimize personalized care in older rectal cancer patients. Authors stated that an assessment of frailty should be prioritized over the use of chronological age in the context of cancer treatment (Montroni et al., 2018). Frailty is described as a state of age-related physiological decline characterized by poor energy levels and muscle strength, weight loss and sedentarism. In the context of surgery, it can place a patient at high vulnerability to increased rates of complications and readmissions, longer LOS, and decreased survival rates (Fagard et al., 2016). The geriatric population is present with diverse levels of functional fitness, presentation of symptoms, psychosocial state, etc. Therefore, the reliance on chronological age is discouraged in the decision-making of the cancer treatment plan. In frailty screenings, components of functional, nutritional and cognitive status are investigated through testing. According to Montroni et al., (2018), the information from the latter tests is considered superior to the utilization of chronological age in treatment plans and patient risk stratification. A study by Gillis et al., (2021) compared frail CRC patients walking over and under 400m in the 6MWT. Frailty was described as patients over the age of 65 years screened positively with the Fried frailty criteria in which assessment of unintentional weight loss, weakness, exhaustion, slow gait, and low physical activity is conducted. Patients with a criteria of 2 and more were included in this study (Fried et al., 2001). After stratifying the patients by functional fitness, they were able to determine that 61% of their <400m group experienced at least one surgical complication within 30 days of the surgery, compared to 21% in the >400m group (p=0.01). Additionally, patients in the <400m group had an increased risk of developing a postoperative complication 6 times greater compared to the >400m group. Median LOS in the <400m group was 6 days (IQR 8) compared to 3 days (IQR 1) in the >400m group (p=0.01) (Gillis et al., 2021). This provides further justification as to why age did not appear to be a predictor of pLOS.

4.3.4. Sex

According to Vlug et al. (2012), the male sex is associated with a pLOS as a 15% decrease in LOS was observed in female patients (Vlug et al., 2012). This was not reflected in our study as it was rejected as a predictor of pLOS. Vlug et al. (2012) cite that a patient's sex was an independent predictor of LOS in CRC surgery due to male patients having a significantly higher incidence an American Society of Anesthesia (ASA) classification of 3 or greater (p=0.015), which is indicative of severe systemic disease (Abouleish, Leib, & Cohen, 2015). An ASA grade equal or greater than

3 describes a patient with one or more moderate to severe diseases including but not limited to diabetes mellitus, hypertension, chronic obstructive pulmonary disorder, morbid obesity (BMI ≥40), active hepatitis, alcoholism, etc., thereby increasing risk of post-operative morbidity. Another reason was the difference in fat distribution, where visceral fat was prominent in males, while subcutaneous fat was higher in females (Vlug et al., 2012). Studies have shown that elevated levels of visceral fat was associated with increased post-operative morbidity (Nitori, Hasegawa, Ishii, Endo, & Kitagawa, 2009).

In our study, the male sex was not a predictor of pLOS. We determined that there was no sex-specific difference between median LOS (males 3 days (IQR 4), females 3 days (IQR 2), p=0.89) and between iLOS and pLOS groups (Males in iLOS 56.7%, males in pLOS 56.6%, p=0.98). We further analyzed the data to determine if we had similar results to the Vlug et al. (2011) study in the male sex and ASA classification. A total of 42% of males had an ASA score equal or greater than 3 compared to 47% in females, which was not significantly different (p=0.46). These results indicate that there is not enough evidence to suggest that males had increased morbidity (defined by ASA grade ≥ 3) in our sample, which is not reflective of the results in the Vlug et al. (2012) study. Then, we examined the relationship between visceral fat and the male sex. We used waist circumference as it widely utilized as a proxy of abdominal adiposity with cut-offs of 102 cm for males and 88 am for females (Ness-Abramof & Apovian, 2008; Y. Park, 2019). Median waist circumference in males was of 98.3 cm (IQR 17) which is below the cut-off for abdominal adiposity in males of 102 cm. Interestingly, the median waist circumference in female patients was 93.5 cm (IQR 18.5), which was higher than the widely used cut-off for abdominal adiposity of 88 cm. The statistics from our sample did not appear to reflect results reported from Vlug et al. (2012). Male and female patients appear to present with similar ASA classification. Females appear to have a higher visceral adiposity which contradicts literature. These findings might partially explain why sex did not appear to be a predictor of pLOS in our study.

4.3.5. BMI

Poelemeijer et al. (2018) found that obesity, defined by a BMI equal or greater than 30 kg/m^2, is an independent predictor of a length of stay greater than 14 days in CRC patients. Comorbidities related to obesity were associated with greater incidence of morbidity, pLOS and readmission rate (Poelemeijer et al., 2018). In our study, BMI was not observed as a predictor of pLOS, which is a contradictory finding. The overall median BMI of our sample was 26.2 kg/m^2 (IQR 8) with no significant difference between iLOS and pLOS groups (BMI_{iLOS} 26.2 kg/m^2 (IQR 7), BMI_{pLOS} 26.9 kg/m^2 (IQR 7), p=0.57). In order to further investigate the effect of obesity on pLOS, we performed a chi-square test to compare obese patients (<30 kg/m^2 or ≥ 30 kg/m^2) and LOS (iLOS or pLOS). A total of 27% of patients in iLOS were obese compared to 35.7% in pLOS which was not significantly different (p=0.22). From these results, we conclude that there is not enough evidence to suggest an association between obesity and LOS in our sample. This could explain why BMI was not accepted as a predictor of pLOS.

A recent review by How et al. (2019) on the effect of obesity on surgical outcomes in CRC demonstrates higher risk of surgical site infections and thromboembolic complications in obese patients. Intraoperative complications including greater blood loss, longer operating times and higher conversion rates were also mentioned. However, while obese patients appear to be at higher risk of complications compared to non-obese individuals, there is not enough evidence to suggesting that obesity alone impacts LOS (How, Choo, Koshy, & Benziger, 2019). Geiger et al. (2011) acknowledges that while there is a common belief that there is a greater technical labor when operating on obese patients, it might be a result of anecdotal experiences as literature remains inconsistent in this topic. In patients with obesity, it is generally recommended by healthcare professionals to lose weight prior to surgery in order to decrease comorbidities. Obesity-related comorbidities are reported to be the main cause of surgical complications and pLOS, not obesity alone (Geiger & Muldoon, 2011; Kirchhoff, Dincler, & Buchmann, 2008). Therefore, It is possible that the effect of BMI is comprised through comorbidity variables such as the Charlson Comorbidity Index and the American Society of Anesthesia score.

4.3.6. The American Society of Anesthesiology classification and Charlson Comorbidity Index

The American Society of Anesthesiology (ASA) classification and the Charlson Comorbidity Index (CCI) are known as comorbidity indices that are widely used in clinical and research settings (Strombom et al., 2019). The following section will discuss the comparison between these two variables, as well as reasons why they were rejected as predictors of pLOS.

The ASA is a well-known tool that evaluates patient’s preoperative physical status and provides an estimation of their anesthetic risk (Abouleish et al., 2015; Daabiss, 2011). It is scored on a 6-

point classification with score of 1 representing a normal healthy patient, and 6 describing a patient declared brain-dead. Updated definitions and examples exist to help anesthetists assess patient's pre-anesthesia comorbidities. A lower ASA grade could have protective effects to pLOS (Ahmed et al., 2010; Dekker et al., 2012; Feroci et al., 2013). The CCI was developed to classify weighed comorbidities of a patient to predict risk of mortality within one year of hospitalization (Charlson, Pompei, Ales, & MacKenzie, 1987). It has been shown that the CCI is an effective predictor of post-operative outcomes including pLOS (Dekker et al., 2012; Faiz et al., 2011; Keller et al., 2014; Kelly et al., 2012; Leung et al., 2009; Zou et al., 2007). Compared to the ASA score, the CCI is much more accessible and simpler as it only requires patient demographic variables. A study has shown that ASA score can be extrapolated from the CCI data. Results show that a CCI ≥ 1 best distinguished between ASA ≥ 3 and < 3 (Mannion et al., 2020). We performed a correlation analysis with the CCI and the ASA as it is another measurement of patient comorbidity. The result showed that the CCI and the ASA score have an average but significant correlation (Spearman $\rho = 0.57$, p=0.00). Both these variables (CCI and ASA) were not shown as predictors of pLOS in our study.

As previously mentioned, Huisman et al., (2016) aimed to identify patients at risk of poor post-operative outcomes by using the TUG as a discriminative test. In this study, the effectiveness of the TUG was compared to the prediction performance of the ASA classification. While both the TUG and the ASA classification are independent predictors of post-operative complications, the TUG could predict twice as many patients. The prediction capacity of the ASA score on LOS was further investigated, where pLOS was defined at greater than 7 days. The percentage of patients in pLOS for each classification was 69.2% for ASA1, 45.8% for ASA2, and 55% for greater than ASA3. A multivariate prediction model showed that pLOS could not be predicted by high ASA-classification (ASA1 vs. ASA2: OR 0.23; 95% CI 0.05–0.99; p = 0.05. ASA1 vs. 3&4: OR 0.37; 95%-CI = 0.08–1.68; p = 0.20 (Huisman et al., 2014). A review on the ASA classification as a tool to measure a patient's fitness prior to surgery was conducted by Mayhew et al. (2019) in which it was stated that this tool should be combined with another clinical variable to help generate greater prediction accuracy of preoperative status (Mayhew, Mendonca, & Murthy, 2019). This shows that a functional and physical test was superior to a comorbidity index in the prediction of pLOS, which is reflective of the results from our study.

Using the ASA as a screening tool of post-operative outcomes in this population has been studied with conflicting results. While some studies report a score greater than 3 increases risk of complications, morbidity, and 30-day mortality (Dekker et al., 2012; Heriot et al., 2006; Tan et al., 2009), other studies could not effectively come to the same conclusion. Kristjansson et al. (2010) aimed to determine how well the Comprehensive Geriatric Assessment (CGA) (physical functioning, comorbidity, medication, nutrition, cognition, and emotional status) could predict complications in geriatric patients compared to age, tumor stage, and ASA status in patients with CRC. Their results confirm that age and ASA status were not predictors (Kristjansson et al., 2010). Only frailty and rectal cancers (compared to colon cancers) were found to be independent predictors of severe complications, which appears to align with the results of our study. We believe a comorbidity index such as the ASA score can independently predict pLOS. However, its impact becomes inferior when tested against more functional variables. This might explain why these comorbidity indices were rejected as predictors of pLOS while the 6MWT was retained.

4.4. Prehabilitation

The preoperative intervention of prehabilitation did not appear either to be a predictor of pLOS. This might be a result from the differences found in the exercise protocols pertaining to exercise supervision and aerobic training intensity.

Of the total prehabilitation subjects from this thesis, 10% received unsupervised (home-based) training instead of supervised training (in-hospital). This presents as a discrepancy in the exercise intervention. An analysis conducted by Awasthi et al., (2019) investigated whether supervised exercise as part of a multimodal prehabilitation program further accelerates the functional recovery after CRC surgery compared to unsupervised exercise. Their results showed the significant superiority of supervised training (n=63) compared to unsupervised training (n=77) in the improvement of perioperative functional capacity in CRC patients (Awasthi et al., 2019). Both groups had similar baseline demographics, with the exception of the supervised group being older (supervised group 69.9 years (SD 10.7) and un-supervised group 65.9 years (SD 11.4), p=0.02).The supervised training group had a significantly greater 6MWT performance compared to the unsupervised group after the prehab intervention (p=0.0009). It was also observed that the supervised group shortened LOS by one day (LOS supervised group was 3 days (IQR 1), LOS un-supervised group was 4 days (IQR 3), p=0.00). Another prehabilitation protocol discrepancy is found in the aerobic training protocols. The aerobic intensity of the protocols was established at either moderate intensity continuous training (MICT) or high interval intensity training (HIIT). The Minnella et al. (2020) study aimed to compare peri-operative functional trajectory in response to two different exercise training protocols (MICT and HIIT) within a 4-week multimodal prehabilitation program. The primary outcome was the change in oxygen consumption at anaerobic threshold (VO_2AT), measured by a CPET. The results show post-intervention improvement in both groups, with no greater performance between the two protocols. With regards to this thesis, all patients (cohorts 1,2,3,4,6) undergoing MICT training were set at an intensity of 60% of their VO_2peak for a duration of 25-35 minutes. As for the HIIT group (cohorts 5 and 7) there were two different exercise protocols that take part of this thesis. This is another factor of discrepancy between prehabilitation protocol. Some (cohort 5) underwent 4 bouts of 2min at 80-90% of their VO_2peak, while some (cohort 7) were subjected to 4 bouts of 3 min at 80-90% VO_2peak. It appears that supervised training and HIIT training independently yields better outcomes than their counterparts. All patients were included in the analysis, which could explain why the variable of prehabilitation was not a predictor of pLOS.

In order to further investigate the preoperative performance of the MICT and HIIT groups within our sample, we performed a sub-analysis with the prehabilitation patients to determine if there were preoperative differences in physical function performance after the intervention between the two groups. Our results shown in Table 6 show that the patients in the HIIT training group performed significantly better in the STS, TUG, ACT, 6MWT, CHAMPS and SF36 post-intervention compared to the MICT group. There was no significant difference in the HGS between groups. A significant difference was found in the LOS, with the HIIT group at a median of 3 days (IQR 2) and MICT group of 4 days (IQR 3). This classifies the patients in the latter group in pLOS while the HIIT group was in iLOS. Considering that prehabilitation is a time sensitive program that has a duration of 4-6 weeks before surgery, healthcare professionals in the surgical pathway should consider implementation of supervised HIIT training, as evidence seems to show that it is the most effective modality and intensity for shortening LOS.

Table 6. - Comparison of Physical Testing Performance of MICT and HIIT prehab groups after intervention

Median (IQR)	MICT	HIIT	p value
Length of stay (days)	4(3)	3(2)	0.00
30s Sit-to-Stand (n)	13 (4)	16 (7)	0.01
Timed-up and Go (s)	6.7 (2.99)	5.8 (1)	0.00
Hand Grip Strength (kg/F)	26.9 (18.2)	30 (14.4)	0.70
30s Arm Curl Test (n)	19 (7)	23 (6)	0.00
6-Minute Walking Test (m)	459 (167)	567 (165)	0.00
CHAMPS (kcal/week)	93 (110.7)	72 (82)	0.02
SF36 (score / 100)	74.6 (30)	81 (25.9)	0.00

4.5. The predictive value of items in the ERAS pathway

All patients were treated within the ERAS protocol. In the context of this study, we have not investigated the impact of the many perioperative practices on pLOS. A study conducted by Pedziviatr et al. (2016) aimed to study the risk factors predicting a LOS greater than three days in CRC laparoscopic surgery following ERAS guidelines. Results demonstrate that patients with LOS greater than three days had a higher rate of complications (18.7 vs. 36.7 %) and a lower rate of ERAS compliance (91.2 vs. 76.7 %). ERAS protocols pertaining to balanced fluid therapy (OR 3.87), early mobilization (OR 20.74), urinary catheterization (OR 4.58) and use of drainage (OR 2.86) were significantly associated with pLOS. The latter ERAS protocol items had more influence on recovery and LOS in laparoscopic CRC surgery compared to other traditional patient risk factors such as patient age, anthropometrics, comorbidities, and cancer stage (Pędziwiatr et al., 2016). The significant ERAS practices predicting pLOS were all post-operative variables. An important differentiation between our study and the Pedziwiatr et al. (2016) study is that our findings provide a preoperative prediction tool that can be used to detect vulnerable patients, thereby providing time for healthcare professionals to intervene and mitigate risk of pLOS.

4.6. Implementing the 6MWT as a preoperative tool to target at-risk patients – why and how?

Known predictors of a prolonged hospital stay in CRC patients include age, sex, obesity, comorbidity, and surgical approach. Our study was able to identify physical function assessed by the 6MWT as a stronger predictor of pLOS. Compared to the other aforementioned predictors, the 6MWT is the only risk factor that is modifiable. Thus, if this assessment could be implemented in the preoperative surgical pathway while using the 431m cut-off, clinicians will be able to identify those who are at risk and perform an intervention to mitigate postoperative impairments.

With increased risk of extending their length of stay, patients with poor walking capacity should be targeted for patient-centered exercise prehabilitation to optimize their physical function prior to surgery. Chen et. al. (2017) provided compelling evidence that this is possible in the context of CRC surgery through compliance to an individualized prehabilitation program. The authors studied whether a 4-week multimodal prehabilitation program was sufficient to improve 6MWT distance in geriatric patients with CRC (Chen et al., 2017). The prehabilitation group received individualized exercise, nutrition and psychosocial interventions, while the control group received standard of care. The participants were preoperatively assessed twice with 4 weeks in between visits. Compared to the control group, the patients undergoing the prehabilitation program significantly improved their walking distance (PREHAB +23.7 ± 6.9 vs. CTRL 5.4 ± 6.2 m, $p = 0.002$). Important changes in physical activity engagement were also reported in the prehabilitation group. From baseline to 4 weeks post-intervention, a significant increase in moderate and vigorous intensity physical activities was seen in the prehabilitation group (PREHAB baseline 2.00 hours vs post-intervention 5.00 hours, $p<0.001$), while no significant changes were seen in the control group (CTRL baseline 1.00 hour vs post-intervention 1.33 hours, $p=0.55$). Post-intervention, the prehabilitation group reported significant higher levels of moderate and vigorous physical activity (PREHAB median 5.00 hours vs CTRL median 1.33 hours, $p = 0.00$). Additionally, the authors concluded that patients undergoing prehabilitation were more likely to meet weekly exercise recommendations for cancer prevention and better quality of life (Chen et al., 2017).

Successfully implementing a preoperative functional screening and intervention programs can present with obstacles. A study conducted by IJsbrandy et. al. (2020) studied the barriers in implementing physical activity programs to cancer survivors in Dutch healthcare institutions. They performed 31 interviews with primary healthcare professionals and organized four focus group interviews with 39 secondary healthcare professionals in order to find out what they thought were barriers. One of the raised obstacles was that professionals were concerned about their lack of knowledge in the field of physical activity for symptomatic populations. Minimal skills could therefore lead to unsuccessful implementation of a program. They were also apprehensive about being at the receiving end of a heavier work load and high pressure to deliver results. The interviewed professionals also raised more systematic issues pertaining to their nation's healthcare organization. Among these included insufficient collaborative work and ineffective communication between hospitals and healthcare professionals, lack of program quality assurance and poor patient triage system. Additionally, limited resources allocated to such projects, scarce financial sources, facilities and materials, were mentioned obstacles to the successful implementation of a physical activity program (C, van Harten, Gerritsen, Hermens, & Ottevanger, 2020).

With cancer and surgery increasing the risk of physical deterioration and poor fitness, physical assessment and activity program should be implemented in hospitals. With most healthcare workers report a lack of knowledge in exercise science, medical institutions should strongly consider an investment in exercise specialists such as kinesiologists to mitigate the functional losses of patients cancer post-surgery. Kinesiologists are exercise specialists who's main objective is to prevent injury and disease through movement, while optimizing function and performance. They are trained to conduct physical function assessments and to design personalized exercise interventions. They should be solicited to work alongside a multidisciplinary team for their use of evidence-based modalities in specialized populations.

4.7. Life after hospital discharge – what about independence?

From diagnosis to post-operative care, the process of overcoming cancer can be daunting for patients. In the context of ERAS programs, the discharge criteria include: ability to adhere to solid food diet, presence of bowel movements, orally controlled pain, adequate mobilization, and no complications requiring hospital care (Lassen et al., 2009). While perioperative ERAS protocols are found to be successful in early discharge, associating a timely hospital discharge with a successful post-operative recovery might not be adequate. Post-discharge syndrome describes a period of vulnerability after leaving the hospital, during which patients are at increased risk for complications, emergency room visits, readmissions, and other adverse events (Goldwater, Dharmarajan, McEwan, & Krumholz, 2018). For some patients, life after discharge equates to functional and emotional limitations as well as experiences of pain and distress. A study by Hofman et. al. (2015) investigated what was most important to patients undergoing CRC surgery. The decline of functional independence appears to be the most devastating post-operative loss in older patients, while morbidity was more important to their younger counterparts (Hofman et al., 2015). As the ERAS protocol to discharge does not account for post-operative functional independence, does it truly reflect the values of geriatric surgical candidates? Prioritizing what is most meaningful to patients should be of utmost importance to clinicians. A study demonstrated that in patients over 65 years old, 59.6% of them experienced a decline in independence, 26.6% demonstrated a loss in functional status, 32% a decline in mobility and 46% were in need of increased care (Berian, Mohanty, Ko, Rosenthal, & Robinson, 2016). Loss of independence was also found to be associated with readmission (OR 1.7; 95% CI, 1.4-2.2) and death (OR 6.7; 95% CI, 2.4-19.3).

Ensuring that the patient is physically ready for surgery might contribute to more meaningful recovery to patients with CRC. According to Lawrence et. al. (2004), preoperative physical conditioning is an important predictor of functional recovery after elective major abdominal operations (Lawrence et al., 2004). Independence is a parameter that encompasses physical function and mobility (Berian et al., 2016). While losses are seen after discharge, they are not permanent. Preoperative functional screening and multimodal prehabilitation can perhaps equip patients with proper education and functional reserve to empower them to move forward through their cancer journey with more confidence.

4.8. Study Limitations

There were some limitations in this retrospective study. Firstly, patients included in this analysis were all treated within the ERAS guidelines. Therefore, our recommendations of using a 431m cut-off for the 6MWT might be limited to ERAS institutions. Additionally, there was presence of variability in exercise component of the prehabilitation. The analysis included all patients receiving prehabilitation despite some discrepancies in supervision modality (home-based vs. in-hospital), aerobic exercise intensity (MICT vs. HIIT), and different HIIT protocols (4 x 2min at 80-90% VO_2peak vs. 4 x 3min at 80-90% VO_2peak). The change in protocols corresponds to the resource accessibility and availability at the time of each study. For instance, the one of our cohort (Gillis et al., 2014) provided unsupervised prehabilitation as there were no facilities available to train the patient. Moreover, specialized stationary bikes were unavailable at the time. With the hiring of a kinesiologist to perform safe supervision, HIIT training also became possible. Further studies should be conducted with a standardized exercise protocol to establish if prehabilitation can predict pLOS. Despite the aforementioned limitations, our study appears to be the first study, to the best of our knowledge, to address physical function tests as predictors of pLOS in CRC.

Chapter 5: Conclusion

The purpose of this thesis was to determine if preoperative physical function tests could predict pLOS in patients with CRC in adult patients with non-metastatic CRC awaiting for elective surgery. In summary, our results indicated predictive value in the patients undergoing rectal tumor resection compared to those awaiting colon resection. Patients undergoing a rectal surgical procedure were at increased risk of pLOS. As for physical function testing, the 6MWT was the only assessment that could effectively predict patients at risk of pLOS, with a lower walking distance indicating an increased risk of pLOS. Physical function determined by the 6MWT could provide superior prediction of pLOS compared to previously reported risk factors of LOS such as age, sex, BMI, comorbidity indices (ASA and CCI), and surgical approach. As physical function is a modifiable risk factor, we believe that it is imperative to put emphasis on its optimization should be implemented in the surgical pathway.

Screening tools are an important element of pLOS in the surgical population. It is necessary to identify patients at high risk of pLOS and to facilitate the effective delivery of appropriate interventions for these individuals. The 6MWT is an inexpensive test that requires minimal time, training, and equipment. As a score of 431m could identify 70% of patients in pLOS group, we believe that implementation of pre-admission 6MWT screening should be a requirement to potentially save a patient from extending their post-operative hospitalization. Multidisciplinary measures and efforts should be taken to ensure optimized functional fitness to reduce risk of pLOS. Healthcare professionals involved in the surgical pathway should encourage preoperative physical assessments to target patients with a 6MWT distance of less than 431m for patient-centered multimodal prehabilitation.

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