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The Impact of Frailty and Sarcopenia in Patients Undergoing Esophagectomy for Esophageal Cancer

Linda Chang Qu, *The University of Western Ontario*

Supervisor: Malthaner, Richard, *The University of Western Ontario*

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Abstract

Esophagectomy remains an integral part of cure for patients with esophageal cancer. The operation can be a source of significant morbidity and mortality, which highlights the importance of preoperative risk assessment and careful patient selection. Sarcopenia, defined as loss of muscle and function, and frailty are two measures of decreased physiologic reserve that have been associated with poor outcome in cancer patients. The first objective of this thesis was to summarize the existing literature on the available tools used to quantify frailty and sarcopenia. The second was to perform the first study using the National Surgical Quality Improvement Program (NSQIP) database to investigate the association between the 5-factor modified frailty index (mFI-5) and adverse outcomes in esophagectomy patients. The final objective was to measure sarcopenia and frailty in the same local esophagectomy patient cohort to investigate the association between these metrics of physiologic reserve and severe postoperative complications requiring intensive care. NSQIP data for esophagectomy patients from 2016-2018 were obtained and local patient data was collected from 2010-2016. Frailty was quantified using mFI-5 and sarcopenia status was attained by normalizing skeletal muscle area on preoperative computed tomography scans by sex and height. Based on the NSQIP database, mFI-5 showed associations with post-esophagectomy 30-day morbidity (i.e., Clavien-Dindo grade IV complications) but not mortality. In the local patient cohort, neither sarcopenia nor mFI-5 demonstrated significant associations with postoperative outcomes. In conclusion, sarcopenia and frailty are markers of physiologic vulnerability but may not correspond with statistically and clinically significant outcomes for esophagectomy patients.

Keywords
Esophageal cancer, esophagectomy, frailty, sarcopenia, NSQIP, mFI, outcomes, Clavien Dindo, morbidity, mortality

Summary for Lay Audience

The definitive surgical treatment for esophageal cancer is an esophagectomy – a complex and physiologically taxing operation in patients already ill patients. The risks of death and severe complications associated with this surgery is high. For this reason, finding a way to understand which patients would do poorly afterwards is important for making decisions about treatment. Sarcopenia is a condition defined by loss of muscle mass and function. Frailty is the overall decline in the body's ability to respond to stress. Both factors have both been linked to poor outcomes in cancer patients. In our research, we first aimed to summarize the ways sarcopenia and frailty are measured. Second, we investigated whether the 5-factor modified frailty index (mFI-5) – a simple and widely used tool to quantify frailty – was associated with poor outcomes in esophagectomy patients that were captured in the National Surgical Quality Improvement Program (NSQIP) database between 2016-2018. Ours was the first study to apply mFI-5 to these patients. Finally, we took our local population of esophagectomy patients and measured both frailty (using the mFI-5) and sarcopenia (using preoperative computed tomography (CT) scans) to see if either metric was more associated with outcomes severe enough to warrant admission to the intensive care unit (ICU). Based on the NSQIP database study, we found that the mFI-5 was associated with severe complications but not death within 30 days of surgery. In our local cohort, we did not find any meaningful indications that sarcopenia or mFI-5 were associated with admission to the ICU. In conclusion, both sarcopenia and frailty are objective measures of physiologic vulnerability, but these two metrics alone may not be enough to tell us whether a patient undergoing an esophagectomy will have a poor outcome that is clinically meaningful.

Co-Authorship Statement

Chapter 1:
Sole Authorship: Linda Chang Qu
Manuscript Review: Richard Malthaner, Kelly Vogt, Michael Ott

Chapter 2:
Study Design: Linda Chang Qu
Data Collection: Linda Chang Qu
Statistical Analysis: Linda Chang Qu
Manuscript Preparation: Linda Chang Qu
Manuscript Review: Richard Malthaner, Kelly Vogt, Michael Ott

Chapter 3:
Study Design: Linda Chang Qu
Data Collection: Linda Chang Qu
Statistical Analysis: Linda Chang Qu
Manuscript Preparation: Linda Chang Qu
Manuscript Review: Richard Malthaner, Kelly Vogt, Michael Ott

Chapter 4:
Sole Authorship: Linda Chang Qu
Manuscript Review: Richard Malthaner, Kelly Vogt, Michael Ott

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List of Abbreviations

- American College of Surgeons (ACS)
- American Society of Anesthesiology (ASA)
- Canadian Study of Health and Aging Frailty Index (CSHA-FI)
- Charlson Comorbidity Index (CCI)
- Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS)
- Chronic obstructive pulmonary disease (COPD)
- Computed tomography (CT)
- Confidence intervals (CI)
- Congestive heart failure (CHF)
- Eastern Cooperative Oncology Group (ECOG)
- European Working Group on Sarcopenia in Older People (EWGSOP)
- Functional Assessment of Cancer Therapy questionnaire (FACT-G)
- Gastroesophageal junction (GE junction)
- Gastroesophageal reflux disease (GERD)
- Hounsfield units (HU)
- Intensive care unit (ICU)
- International Statistical Classification of Diseases, Tenth Revision (ICD-10)
- Lean psoas area (LPA)
- London Health Sciences Centre (LHSC)
- Magnetic resonance imaging (MRI)
- Modified frailty indices (mFI)
- National Surgical Quality Improvement Program (NSQIP)
- Participant User Files (PUF)
- Revised Cardiac Risk Index (RCRI)
- Skeletal muscle index (SMI)
- Society of Thoracic Surgeons (STS)
- Squamous cell carcinomas (SCC)
- Surgical site infection (SSI)
- Surveillance, Epidemiology and End Results (SEER)
- World Health Organization (WHO)

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Chapter 1 – Introduction

1.1 Epidemiology and Etiology of Esophageal cancer

Esophageal cancer is one of the most lethal gastrointestinal tract malignancies and a major cause of cancer mortality worldwide. The incidence of esophageal cancer has increased sharply over the past few decades. According to the GLOBOCAN 2020 estimates, esophageal malignancies rank 7th in terms of incidence, with 604 100 new cases diagnosed in 2020[1]. It accounted for 5.5%, or 1 in 20, of all cancer deaths, making esophageal cancer the 6th leading cause of death from a malignant neoplasm in the world[1].

The highest rates of esophageal cancer are found in Southern African countries, as well as the Asian "cancer belt" that extends from China to eastern Turkey and northeastern Iran[1–3]. Cancers arising from the esophagus are relatively uncommon in North America, where the rate of new cases per year is 4.3 per 100,000, compared to 18 per 100 000 in Eastern Asia[4]. Its incidence, however, has steadily risen over the past 25 years[5].

The risk of esophageal carcinoma increases with age, with a mean age at diagnosis of 66 years. Overall, esophageal cancer is four times more common and slightly more lethal in men than in women. Survival varies widely depending on cancer site, histopathology, treatment modality, and stage of disease. According to the Surveillance, Epidemiology and End Results (SEER) registry estimates from 2010-2016, the overall 5-year survival for esophageal cancer is just under 20%. This poor survival is largely because esophageal cancer is often diagnosed at a late stage. If the disease is confined to local or regional tissues, survival ranges from 25-47%. Small tumors are often asymptomatic and detected by chance. Once symptoms are present (e.g., dysphagia, weight loss), esophageal cancers have usually become locally invasive and may have metastasized to lymph nodes or other organs. Most patients have advanced disease with distant metastasis at the time of diagnosis (39%). For the these patients, the 5-year survival is only 5% [6, 7].

The two most common histological types of esophageal cancer are squamous cell carcinomas (SCC) and adenocarcinomas. Other rare malignancies of the esophagus, including sarcomas and small cell carcinomas, represent less than 2% of all esophageal cancers. Even rarer are cases of melanomas, leiomyosarcomas, carcinoids, and lymphomas[8]. SCC arises from the stratified squamous epithelial lining and is the predominant histologic type of esophageal cancer worldwide[4]. Transition models describe squamous epithelium undergoing inflammatory changes that progress to dysplasia and *in situ* malignant change, resulting in SCC[9]. It is relatively evenly distributed between the middle and lower third of the esophagus, in contrast to adenocarcinomas, which is predominantly found in the distal esophagus. Adenocarcinoma arises from the columnar-lined metaplastic epithelium, commonly known as Barrett's esophagus, which replaces the squamous epithelium and may progress to dysplasia[10]. Gastroesophageal reflux disease (GERD) can damage the lining of esophagus causing Barrett' s esophagus. Although Barrett's only develops in approximately 5 to 8% of patients with GERD, patients with Barrett's esophagus have a 50 to 100 times increase in their risk of developing cancer compared to the general population[11].

1.2 Treatment of esophageal cancer

Treatment of esophageal cancer depends on the stage of cancer at presentation (Table 1). In medically fit patients in the absence of systemic metastasis (Stage I – III disease), surgery is a vital component of curative therapy. An esophagectomy – the surgical resection of the esophagus - is a long, complex procedure that has historically been associated with significant perioperative morbidity and mortality[12,13].

Table 1 – Staging of Esophageal cancer[14,15]

Stage	Description
Stage 0	Early-stage; carcinoma in situ, a precancerous change
Stage 1	Early-stage; the tumour is small and has not grown outside of the organ it started in
Stage 2 - 3	Locally advanced; the tumour is larger or has grown outside of the organ it started into nearby tissue with involvement of lymph nodes
Stage 4	Metastatic; the cancer has spread through the blood or lymphatic system to a distant site in the body

The first successful esophagectomy for intrathoracic esophageal cancer was reported almost 100 years ago by Torek in 1913[16]. It was not until 20 years later that resection followed by immediate reconstruction was described in a series by Oshawa of Japan[17]. The early experience with esophagectomy from the 1950s to 1970s was plagued with high rates of perioperative mortality, reaching up to 30%[18]. As the disease, medical science, and technology evolved, so have the surgical techniques, which now include at least seven different surgical procedures that can be labeled "esophagectomy." Considerable advances in the understanding, treatment, and management of esophageal cancer in the second half of the 20th century greatly improved operative mortality. Studies from high-volume centers in the last 20 years have reported mortality less than 5% [19,20]. Despite these advances, morbidity after esophagectomy remains substantial, with rates over 60% in some series [21–23].

Over the past few decades, treatment modalities have evolved into a complex array of therapeutic choices involving some combination of chemotherapy, radiation therapy, and surgical resection. For early-stage minimally invasive esophageal cancer (Table 1), resection alone offers high rates of cure. In a comparison between endoscopic and surgical resection of Barrett's esophagus – a precancerous change to the esophageal epithelium – surgery was associated with higher risk of morbidity and procedure-related mortality but comparable overall survival [24,25]. It should be noted, however, that the recurrence rate is higher in patients treated with endoscopic resection, and thorough endoscopic surveillance is necessary[24,25].

Although preoperative chemoradiation remains a subject of debate for early-stage tumors, the implementation of multimodal strategies for locally advanced (Table 1) esophageal cancer has improved both recurrence rates as well as patient survival[26–28]. Neoadjuvant chemoradiotherapy followed by surgery is a strategic option in the treatment of potentially resectable advanced esophageal cancer. The benefit of neoadjuvant chemoradiation was historically controversial because of contradictory results in the early randomized studies[29–32]. More recent randomized studies and meta-analyses have provided strong evidence for survival benefit to support neoadjuvant therapy followed by surgery compared to surgery alone for patients with stages III and IVA esophageal cancer [27,33,34]. It is currently common practice to treat locally advanced disease with tri-modality therapy (concurrent chemotherapy and radiation followed by surgery) after the encouraging results of the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) were published in 2012[27]. This study reported a remarkable increase in survival in patients with locally advanced esophageal cancer undergoing esophagectomy after chemoradiotherapy with similar rates of postoperative complications. It should be noted, however, that the CROSS trial only recruited patients who had a World Health Organization (WHO) performance status score of 2 or lower (on a scale of 0 to 5, with 0 indicating fully active, 1 unable to carry out heavy physical work, and 2 up and about more than half the day but unable to work) and had lost 10% or less of body weight.

The emphasis on performance status in patient selection and implicit recognition of this dimension on treatment outcome can also be seen in recent studies for adjuvant therapy. In the 2021 CheckMate 577 trial – a global, randomized, double-blind, placebo-controlled phase III trial of patients who received neoadjuvant chemoradiotherapy and resected (R0) stage II or III esophageal cancer but was found to still have residual pathological disease - receiving the checkpoint inhibitor, nivolumab, increased median disease-free-survival and decreased risk of disease recurrence and death for both adenocarcinomas and squamous cell carcinomas[35]. It is important to note that the patient selection for this trial only included those with an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1, meaning they were fully active or only restricted in physically strenuous activity. The ECOG Performance Status is commonly used as a prognostic tool or selection criterion in patients with active cancer going under treatment[36,37]. It is one of many tools used to quantify functional status as related to physiologic reserve and frailty, which are patient factors that may explain differences in disease and treatment outcomes. This inclusion criterion of only patients with good performance status was similarly seen in the landmark 2006 MAGIC trial, which found that peri-operative chemotherapy improves the five-year progression-free and overall survival in patients with stage II and III adenocarcinoma of the distal esophagus and stomach[26]. By excluding patients with poor performance status, it is clear that this parameter is a significant consideration in the assessment of a patient's ability to tolerate a proposed treatment. We anticipate seeing increasing numbers of patients with poor performance status, and as such, the impact that has on the recovery path after intervention must be further elucidated.

1.3 Post-esophagectomy Complications

The overall incidence of post-esophagectomy complications ranges from 20-68%, which includes both complications specific to the procedure (e.g., anastomotic leaks, chylothorax) and systemic complications (e.g., pneumonia, myocardial infarction, prolonged ventilator requirement) [21,35,36]. Anastomotic leaks, one of the most serious postoperative complications, happen to one in ten patients; however, some studies report leaks rates as high as 26% [38–43]. Anastomotic leak is associated with a significant increases in mortality[44,45]. Cardiorespiratory complications are also relatively common after esophagectomy, including pneumonia, myocardial infarction, and transient arrhythmia. Many of these complications necessitate intensive care unit (ICU)-level care while they are being managed.

Preoperative factors that are known to increase the risk of complications following esophagectomy include age, pulmonary compromise (e.g., chronic obstructive pulmonary disease), malnutrition, renal or hepatic dysfunction, and emergency surgery[37]. Comorbid illnesses, such as cardiovascular disease, diabetes, chronic obstructive pulmonary disease (COPD), and hypertension, increase the risk of postoperative rates of anastomotic leaks, cardiorespiratory complications, reoperation, and death following an esophagectomy [46,47].

1.4 Measurements of physiologic reserve

A major challenge for patients with esophageal cancer is the impact of the disease and treatment on physiological reserve. These patients are often malnourished at diagnosis due to local tumor effects causing symptoms such as dysphagia, vomiting, inadequate nutritional intake, fatigue, weight and muscle loss[48, 49], which results in a suboptimal state for treatment [50, 51]. Compounding disease-related declines in physiologic reserve are the health consequences that come with aging. According to the United States census bureau, 20% of Americans will be older than 65 years in 2030 and half of them will need an operation - equating to about 36 million older surgical patients[52]. The incidence of esophageal cancer increases with age, and the process of aging is associated with an increasing prevalence of frailty, comorbidities, and a decline of functional reserve. This can contribute to a higher risk of complication, particularly in malnourished surgical patients.

Post-operative complications are multifactorial and can impact not only the patient’s quality of life, but also delay adjuvant therapy and adversely affect survival. It is therefore crucial to identify those patients with poor prognostic indicators. In recent years, there has been a growing interest in pre-surgical optimization in an effort to improve physiologic reserve and decrease postoperative morbidity. This has led to investigations into specific patient factors, such as frailty and sarcopenia, which might be used in quantifiable preoperative risk stratification. While evidence suggest there is a link between lower physiologic reserve and poor post-operative outcomes, a clear and actionable method of identifying patients at higher risk who are candidates for esophagectomy is still known.

1.4.1 Frailty

Frailty is a multidimensional state of increased vulnerability. In medicine, the precise definition of frailty is an evolving one, but it is generally defined as an age-related cumulative decline in physiologic reserve across multiple systems. With the aging global population, frailty is almost unavoidable[53,54]. Frailty in the general population, however, markedly differs from the hospitalized population. In community-dwelling persons between ages 65 to 90 years, prevalence is typically <30%[55]. In the acute care hospital setting, the prevalence of frailty has been estimated to be up to 80% in older patients[56,57].

Not only is frailty pervasive, but it is also an important prognostic factor for adverse health outcomes in many diseases. In older, nonsurgical patients, this phenotype is well-studied. Recently, a large cohort study developed a hospital frailty risk score based on the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) diagnostic codes and found frailty was significantly associated with 30-day mortality and 30-day readmission[58]. This paper represents one of the many studies that have demonstrated frailty is a predictor for many adverse health outcomes, including disability, falls, delirium, hospitalization, and mortality[56,58–60].

Similarly, frailty is equally, if not more, prevalent in the surgical patient population. In a study of 594 patients presenting for elective surgical procedures, 42% of patients had some element of frailty present[61]. Thoracic surgical candidates are no exception; in fact, they are one of the most frail surgical populations, as demonstrated by a recent prospective cohort study of 125 patients that found two thirds of patients had at least one frailty trait, with 12% meeting 3 or more criteria of frailty[62]. Surgery in the already frail population introduces an additional level of stress, and therefore opportunity for morbidity. Emerging research has established frailty as a strong predictor of adverse outcomes and is associated with at least a 2-fold increase in operative mortality, postoperative complications, and rates of readmission in the elderly undergoing surgery for cardiac, colorectal, vascular, and orthopedic procedures [61,63,64]. However, recent studies have also shown that frailty-related adverse outcomes are not limited to the elderly. A 2019 multi-centre prospective cohort study in adult emergency surgical admissions found that worsening frailty at any age is associated with significantly poorer patient outcomes, including increased length of hospital stay, 30-day readmission and 30-day mortality[65].

Despite the importance of frailty and its impact on health outcomes, there is no consensus on the standard of measurement, much less frailty assessment in the preoperative setting. Surgeon impressions, although potentially accurate, lack reliability and reproducibility[66,67]. A recent review on the assessment of frailty in the acute care setting found that two thirds of articles on these subject identified participants as frail without actually measuring frailty[59]. The ones that did had great variability in the tools used[59]. Over the past 20 years, dozens of frailty assessment instruments have been developed for the purpose of risk stratification. Although the approaches may differ, all seek to capture some element that suggests decreased physiologic reserve. The majority of these instruments fall into two predominant models. The first is the frailty phenotype instrument initially described by Fried *et al*.[68], where motor and activity measures are aggregated into a score that spans from robust to frail. The second is the frailty index, as described by Mitnitski *et al*.[69], where co-morbidities, social factors, and psychological decline measures are incorporated into an index; the higher the number of conditions, the higher the frailty score[70] (Table 2).

Table 2 – Comparison of frailty assessment tools

Instrument	Type	Number of items	Domains
Fried Phenotype[68]	Ordinal (0-5, ≥3 frail)	5	Physical
FRAIL Scale[71]	Ordinal (0-5, ≥3 frail)	5	Physical
Frailty Index[69]	Continuous (combination of tests and self-report)	92	Physical, psychosocial, social
Edmonton Frail Scale[72]	Ordinal (0-17 score with 5 levels from not frail to severe frailty)	11	Physical, psychosocial, social
Clinical Frailty Scale - Canadian Study of Health and Aging[73]	Ordinal (1-7 levels from robust to complete dependence)	70	Physical, psychosocial
11-factor Modified Frailty Index[74]	Dichotomous (frail or not frail)	11	Physical
5-factor Modified Frailty Index[75]	Dichotomous (frail or not frail)	5	Physical

Currently, there is no standardized frailty assessment tool used perioperatively. In fact, despite guidelines from specialty societies and national institutions that recommend frailty assessment as best practice[76,77], there is currently little evidence to suggest that frailty assessment is routinely conducted in the preoperative setting[78]. One barrier is the lack of clarity on which measurement tool to use – there are more than 50 frailty instruments or proxy measures described in the literature that have been used in clinical settings[79,80]. Examples of frequently used frailty instruments include the Fried Scale[68], FRAIL scale[71], Frailty Index (a model based on accumulating deficits)[69], Edmonton Frail Scale (a reduced version of the accumulating deficits)[72], and the National Surgical Quality Improvement Program (NSQIP) Modified Frailty Index (mFI)[81] (Table 2). Other well-studied approaches of single physical performance metrics include the 6-min walk test[82], hand-grip strength[83], and gait speed[84].

While predictive accuracy is fundamental to choosing a risk stratification instrument, any frailty tool used in clinical practice must also be simple, accessible, and feasible. Within the surgical literature, there is limited data formally assessing the feasibility of frailty instruments. Even more sparse is the evidence supporting, using, and validating frailty assessment tools in thoracic surgery patients[85] - a group with high rates of frailty[62]. Incorporating risk stratification of this patient population into a standard preoperative work-up is clearly feasible, as demonstrated by Hirpara *et al*. in a 2019 study that investigated frailty assessment in the thoracic surgery population using various scales[86]. Of the 8 frailty measurements used in this study, including physiotherapy tests (6-min walk, gait speed, hand-grip strength), risk stratification (Charlson Comorbidity Index (CCI), Revised Cardiac Risk Index (RCRI), modified Frailty Index), and quality of life questionnaires, Hirpara *et al*. reported 100% completion rate for the frailty indices[86]. Furthermore, despite a small sample size and heterogenous population of 40 patients, they found that the mFI (11-factors) was shown to approach significance ($P = 0.06$) in predicting post-operative complications[86].

Esophagectomy patients – especially those with esophageal cancer – are woefully understudied in the context of frailty. Despite the existence of over 50 frailty assessment tools and proxies, there remains a gap in the literature with respect to how frailty impacts patients undergoing esophageal resection. First, there are currently no accurate estimates of the incidence of frailty within this patient population. Two prospective observational cohort studies designed to address this question are still ongoing – a study of 60 patients based in Denmark is due to conclude in 2022[87], another study by the Cleveland Clinic of 360 patients (esophagectomy and lobectomy combined) will be completed in 2023[88]. To date, only a handful of established frailty measures have been studied in the context of esophagectomy outcomes. In its simplest form, frailty as measured by physiologic metrics has shown promising results in terms of identify patients at risk for morbidity and mortality. In a prospective study of 61 patients, Chen *et al*. found that esophagectomy patients with weak hand-grip strength prior to operation had exceedingly high rates of morbidity within six months such that 100% of patients with grip strength less than 20kg experienced complications as compared with only 20%

in those with grip strengths over 40kg[89]. Another recent study of 77 patients by Tang *et al*. created a brand-new scale using a composite of 4 different physiologic metrics, including upper body strength (grip strength), lower body strength and balance (30-second chair sit-stands), muscle mass (psoas muscle area to height ratio), and cardiopulmonary endurance (6-minute walk distance)[90]. Their quantitative "Esophagectomy Vitality Index" appeared to outperform the established 11-factor NSQIP mFI in predictive accuracy for post-esophagectomy morbidity and mortality[90]. Far from discrediting the mFI, Tang *et al*.'s study of only 77 patients and low rate of desired outcomes (1 mortality, 1.3%; 18 complications, 23%) raises further interest in just how much value the mFI can provide for the esophageal patient population. This is because physiologic measurements are time-consuming and require adequate space, special equipment or personnel, which can be a barrier to adoption and completion in the clinical setting[86]. The mFI, on the other hand, can be readily obtained from available clinical information in both a prospective and retrospective manner. Using the NSQIP database, which collects patient data from across North America and Europe, the mFI has been robustly applied to a wide range of operations. Due to the low number of esophageal cancer patients in general, and even lower still the ones amenable to surgery, the mFI needs to be similarly evaluated in esophagectomy patients using the NSQIP database.

1.4.1.1 American College of Surgeons National Surgical Quality Improvement Program (NSQIP) modified Frailty Index (mFI)

The Modified Frailty Index developed by the American College of Surgeons National Surgical Quality Improvement Program is one of many scales that exist to measure frailty. The beauty of the mFI is its simplicity and ease of use, as demonstrated by Hirpara *et al*. in their 2019 study where they demonstrated a 100% completion rate using the mFI as part of a pre-operative frailty assessment for 40 patients with lung or esophageal cancer.

Originally, the NSQIP mFI contained 11 variables (mFI-11) that mapped to variables from the Canadian Study of Health and Aging Frailty Index (CSHA-FI) (Table 3), a 70-item scale based on the concept of accumulating clinical deficits, which has been shown to be effective in predicting morbidity and mortality in patients[73,91,92]. The index is obtained by dividing the total number of positive variables present by 11[74]. Due to the simplicity of the mFI, it has since gained interest in the academic surgical community as a viable contender for preoperative risk stratification.

Velanovich *et al*. in 2013 were one of the first groups to hypothesize that preoperative frailty, defined using the NSQIP mFI, could predict postoperative morbidity and mortality[74]. Using NSQIP data from 971,434 patients undergoing multiple different domains of subspecialty surgeries obtained over a 4 year period (2005-2009), they demonstrated that there was a stepwise increase in risk of both mortality and morbidity for each unit increase in mFI [74]. This applied to a wide range of surgical subspecialties. Since then, similar findings have been replicated in NSQIP studies within surgical disciplines such as otolaryngology[93], urology[94], general surgery[81,95], orthopedic surgery[96], and more. A 2018 meta-analysis of 16 studies – the first paper to synthesize the evidence across multiple surgical specialties – demonstrated mFI-11 as a prognostic indicator that strongly correlates with post-surgical morbidity and morality. Frail patients (patients with mFI scores above zero) were twice as likely to have major complications (RR 2.03, 95%CI 1.26-3.29; P = 0.004) and 4 times more likely to die (RR 4.19, 95% CI 2.96-5.92; P < 0.001) compared to non-frail patients[97].

Table 3 - NSQIP mFI-11 preoperative risk factors mapped to items of CSHA-FI

	NSQIP mFI-11	CSHA-FI
1	**Functional health status before surgery*** - partially dependent - totally dependent	Changes in everyday activity
		Problems with getting dressed
		Problems with bathing
		Problems with carrying out personal grooming
		Problems with cooking
		Problems with going out alone
2	**Diabetes mellitus*** - noninsulin - insulin	History of diabetes mellitus
3	**History of severe COPD***	Lung problems
4	Current pneumonia	Respiratory problems
5	**Congestive heart failure within 30 days before surgery***	Congestive heart failure
6	Cardiac problems - History of myocardial infarction within past 6 months before surgery - Previous percutaneous coronary intervention or percutaneous - Previous cardiac surgery - History of angina within 1 month before surgery	Myocardial infarction
		Cardiac problems
7	**Hypertension requiring medication***	Arterial hypertension
8	Impaired sensorium	Clouding or delirium
		History relevant to cognitive impairment or loss
		Family history relevant to cognitive impairment
9	History of transient ischemic attack	Cerebrovascular problems
10	Cerebrovascular accident or stroke with neurologic deficit	History of stroke
11	History of revascularization or amputation for peripheral vascular disease Rest pain or gangrene	Decreased peripheral pulses

CSHA-FI = Canadian Study of Health and Aging frailty index; COPD - chronic obstructive pulmonary disease; NSQIP - National Surgical Quality Improvement Program.
*mFI-5 factors

Within the NSQIP literature, esophagectomy patients are understudied. Hodari *et al*. published one of the first studies looking at mFI-11 score and adverse outcomes in esophagectomy patients. Using a cohort of 2095 patients who underwent an esophagectomy between 2005 to 2010, they found that among the parameters associated with postoperative outcomes, frailty was significantly associated with risk of perioperative morbidity and mortality. The incidence of perioperative mortality incrementally increased with the frailty score, with mortality only 1.8% among patients with a frailty score 0 vs. 23.1% among those patients with a frailty score 5 (P = 0.001)[98]. It should be noted that the maximum score was only 5 out of 11, indicating there may be room for further simplification of this index. Three other studies subsequently confirmed the association between higher mFI score and mortality[81,98], as well as major postoperative complications, and prolonged length of stay in hospital[99].

In the last decade however, many NSQIP variables have been modified or removed, as previous literature has shown that frailty indices with as few as 10 variables are reliable[100]. In 2011, the reporting of some preoperative patient comorbidities, such as pneumonia, cardiac problems, and a history of transient ischemic attack, was made optional. Starting in 2012, NSQIP stopped recording some variables altogether, making this the last year containing all 11 comorbidities making up the original mFI-11. Gani *et al*. highlighted this problem of missing data, questioning the capability of using the 11-factor mFI within clinical evaluation and for future research[101]. As of 2015, only 5 of the original 11 factors remained. The 5 remaining variables are: functional status, diabetes, congestive heart failure, hypertension requiring medication, and severe COPD[102].

This data issue prompted a transition from the 11-factor to the 5-factor Modified Frailty Index (mFI-5). Several studies have attempted to validate the value of this new scale for surgical risk stratification in a variety of operations. In a 2017 publication, Subramniam *et al*. was to the first to directly compare mFI-5 to its 11-factor predecessor. They demonstrated that mFI-5 was an equally effective predictor for mortality, post-operative complications, and unplanned 30-day readmission across all sub-specialty surgeries, except for cardiac and vascular surgery[103]. Since then, the 5-factor mFI has been used to successfully predict complications in several surgical subspecialties, including thoracic surgery[75,104–106]. However, within thoracic surgery, there have been no studies specifically examining the value of mFI-5 in esophagectomy outcomes.

1.4.2 Sarcopenia

The plethora of frailty assessment tools designed to quantify physical and psychosocial parameters as a proxy for physiologic reserve still seem to fail to capture or account for the impact of functional status. In this respect, morphometric analyses, such as sarcopenia, may offer unique insight into measures of patient health that can affect post-surgical outcomes. Sarcopenia is a term first introduced in 1989 by Irwin Rosenberg; it stems from the Greek words “sarx” meaning flesh and “penia” meaning loss or poverty[107]. In medicine, sarcopenia was originally defined by the 2010 European Working Group on Sarcopenia in Older People (EWGSOP) as the presence of low muscle mass and low muscle function (low muscle strength or low physical performance)[53]. In 2019, the revised EWGSOP2 operational definition identifies probable sarcopenia with presence of low muscle strength and confirms the diagnosis with low muscle quantity or quality. If there is presence of low physical performance, sarcopenia is considered severe[108]. This shift in emphasis from muscle mass to muscle strength is relatively new and not yet widely adopted in research. This is likely because assessments of muscle strength, such as grip strength or chair stand test, are not collected as part of routine clinical assessment. Given the retrospective nature of most studies on sarcopenia, this parameter has not been extensively studied or incorporated into more accessible measurements of muscle mass, such as of skeletal muscle area which is derived from CT or magnetic resonance imaging (MRI). Nevertheless, much literature has been written about using muscle mass alone as a parameter for diagnosing sarcopenia.

Sarcopenia is part of the normal aging process, where muscle loss starts at 30 years of age and accelerates after 70 years[54]. In the general population, estimated prevalence in those between 60 to 70 year old is 5 to 13%; this increases to 11 to 50% in people over

80 years of age[53]. Although it is primarily associated with aging, sarcopenia is not exclusive to the elderly. Malignancy is one of the most notable pathological conditions that promotes muscle atrophy[109] as patients experience malnutrition, decreased activity levels, and cachexia. One systematic review of 35 articles across a wide range of cancers found that 38.6% of adult cancer patients awaiting therapy were sarcopenic[110]. Others show the prevalence of sarcopenia differ widely from 14% to 78.7% depending on the cancer diagnosis[111].

Over and over again, sarcopenia has been found to be an independent prognostic factor for reduced survival. It has been linked to morbidity and mortality in various solid tumours, including breast[112], colorectal[113], pancreatic[114], esophageal[115] and other gastrointestinal cancers[116]. Furthermore, in the surgical cancer population, sarcopenia is significantly and independently associated with post-operative complications, chemotherapy-induced toxicity and poor survival[110]. For esophageal cancer in the context of surgical resection, the literature on the association between sarcopenia and post-operative outcomes is only emerging over the last 10 years. In the esophageal cancer population, the role of sarcopenia remains controversial, as findings are often inconsistent. This is in large part because, despite a clear definition, there is no consensus on diagnostic criteria or standardized measurement until very recent recommendations by the updated guidelines from EWGSOP2. There is considerable variation within sarcopenia literature, as the number of reports relating to body composition assessment in patients undergoing surgical resection for esophageal cancer continue to rise. As such, meta-analyses attempting to synthesize the existing body of work contain significant heterogeneity in terms of surgical approach and technique (i.e., abdominal vs. thoracic, open vs. minimally invasive), histology (i.e., adenocarcinoma, SCC), neoadjuvant treatments, clinical stages, and sarcopenia criteria (i.e., psoas vs. skeletal muscle index).

Although the measurement of muscle mass in sarcopenia has been largely established using CT measures, there is still much variation. For example, some studies use lean psoas area (LPA) – the total area of the psoas muscle in a cross-sectional CT scan measured at the 3rd or 4th lumbar vertebrae (L3 or L4) normalized by height. Others use the Skeletal Muscle Index (SMI, cm^2/m^2) – calculated by the formula total area of skeletal muscle measured on CT at L3 (cm^2) divided by height (m) squared[117]. The SMI is the predominant method of calculation because it provides a quantifiable, reproducible and objective measure of sarcopenia that has been found to correlate both with body composition and cancer patient prognosis[118]. However, defining parameters for body composition continues to be a challenge since there is no universally agreed upon cut-off threshold for sarcopenia. As such, interpretation of sarcopenia literature must be approached with a nuanced eye.

Perhaps not surprisingly, in the studies examining the impact of sarcopenia on esophageal cancer resection, results with respect to postoperative morbidity varies considerably. A 2013 study by Sheetz *et al*. – one of the early forays into sarcopenia and esophagectomy outcomes – examined a cohort of patients undergoing transhiatal esophagectomy for cancer. They did not find LPA to be a significant factor in developing major morbidities, such as pulmonary complications[119], which was similarly reported by Nakashima *et al*. who used Skeletal Muscle Index (SMI) for their sarcopenia assessment[120]. However, several subsequent Japanese studies have since refuted these findings with respect to postoperative pulmonary complications, where the risk in sarcopenic patients defined using SMI were found to be 2- to 4-fold compared to their non-sarcopenia counterparts. Additionally, the incidence of prolonged ventilatory support, reintubation for respiratory failure, pleural effusions, and pneumonia were higher in patients with sarcopenia[121–125] – suggesting that the presence of sarcopenia appeared to be an independent predictor of pulmonary complications. Two meta-analyses also support these findings, one of which found in their subgroup analysis that sarcopenic patients were almost 2 times more likely to experience postoperative pneumonia[126]. Interestingly, when it comes to non-pulmonary complications, particularly anastomotic leaks, there is virtually no evidence to support that sarcopenia is a significant risk factor[121–128].

The results with respect to post-surgical mortality are also varied. One study found that sarcopenia may not be a significant predictor of overall survival or disease free survival in patients receiving neoadjuvant chemoradiation; however, in patients not receiving neoadjuvant therapy, both overall and disease free survival are better in the absence of sarcopenia[119]. Few studies assess mortality however, the ones that do have not demonstrated sarcopenia as a significant risk factor for short term survival (in-hospital or 30-day) [126,128,129]. Where long term survival is concerned, sarcopenia perhaps warrants more consideration. A meta-analysis by Deng *et al*. which examined 11 cohort studies consisting of 1520 patients who underwent esophagectomy for esophageal cancer of various stages found that patients with sarcopenia had a significantly lower 3-year as well as 5-year overall survival compared to those without[130]. Similarly, Boshier *et al*. also reported lower long term survival in sarcopenia patients overall[126]. However, a more recent meta-analysis from 2020 also with 11 studies, but representing 1979 patients, found no difference in mortality rates between patients with and without sarcopenia[127].

Despite the inconclusive evidence with respect to post-operative outcomes, sarcopenia has proven to be an important measure of patient health. It is also clear that, just like frailty indices and other instruments designed to assess functional capacity, sarcopenia still provides an incomplete picture. Its utility as a risk stratification tool for esophageal cancer patients undergoing oncologic resection certainly warrants further investigation. Given the limited evidence to support the predictive superiority of a single instrument, perhaps there are yet other ways to improve on the existing methods.

1.5 Hypothesis and objectives

To the best of our knowledge, there have been no studies thus far specifically examining the predictive value of mFI-5 in post-esophagectomy outcomes for esophageal cancer patients, nor have there been studies directly comparing frailty versus sarcopenia in the same cohort of patients. Given the prevalence of malnutrition, sarcopenia, and frailty, as well as the high rate of morbidity and mortality associated with esophageal cancer and surgical resection, we aim to further investigate mFI-5 and sarcopenia to aid both patients and health care providers in making the most informed treatment decisions.

Pre-operative identification of factors associated with post-esophagectomy morbidity may provide us an opportunity for patient optimization to minimize negative outcomes. The current literature does not provide evidence to support the ideal way to identify patients with poor physiologic reserve undergoing esophagectomy. We hypothesize that frailty and or/sarcopenia measurement may be useful markers for increased risk of post-operative morbidity and mortality. This thesis investigates two tools – the NSQIP 5-Factore modified frailty index and sarcopenia as measured by skeletal muscle index using total skeletal muscle area – to understand their association with post-operative outcomes in patients undergoing esophagectomy for esophageal cancer.

Chapter 2 – NSQIP 5-Factor Modified Frailty Index is Associated with Morbidity not Mortality after Esophagectomy for Esophageal Cancer

2.1 Introduction

Esophageal cancer is one of the most highly lethal gastrointestinal tract malignancies. It is 7th in incidence and 6th in cancer mortality worldwide[1]. The incidence of esophageal cancer has increased sharply over the past few decades. An esophagectomy is the cornerstone of treatment and historically associated with significant perioperative morbidity and mortality[12,13]. The increased risk of postoperative complications is compounded by malnutrition caused by dysphagia and cancer cachexia, resulting in physiological and functional compromise.

Frailty is a multidimensional state of increased vulnerability and not limited to the elderly. Frailty at any age is associated with significantly poorer post-operative patient outcomes, including increased length of hospital stay, readmission and mortality[65]. Thoracic surgery patients have a high proportion of frailty, as demonstrated by a recent prospective cohort study of 125 patients that found two thirds of patients had at least one frailty trait, with 12% meeting three or more criteria of frailty[62].

The mFI derived from the variables of the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) is one of many scales that exist to measure frailty. Originally, the NSQIP mFI contained 11 variables that mapped to variables from the Canadian Study of Health and Aging Frailty Index (CSHA-FI) (Table 2), a 70-item scale based on the concept of accumulating clinical deficits, which has been shown to be effective in predicting morbidity and mortality in a wide variety of patient populations[73,91,92]. In 2015, the 11-factor index (mFI-11) was simplified to only five factors (mFI-5) after eliminating factors where reporting was optional and therefore inconsistently recorded (Table 3). In the original mFI-11, the incidence of postoperative mortality in esophagectomy patients incrementally increased with frailty score[98]. Further, mortality among non-frail patients was only 1.8% compared to 23.1% among patients with a frailty score 5 ($P = 0.001$)[98]. Since the simplification of the modified frailty index, however, the mFI-5 has not been re-examined in the esophagectomy population. A better understanding of how the mFI-5 is associated with surgical outcome is imperative to define the utility of this frailty index as a risk stratification tool in this patient cohort.

In this study, we used the ACS NSQIP 5-factor modified frailty index to investigate the association between frailty and postoperative severe complications and mortality in patients undergoing esophagectomy for esophageal cancer. We hypothesized that frailty would be associated with a higher rate of complications and death.

2.2 Methods

We obtained data on all patients who underwent an esophagectomy between 2016-2018 from the ACS NSQIP Participant User File (PUF)[102]. The NSQIP PUF is a Health Insurance Portability and Accountability Act (HIPAA)-compliant data file containing postoperative 30-day patient data collected from over 700 hospitals largely in North America, with a few participating locations in Australia, Europe, Asia, and the Middle East. The database incorporates more than 270 variables including demographics, surgical profiles, comorbidities, and preoperative and intraoperative variables. Data are captured by trained surgical clinical reviewers both in hospital and after discharge [102]. Data are captured for the first 30 post operative days[102]. In order to obtain complete data on this patient population, both the main PUF and procedure-specific esophagectomy PUF were used. The procedure-specific esophagectomy PUF contained information on neoadjuvant treatment status and pathologic diagnosis, which were not available in the main PUF. The years 2016-2018 were selected because this period represents the years for which the procedure-specific esophagectomy PUF was available. Patients were included if they were over 18 years of age, underwent an esophagectomy for esophageal cancer or dysplasia, and had complete records for the mFI-5 fields and outcomes of interest.

The mFI-5 frailty index consists of 5 non-overlapping clinical conditions: 1) hypertension requiring medication, 2) diabetes mellitus requiring treatment with oral agents or insulin, 3) history of severe COPD; 4) functional status, and 5) congestive heart failure (CHF) in 30 days before surgery [102]. Functional status was broken down into independent, partially dependent, or totally dependent – a point was counted for this variable if the patient was partially or totally dependent. The mFI score was calculated for each patient by adding the number of variables present in NSQIP for each patient, with 0–5 total points possible. In keeping with other studies using mFI, we chose to not assess weights to each factor to keep the determination of the FI as simple as possible [81,98,103]. Additional comorbidities were extracted from the database to provide a fulsome description of the patient population. These included smoking, dyspnea, ventilator dependent status, ascites, dialysis, disseminated cancer, open wound or wound infection, chronic steroid use, more than 10% weight loss in last 6 months, bleeding disorder, transfusion within last 72 hours, and preoperative sepsis (Table 6).

The primary outcome was the association between mFI-5 score and severe postoperative complications within 30 days. Postoperative complications were evaluated using the Clavien-Dindo classification system, with severe complications categorized as grade IV based on the Clavien-Dindo grading criteria (Table 4). Clavien-Dindo grade IV complications are defined as those which are life-threatening and therefore require management in the intensive care unit (ICU). Within NSQIP, we considered the following complications grade IV: reintubation, ventilation >48hr, cardiac arrest, myocardial infarction, renal failure requiring dialysis, stroke/CVA, and septic shock. These complications were chosen either because of the known need to for an ICU setting (e.g. vasopressor support for shock state in sepsis), or in accordance with the clinical examples of complications grades proposed by the Clavien-Dindo system[131,132].

Table 4 – Clavien-Dindo classification of surgical complications[131] and corresponding NSQIP categories[102]

Grade	Definition
I	Any postoperative complications that do not require interventions - Superficial SSI, acute renal failure, renal insufficiency, neurologic deficit/peripheral nerve injury
II	Postoperative complications requiring pharmacologic interventions - Deep incisional SSI, organ/space SSI, wound disruption/dehiscence, deep vein thrombosis, pulmonary embolism, pneumonia, urinary tract infection, transfusion, sepsis
III	Postoperative complications requiring surgical, radiologic, or endoscopic interventions - Reoperation
IV	Life-threatening complications requiring intensive care unit management - Ventilator >48 hr, reintubation/unplanned intubation, septic shock, myocardial infarction, cardiac arrest, stroke/CVA, progressive renal failure requiring dialysis
V	Complications leading to death

SSI = surgical site infection

Secondary outcomes included 30-day mortality, length of stay >30 days, return to the operating room, and anastomotic leak. According to NSQIP, length of stay >30 days is counted for patients who have a continuous stay in the acute care setting more than 30 days after surgery. Return to the operating room status is recorded to include all major surgical procedures that required the patient to be taken to the surgical operating room for intervention of any kind.

2.2.1 Statistical Analysis

The available data were described as means with standard deviations for normally distributed continuous variables, medians with interquartile ranges for non-normally distributed continuous variables, and frequencies with associated percentages for categorical variables. Shapiro-Wilk normality test was used to determine normality of continuous variables: age, body mass index (BMI), total length of stay, and operation duration.

Relationships between categorical variables were assessed using Pearson chi-squared or Fischer's exact test, where appropriate. Relationships between categorical and continuous variables were assessed using one-way ANOVA or Kruskal-Wallis rank sum test, where appropriate. Univariate logistic regression was used to determine the odds ratio (OR) in unadjusted comparisons between higher mFI scores to mFI 0 for both major postoperative complications and mortality.

Multivariate logistic regression was used to obtain an adjusted estimate of the association between mFI score and outcomes of interest. Variables for inclusion were chosen based on: 1) known clinical association with adverse surgical outcomes based on existing literature[133–136], or 2) a statistically significant relationship ($p<0.10$) with increase mFI score based on univariate analysis. Variables included: age, sex, BMI, American Society of Anesthesiology (ASA) classification, operative duration, emergency surgery status, and neoadjuvant therapy status. Since only 7 patients (0.3%) had an ASA of 1, this category was combined with ASA 2, which had 420 patients (16.4%). This new ASA variable of 1+2 was used to compare against ASA 3 and ASA 4.

There was significant collinearity between preoperative chemotherapy and radiation, as expected based on the current standard of neoadjuvant treatment. In order to avoid over fitting the model, neoadjuvant therapy status was turned into a binary variable where a positive status was recorded for patients who underwent either chemotherapy or both forms of therapy. There was no significant collinearity between other variables in the model (Figure 1).

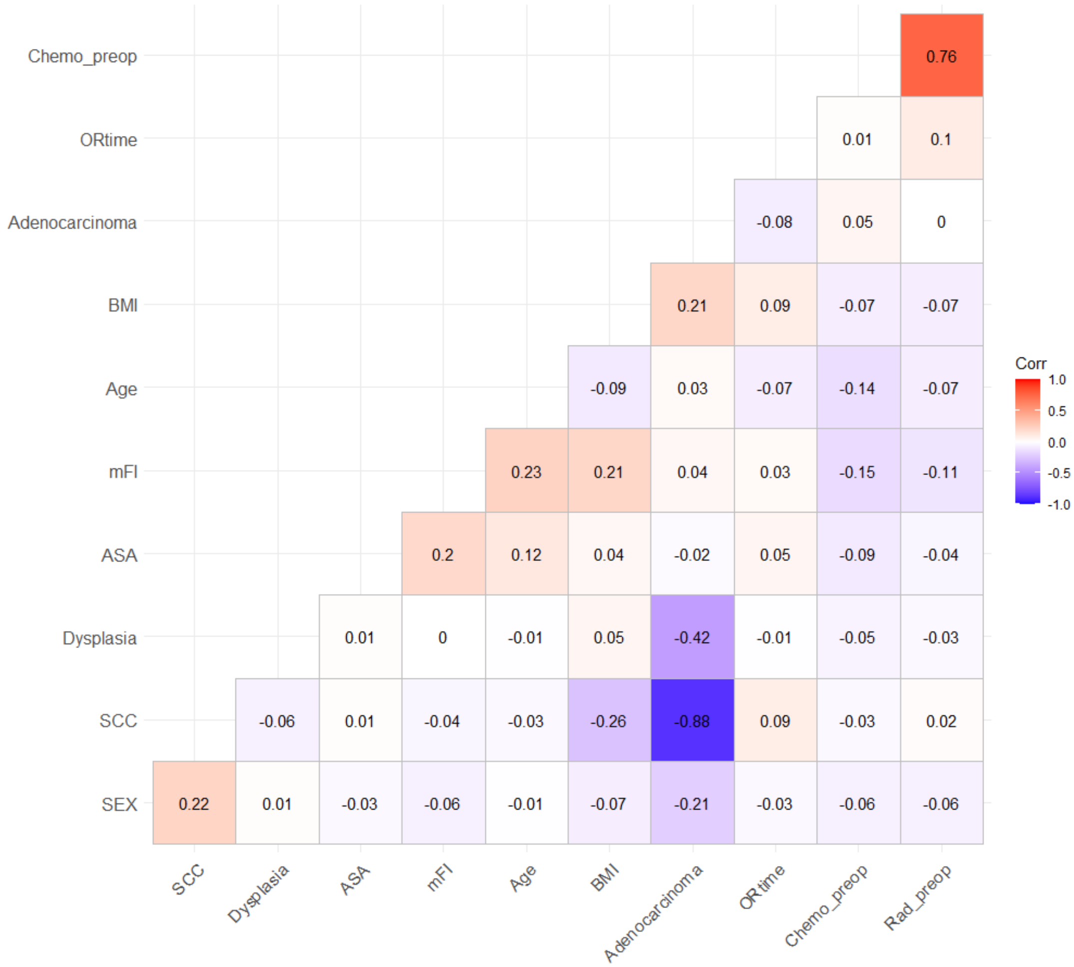

Figure 1. Pearson correlation coefficients for included NSQIP variables

Cases with missing data for any variable of interest were excluded on a case-by-case basis. Although the missing data was presumed to be not at random, we did so because the proportion of cases with missing data was very small compared to the total sample size (<2%). Specifically for the data required to determine a mFI score, 5 cases (0.19%) were excluded due to missing data. Readmission as an outcome was omitted altogether since over one third of patients (832 of 2567, 32.4%) did not have data recorded for this variable. *A priori* we planned to complete subgroup analysis based on pathology, with the hypothesis that the impact of frailty on post-operative outcomes would differ in patients with squamous cell carcinoma and adenocarcinoma. Due to the small number of patients with higher mFI scores, these analyses were significantly underpowered and therefore not reported.

Results from regression analyses are presented as adjusted odds ratios along with 95% confidence intervals (CI) and P values. In all comparisons, a p-value of less than 0.05 was considered significant. All statistical analysis was carried out using SPSS software, version 27 (IBM, Armonk, New York, USA).

2.3 Results

2.3.1 Patient Demographics

A total of 3,049,617 patients were included in the NSQIP database, between 2016-2018, 3,279 of whom underwent esophagectomy. Excluded patients totaled 712 and were excluded for the following reasons: no data recorded for functional status (5), non-esophageal cancer or dysplasia on pathology (572 no malignancy, 51 other malignancy, 69 benign, 15 unknown pathology). In total, 2,567 cases were included in the final analysis.

Patient demographics are outlined in Table 5. The median age was 65 (IQR 58-71) and the median BMI was 27 (IQR 23.7-30.7). The majority were male (83.35%) with ASA 3 classification (76.3%). Adenocarcinoma (86.9%) was the most common diagnosis. Calculated mFI-5 scores for all patients in the study sample ranged from 0 to 3; no patients who underwent an esophagectomy had a frailty score of 4 or 5. The number of patients with each mFI score were as follows: mFI 0 = 1103, (43%), mFI 1 = 982 (38.3%), mFI 2 = 435 (16.9%), and mFI 3 = 47 (1.8%). Increasing mFI scores were associated on univariate analysis with increasing age ($P < 0.001$), and BMI ($P < 0.001$), male sex ($P<0.001$), and not receiving neoadjuvant chemotherapy ($P < 0.001$) and radiation therapy ($P < 0.001$) (Table 5). The most common comorbidity was hypertension requiring medication (48.9%), followed by weight loss greater than 10kg in the last 6 months (21.8%) (Table 6).

Table 5 - NSQIP esophagectomy patient demographics by mFI-5 score

Characteristic	Overall N = 2567	mFI-5 Score 0 N = 1103	1 N = 982	2 N = 435	3 N = 47	p-value
Age (years)						
Median [IQR]	65 [58-71]	62 [55-69]	67 [60-72]	68 [61-73]	69 [60.5-73]	<0.001
BMI (kg/m^2)						
Median [IQR]	27 [23.7-30.7]	25.8 [22.7-29]	27.6 [24.4-31]	28.8 [25.1-32.8]	30.4 [25.9-34.2]	<0.001
(Missing data)	4 (0.2%)	1 (0.1%)	2 (0.2%)	1 (0.2%)	0 (0.0%)	
Sex						
Male	2138 (83.3%)	883 (80.1%)	851 (86.7%)	358 (82.3%)	46 (97.9%	<0.001
Female	429 (16.7%)	220 (19.9%)	131 (13.3%)	77 (17.7%)	1 (2.1%)	
Pathology						
Adenocarcinoma	2230 (86.9%)	939 (85.1%)	866 (88.2%)	384 (88.3%)	41 (87.2%)	0.16
SCC	272 (10.6%)	136 (12.3%)	92 (9.4%)	39 (9.0%)	5 (10.6%)	0.10
Dysplasia	65 (2.5%)	28 (2.5%)	24 (2.4%)	12 (2.8%)	1 (2.1%)	0.97
ASA Classification						-
1	7 (0.3%)	6 (0.5%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	
2	420 (16.4%)	256 (23.2%)	139 (14.2%)	25 (5.7%)	0 (0.0%)	
1+2	427 (16.6%)	262 (23.7%)	140 (14.3%)	25 (5.7%)	0 (0.0%)	-
3	1959 (76.3%)	785 (71.2%)	771 (78.5%)	364 (83.7%)	39 (83.0%)	
4	178 (6.9%)	55 (5.0%)	69 (7.0%)	46 (10.6%)	8 (17.0%)	
(Missing data)	3 (0.1%)	1 (0.1%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	
Neoadjuvant Chemotherapy	1,775 (69.1%)	853 (77.3%)	638 (65.0%)	254 (58.4%)	30 (63.8%)	<0.001
(Missing data)	27 (1.1%)	8 (0.7%)	12 (1.2%)	7 (1.6%)	0 (0.0%)	
Neoadjuvant Radiation	1,524 (59.4%)	730 (66.2%)	541 (55.1%)	228 (52.4%)	25 (53.2%)	<0.001
(Missing data)	31 (1.2%)	9 (0.8%)	14 (1.4%)	8 (1.8%)	0 (0.0%)	

Table 6 – NSQIP esophagectomy patient comorbidities by mFI-5 score

Comorbidity	Overall N = 2567	mFI-5 Score 0 N = 1103	1 N = 982	2 N = 435	3 N = 47
Hypertension on medication*	1,254 (48.9%)	0 (0.0%)	788 (80.2%)	421 (96.8%)	45 (95.7%)
Diabetes*	506 (19.7%)	0 (0.0%)	122 (12.4%)	342 (78.6%)	42 (89.4%)
Chronic obstructive pulmonary disease*	203 (7.9%)	0 (0.0%)	66 (6.7%)	96 (22.1%)	41 (87.2%)
Functionally dependent*	20 (0.8%)	0 (0.0%)	6 (0.6%)	6 (1.4%)	8 (17.0%)
Congestive heart failure*	10 (0.4%)	0 (0.0%)	0 (0.0%)	5 (1.2%)	5 (10.6%)
Smoking	630 (24.5%)	290 (26.3%)	228 (23.2%)	97 (22.3%)	15 (31.9%)
Dyspnea	228 (8.9%)	68 (6.2%)	76 (7.7%)	69 (15.9%)	15 (31.9%)
Ventilator dependent	3 (0.1%)	2 (0.2%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Ascites	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
On dialysis	6 (0.2%)	2 (0.2%)	1 (0.1%)	2 (0.5%)	1 (2.1%)
Disseminated cancer	93 (3.6%)	43 (3.9%)	34 (3.5%)	12 (2.8%)	4 (8.5%)
Open wound/wound infection	15 (0.6%)	6 (0.5%)	8 (0.8%)	1 (0.2%)	0 (0.0%)
Steroid use for chronic condition	68 (2.6%)	22 (2.0%)	32 (3.3%)	13 (3.0%)	1 (2.1%)
>10% weight loss in last 6 months	560 (21.8%)	269 (24.4%)	199 (20.3%)	83 (19.1%)	9 (19.1%)
Bleeding disorder	93 (3.6%)	31 (2.8%)	37 (3.8%)	23 (5.3%)	2 (4.3%)
Transfusion ≥1 units PRBCs in 72 hours before surgery	6 (0.2%)	3 (0.3%)	2 (0.2%)	1 (0.2%)	0 (0.0%)
Preop sepsis	21 (0.8%)	11 (1.0%)	6 (0.6%)	3 (0.7%)	1 (2.1%)

2.3.2 Outcomes

Outcome distribution by mFI-5 score are displayed in Table 7. Clavien-Dindo grade IV complications occurred in 14.6 % (374 of 2,567) of patients within 30 days. The proportion of Clavien-Dindo IV complications increases significantly with higher mFI scores ($p<0.001$). Overall mortality was 2.6% and was not significantly associated with frailty on univariate analysis ($p = 0.15$). Frailty was, however, found on univariate analysis to be associated with the following outcomes: length of stay (p=<0.001), length of stay > 30 days ($p=0.008$), anastomotic leak ($p<0.001$), superficial SSI ($p=0.025$), organ space SSI ($p=0.002$), pneumonia ($p<0.001$), reintubation ($p<0.001$), prolonged intubation ($p<0.001$), sepsis ($p=0.043$) and septic shock ($p=0.002$).

Multivariate logistic regression analyses controlling for age, sex, BMI, ASA class, total operation time, emergency surgery status, and neoadjuvant status demonstrated association between higher levels of frailty and complications (Table 8). Specifically, patients with a mFI-2 had 1.53 times greater odds of Clavien-Dindo grade IV complications, and those with mFI-3 had 2.35 times greater odds than those with an mFI of 0.

Higher mFI scores had a larger proportion of patients who died within 30 days. Although the odds ratio increased with higher mFI score, neither univariate nor multivariate analyses for mortality reached significance.

Table 7 – NSQIP Outcomes and corresponding mFI-5 score, N (%)

		mF-5 Score				
Complications	**Overall N = 2567**	**0 N = 1103**	**1 N = 982**	**2 N = 435**	**3 N = 47**	**p-value[1]**
Clavien-Dindo IV	374 (14.6%)	123 (11.2%)	153 (15.6%)	86 (19.8%)	12 (25.5%)	<0.001
Mortality	67 (2.6%)	21 (1.9%)	29 (3.0%)	15 (3.4%)	2 (4.3%)	0.15
Length of hospital stay (days)						
Median [IQR]	9 [7-12]	8 [7-11]	9 [7-13]	9 [7-14]	9 [7-14]	<0.001[2]
Length of stay >30 days	123 (4.8%)	36 (3.3%)	56 (5.7%)	27 (6.2%)	4 (8.5%)	0.008
Return to OR	411 (16.0%)	128 (11.6%)	178 (18.1%)	98 (22.5%)	7 (14.9%)	<0.001
Anastomotic leak	357 (13.9%)	108 (9.8%)	160 (16.3%)	82 (18.9%)	7 (14.9%)	<0.001
Superficial SSI	120 (4.7%)	39 (3.5%)	48 (4.9%)	29 (6.7%)	4 (8.5%)	0.025
Deep SSI	28 (1.1%)	7 (0.6%)	14 (1.4%)	7 (1.6%)	0 (0.0%)	0.19
Organ space SSI	262 (10.2%)	88 (8.0%)	106 (10.8%)	61 (14.0%)	7 (14.9%)	0.002
Pneumonia	344 (13.4%)	115 (10.4%)	146 (14.9%)	72 (16.6%)	11 (23.4%)	<0.001
Reintubation	282 (11.0%)	87 (7.9%)	119 (12.1%)	66 (15.2%)	10 (21.3%)	<0.001
Pulmonary embolism	44 (1.7%)	19 (1.7%)	16 (1.6%)	7 (1.6%)	2 (4.3%)	0.49
Prolonged ventilation >48hr	226 (8.8%)	75 (6.8%)	95 (9.7%)	46 (10.6%)	10 (21.3%)	<0.001
Acute renal failure	27 (1.1%)	7 (0.6%)	11 (1.1%)	7 (1.6%)	2 (4.3%)	0.052
Progressive renal failure	16 (0.6%)	5 (0.5%)	6 (0.6%)	5 (1.1%)	0 (0.0%)	0.46
DVT	65 (2.5%)	20 (1.8%)	30 (3.1%)	15 (3.4%)	0 (0.0%)	0.12
Stroke/CVA	4 (0.2%)	2 (0.2%)	1 (0.1%)	1 (0.2%)	0 (0.0%)	0.84
Myocardial infarction	23 (0.9%)	3 (0.3%)	6 (0.6%)	12 (2.8%)	2 (4.3%)	<0.001
Cardiac arrest	43 (1.7%)	15 (1.4%)	16 (1.6%)	11 (2.5%)	1 (2.1%)	0.34
Bleeding requiring transfusion	291 (11.3%)	113 (10.2%)	109 (11.1%)	62 (14.3%)	7 (14.9%)	0.13
Sepsis	130 (5.1%)	41 (3.7%)	60 (6.1%)	26 (6.0%)	3 (6.4%)	0.043
Septic shock	138 (5.4%)	43 (3.9%)	55 (5.6%)	34 (7.8%)	6 (12.8%)	0.002
C. difficile infection	47 (1.8%)	16 (1.5%)	18 (1.8%)	11 (2.5%)	2 (4.3%)	0.22

SSI = surgical site infection; CVA = cerebral vascular event; DVT = deep vein thrombosis
[1] Pearson's Chi-squared test; Fisher's exact test
[2] Kruskal-Wallis rank sum test

Table 8 – Adjusted Odds Ratio of Clavien-Dindo IV complications for mFI-5 score and covariates of multivariate logistic regression

Variable	Odds ratio (P; 95% CI)
mFI 1 (vs. 0)	1.28 (0.070; 0.98 - 1.68)
mFI 2 (vs. 0)	1.53 (0.011; 1.10 - 2.11)
mFI 3 (vs. 0)	2.35 (0.017; 1.16 – 4.74)
ASA Class 3 (vs. 1+2)	1.84 (0.002; 1.25 – 2.70)
ASA Class 4 (vs. 1+2)	2.10 (0.006; 1.24 – 3.57)
Age	1.01 (0.128; 0.99 – 1.02)
Sex	1.22 (0.186; 0.91 – 1.63)
BMI	0.99 (0.390; 0.97 – 1.01)
Operative duration	1.00 (0.000; 1.00 – 1.00)
Emergency surgery	2.83 (0.246; 0.49 – 16.34)
Neoadjuvant therapy	0.62 (0.000; 0.49 – 0.078)

2.4 Discussion

The impact of frailty as a risk factor is difficult to assess for cancer patients undergoing esophageal resection. In this study, we investigated the association between the NSQIP mFI-5 and 30-day post-esophagectomy outcomes in those with dysplasia and malignant esophageal pathologies. These outcomes included severe ICU-level complications, mortality, length of stay >30 days, return to the operating room for any reason, and anastomotic leak. Although higher mFI-5 score was associated with significantly higher odds of severe complications, and to a lesser extent, return to the operating room and anastomotic leak, the same level of significance could not be said about mortality and prolonged hospital stay, although there is a trend towards increased risk.

Patient selection is crucial to reducing the inherent risk of surgery in the oncology patient population. How the stress of surgery affects patients is multifactorial; having an accurate perception of surgical risk is important for treatment planning. Risk calculators for preoperative stratification of surgical patients have been used for decades - the American Society of Anesthesiologists physical status (ASA-PS) classification, developed over 70 years ago, is still the most widely used tool for risk assessment by surgeons and anesthesiologists. Although the ASA classification has good predictive power for complications, mortality, and length of stay despite being highly subjective and moderate inter-rater reliability[137], the operative risk for a high-risk patient undergoing bunion surgery is quite different than the operative risk for the same patient undergoing an esophagectomy. Inaccurate estimations of morbidity and mortality can lead to inadequate information being provided during the consent process and poor resource allocation in the postoperative period.

Emerging research has established frailty as a strong predictor of adverse outcomes and is associated with increased operative mortality, postoperative complications, and rates of readmission[61,63,64,73]. Several frailty assessment tools have been developed that focus on simple motor and activity measures. Both grip strength[138] and gait speed[139] have been proposed as useful single markers of physical frailty, in addition to being components of validated frailty scales, such as the Fried Frailty Phenotype[68] and FRAIL scale[140,141]. In clinical practice, the application of these frailty assessment tools have been limited, likely because of the resources required to obtain physical measurements. More complex risk stratification tools, such as the Edmonton Frail[72] and CSHA-FI[73,91], take into account both physical and psychosocial metrics in an attempt to produce results with more granularity. Although the 70-item CSHA-FI is a well validated frailty assessment tool[73,91], the sheer scope of its variables and time constraints in a clinical setting likely remains a barrier to routine adoption for surgical patients.

For esophageal cancer patients undergoing resection, there are currently no well-validated esophagectomy-specific risk stratification tools, despite several attempts over the years[142–145]. The variability in surgical approach, preoperative nutritional status, neoadjuvant therapy, and extent of disease likely all contribute to the challenges in developing a risk calculator in this patient population. In 2016, the Society of Thoracic Surgeons (STS) revised their model for perioperative risk for esophagectomy in cancer patients. Using the STS General Thoracic Surgery Database of over 4000 patients, they developed a multivariable risk model for major morbidity, mortality, as well as a combined morbidity and mortality composite outcome. The covariates were a comprehensive set of variables, including patient characteristics, surgical approach, and oncologic factors. Although the c-statistic for the STS model was 0.71 for morbidity and 0.63 for mortality[144], this was produced from an exhaustive list that is impractical for use in a clinical setting. Since this list includes many of the same esophagectomy-associated factors identified by the much simpler NSQIP mFI, such as hypertension, diabetes, and cardiovascular problems, the mFI could represent a much more versatile tool that achieves similar results.

The original NSQIP mFI-11, based on the validated 70-item CSHA-FI, has been studied in several surgical population, including thoracic surgery[9,24–26]. The mFI-11 generated a frailty score from 11 variables that could be calculated using information easily obtained from existing clinical documentation, making it an attractive option in the clinical setting. It was suggested that fewer NSQIP data points in a limited model (i.e. five variables) could produce comparable risk assessment compared to a full model (i.e. 21 variables)[146]. As such, the mFI-11 was simplified to the mFI-5 with five variables in 2015. Interestingly, the mFI-5 still retained many of the same esophagectomy-associated risk factors identified by the STS risk model. Compared to the STS model, the c-statistic of both the mFI-11 and mFI-5 in thoracic surgery patients were comparatively higher for morbidity (0.73) and mortality (0.77)[103]. Although not esophagectomy-specific, this raised the possibility of the mFI having similar predictive values if applied to the esophagectomy cohort.

Overall, application of any version of the mFI in esophagectomy patients has been limited. In one study of the mFI-11 using NSQIP data, Hodari et. al found those with frailty had a high and statistically significant risk of death within 30 days (OR 31.84, p=0.015) compared to those without frailty[98]. Despite the fact that mortality was proportionally similar between their study and ours (3.5% vs. 2.6%), mFI-5 was no longer significantly associated with mortality in either the univariate or multivariate analysis, regardless of score. In contrast, mFI-5 was still associated with a number of adverse outcomes. In our multivariate analysis, mFI 2 and 3 reached significance for

Clavien-Dindo grade IV complications (p=0.027), while mFI 1 and 2 reached significance for anastomotic leak (p<0.000) and return to the operating room (p<0.000).

While meaningful statistical analysis of adverse outcomes is hindered by both the small sample size of mFI 3 patients (47 of 2567, 1.8%) and the small proportion of patients who experienced them, this is also likely a testament to the stringent patient selection for this surgery. No one in our study had an mFI score over three, meaning patients who had four or five of the mFI comorbidities were not offered surgery. Simplifying mFI-11 to mFI-5 may have reduced the burden of data collection, but it may have also impaired the ability to examine frailty specific to esophagectomy patients. The simplified mFI-5 may no longer be nuanced enough to explore vulnerabilities specific to esophageal cancer and esophagectomies, thereby underestimating the true markers of frailty in these patients. In a study that specifically addressed risk factors for anastomotic leak after esophagectomy for cancer using NSQIP data, Hall *et al*. discovered four variables that were independently associated with anastomotic leak[147]. Only the diabetes variable is part of the mFI-5. More recently, Gray *et al*. applied the mFI-5 to a cohort of 240 patients at their local institution and found it lacking in discriminatory performance for severe and all complications, with c-statistics of only 0.52 and 0.51 respectively. It should be noted that based on our experience with the small proportion of patients in the higher mFI score categories as noted above, validation of the results in a much larger sample size is likely warranted. Ultimately, a surgeon's decision to operate is multifaceted; it is possible those with higher frailty scores (i.e., mFI 3) possess or lack other qualities unaccounted by mFI-5 that make the surgeon believe they would make good surgical candidates.

The strengths of our study include a large sample size with consistent reporting of granular details from a multicentered cohort and a focus on severe clinically significant complications in the first and only study to use mFI-5 in esophagectomy patients. There are, however, some limitations of our study largely due to the nature of NSQIP data and the difficulties in defining frailty. First, given the small number of mFI 3 patients, a larger sample size is needed to reliably explore the relationship between mFI score and the outcomes of interest. Second, there are discrepancies between the all-procedure PUF and procedure-specific PUF. For instance, diagnosis might be listed as “No malignancy” in one but as “Neoplasm of the cardia” in the other. It is unclear if these inconsistencies are intentional and based on other criteria, or simply due to human error in data collection. In our study, the pathology from the esophagectomy PUF was used, as this set of data was specific and likely more accurate for the population of interest. Furthermore, the mFI-5 has not been prospectively validated. By virtue of this being a retrospective study, we could only establish association. As such, it is difficult to know the overlap of comorbidities within the mFI-5 as predictors of postoperative risk and as indicators of frailty, and the temporal relationships between risk factors and outcome.

In conclusion, the simplified mFI-5 is associated with morbidity but not mortality in patients who have undergone esophagectomy for esophageal cancer. Specifically, it is significantly associated with 30-day ICU-level complications, return to the operating room, and anastomotic leak. This study highlights the possibility that mFI-5, as compared to its mFI-11 predecessor, may not have enough nuance in the frailty assessment specific to the esophagectomy population.

Chapter 3 – Sarcopenia and Modified Frailty Index are Not Associated with Adverse Outcomes After Esophagectomy for Esophageal Cancer – A Retrospective Cohort Study

3.1 Introduction

Esophageal cancer is a highly morbid disease with a 5-year overall survival of under 20%[7]. Weight loss, poor nutritional status, and depletion of lean muscle mass are common in esophageal cancer patients[49], where the mainstay of treatment is surgical resection. An esophagectomy is a complex and physiologically demanding procedure with high rates of surgery-related morbidity[21–23].

Preoperative physiologic decline and cancer-related cachexia have been implicated in poor perioperative outcomes for cancer patients but remain difficult to measure. Clinical indicators of frailty (i.e., frailty indices), as well as radiographic measures (i.e., skeletal muscle mass calculations), have previously been used to evaluate the link between physiological reserve and adverse outcome with varying degrees of success.

Sarcopenia, defined as a state of low skeletal muscle mass and function, has been associated with an increased risk of postoperative complications in esophageal cancer patients after esophagectomy[110]. In a recent meta-analysis, sarcopenia was shown to be a predictor of poor overall survival and disease-free survival in this patient population[130]. Similarly, clinical scores aimed at identifying patients with low physiologic reserve – such the Modified Frailty Index (mFI) from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) – have been promoted as a simple, clinically-feasible measure of frailty in thoracic surgery patients[86]. The original iteration of the mFI was demonstrated to be significantly associated with both postoperative morbidity and mortality in esophagectomy patients[148]. Since then, however, the mFI has been simplified to 5 factors (mFI-5), and the association between this new score and adverse outcomes in this patient population is conflicting[149].

Identifying disease and procedure-specific measures of perioperative risk is important for improving both patient selection and the care of surgical patients. With more accurate estimations of morbidity and mortality, interventions may be undertaken in patients with poor prognostic indicators in the perioperative period. A better understanding of surgical risk will also allow patients and surgeons to make more informed decisions during the consent process.

Given the lack of clarity around whether radiographic or clinical measures of physiologic reserve more accurately align with post-operative outcomes, in this study, we evaluated both sarcopenia and the NSQIP mFI-5 and their association with adverse surgical outcomes in the same cohort of patients undergoing esophagectomy for esophageal cancer. We hypothesized that sarcopenia may be more strongly associated with adverse outcomes than the mFI-5.

3.2 Methods

We retrospectively reviewed all consecutive patients who underwent an esophagectomy at London Health Sciences Centre (LHSC) from January 2010 to December 2016. LHSC is a tertiary care referral centre for thoracic surgery, with a catchment area of over 1.5 million patients. Patients were identified from the prospectively collected local thoracic surgery operative database. Patients were included if they were over 18 years of age with esophageal dysplasia or cancer and a CT scan within 12 weeks prior to surgery. Patients were excluded if they had benign disease, recurrent or unresectable cancer discovered intraoperatively, non-esophageal malignancy, or concurrent resection of other organ systems in addition to an esophagectomy. Patients were also excluded if they did not have a documented height in the medical record, as this is essential to determine sarcopenia status. The study was approved Western University Research Ethics Board.

Data were obtained from the thoracic surgery operative database, as well as the medical record for all included patients. Demographics data extracted included: age, sex, weight, height, date of surgery, functional status or ECOG score, ASA classification, presence of diabetes, CHF, hypertension requiring medication, COPD, and neoadjuvant treatment status.

3.2.1 Sarcopenia Measurement

The skeletal muscle mass was determined on preoperative CT scans within 12 weeks prior to surgery. If a patient had undergone multiple CT scans, we used the last CT scan prior to their esophagectomy. Aquarius NET server (TeraRecon, Inc., San Mateo, CA) was used to measure the cross-sectional skeletal muscle mass at the level of the third lumbar vertebra (L3). The skeletal muscle at the L3 level is known to correlate with both the whole-body fat-free mass and appendicular skeletal muscle mass[150]. We selected a single image on the level of L3 with both transverse processes and delineated abdominal muscles. Psoas, quadratus lumborum, paraspinal, transverse abdominal, external oblique, internal oblique, and rectus abdominis muscles were included. The distinction between muscle and other tissues was based on Hounsfield units (HU). A threshold range of -29 to 150 HU was used to define skeletal muscle. The selected area was manually adjusted, and the muscle area was calculated automatically by the software (Figure 2). The cross-sectional total muscle area at the level of L3 (cm^2) was divided by the square of height (m^2), which produced the skeletal muscle index (SMI). This method is suggested as the preferred method of measuring the muscle mass of cancer patients[116]. SMI limit for sarcopenia was < 52.4 cm^2/m^2 for men and < 38.5 cm^2/m^2 for women, based on a previous study by Prado *et al*.[116].

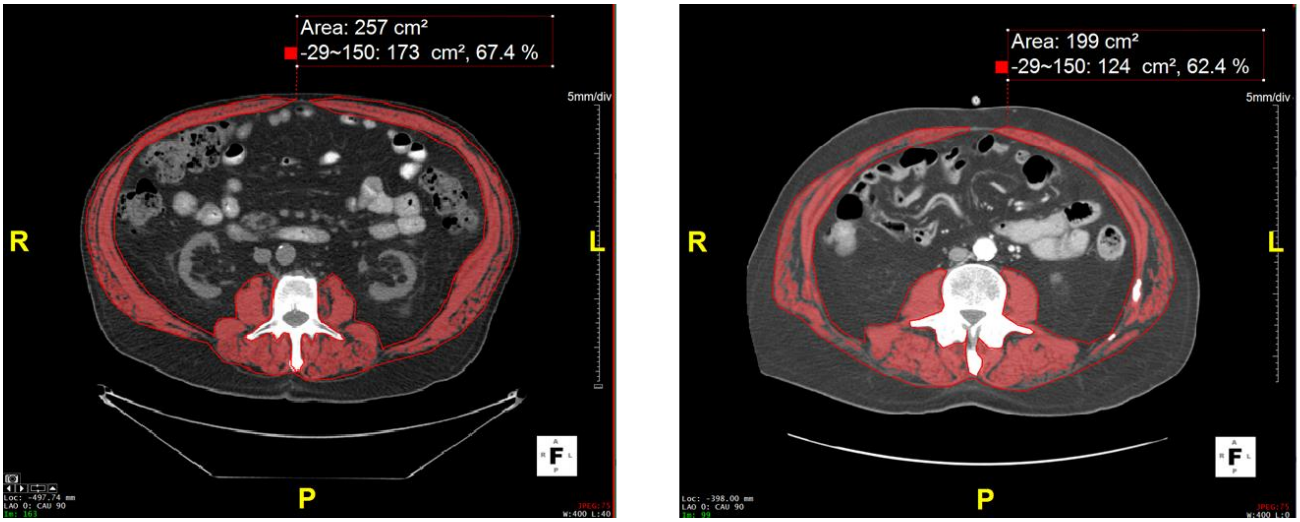

Figure 2. Abdominal computed tomography assessment of body composition for two male patients with esophageal cancer using skeletal muscle area normalized by height. Patient (A) does not have sarcopenia (skeletal muscle index 62.03 cm^2/m^2) compared to patient (B) who is sarcopenic (skeletal muscle index 38.58 cm^2/m^2).

3.2.2 Frailty Measurement

Frailty was assessed using the ACS NSQIP 5-factor modified frailty index, which consists of 1) hypertension requiring medication, 2) diabetes, 3) COPD; 4) functional status, and 5) CHF. This information was collected from preoperative assessment notes similar to the definitions found in the ACS NSQIP PUF[102].

Patients were classified as either independent or partially dependent based on documented ECOG score, exercise tolerance, or assistance with activities of daily living. Patients with an ECOG score of 1 or more, exercise tolerance noted to be reduced, or noted to require additional supports with activities of daily living (ADL) were classified as partially dependent. Where these components of functional status were not mentioned, and the clinical notes suggested the patient was likely independent, functional status was classified as such.

The mFI-5 score was calculated for each patient by adding the number of variables present, with 0–5 total points possible. We chose to not assign weights to each deficit to keep the determination of the mFI-5 as simple as possible, which is in keeping with other studies using the mFI[81,98,103].

3.2.3 Outcomes of interest

The primary outcome was unplanned ICU admission within 30-days. This was chosen as a composite marker for severe surgical complications according to the Clavien-Dindo classification, where grade IV is defined as a life-threatening complication requiring ICU management[132]. Compared to our NSQIP study, ICU admission since this was more reliably documented and clinically relevant outcome, whereas details of specific complications were not always available.

Secondary outcomes included 30-day readmission due to surgical complications, 90-day all-cause mortality, hospital stay over 30 days, return to the operating room, and anastomotic leak of any grade. Return to the operating room status is recorded to include all major surgical procedures that required the patient to be taken to the operating room for intervention of any kind.

3.2.4 Statistical Analysis

Data were described as means with standard deviations for normally distributed continuous variables, medians with interquartile ranges for non-normally distributed continuous variables, and frequencies with associated percentages for categorical variables. Shapiro-Wilk normality test was used to determine normality of continuous variables: age, BMI, total length of stay, and operation duration. A convenience sample size of all patients who underwent an esophagectomy between 2010-2016 were included, in line with the record keeping of the esophagectomy database.

Relationships between categorical variables were assessed using Pearson chi-squared test or Fischer’s exact test, where appropriate. For continuous variables, one-way ANOVA or Kruskal-Wallis rank sum test was used to compare between groups. Univariate logistic regression was used to determine the odds ratio in unadjusted comparisons between sarcopenia status and outcomes, as well as mFI-5 scores and outcomes.

Multivariate logistic regression models were completed to provide an adjusted estimate of the independent contribution of sarcopenia and mFI-5 score on the outcome of unplanned ICU admission. Variables were chosen for the models based on 1) demonstrated statistical significance with sarcopenia and/or mFI-5 score on univariate analysis, or 2) a known to be clinically associated with adverse surgical outcomes based on existing literature. Due to the small sample size of the final analysis, only three additional covariates were included in the multivariate logistic regression: age, ASA classification, and neoadjuvant therapy status. ASA classification has been shown to be reliable predictor of poor postoperative outcomes[151,134,152] and was used in this study as an overall marker of comorbidity. Since no patients had an ASA of 1 and only five had an ASA of 2, ASA 1, 2, and 3 were combined into a new ASA variable to compare ASA 1-3 versus ASA 4. Neoadjuvant therapy was coded as having been received if the patient received chemotherapy, radiation therapy, or both to treat their esophageal cancer prior to operative intervention.

Results from regression analyses are presented as adjusted odds ratio (OR) along with 95% CI and P values. In all comparisons, a p-value of less than 0.05 was considered significant. All statistical analysis was carried out using SPSS software, version 27 (IBM, Armonk, New York, USA).

3.3 Results

3.3.1 Patient Demographics

A total of 331 patients underwent an esophagectomy at LHSC from 2010 to 2016. There were 126 patients who were excluded, primarily due to the lack of height recorded (n = 12) or availability of preoperative CT scans within 12 weeks (n = 81). Other reasons for exclusion included extensive concomitant major resection of other organ systems, inability to complete resection, and non-esophageal malignancy on pathology (n = 33). A total of 205 patients who underwent esophagectomy for esophageal cancer were included in the final analysis.

Patient demographics are summarized in Table 9 and 10. The median age was 66 years (IQR 58-72) with the median BMI being 26.5 (IQR 23-30.9). Of the analysis population, 118 patients (57.6%) were classified as sarcopenic and 87 patients (42.4%) non-sarcopenic. Calculated mFI-5 scores for all patients in the study sample ranged from 0 to 3; no patients who underwent an esophagectomy had a mFI-5 score of 4 or 5. The number of patients with each mFI score were as follows: 91 patients had mFI 0 (44.4%), 72 patients had mFI 1 (35.1%), 34 patients had mFI 2 (16.9%), and 8 patients had mFI 3 (3.9%). Within the mFI, hypertension requiring medication was the most common comorbidity (80 of 205, 39%), followed by diabetes (43 of 205, 21%) (Table 11). Patients with sarcopenia and patients with higher mFI-5 scores were significantly older ($P < 0.001$ and $P = 0.017$, respectively). Conversely, lower BMI was found in patients with sarcopenia ($P < 0.001$) while higher BMI was seen in patients with higher mFI-5 score ($P = 0.081$).

Median operation duration was 272 minutes (IQR 223 – 334) and was not significantly different between groups. Most study patients were male (170 of 205, 82.9%). Sex was associated with sarcopenia status ($p = 0.002$), with a higher proportion of men in the sarcopenia group (106 of 118, 89.8%). Sex was not associated with mFI score ($p = 0.41$).

The most common pathology was adenocarcinoma (168 of 205, 82%), which made up a larger proportion in the non-sarcopenic group (78 of 87, 89.7%) compared to the sarcopenic group (90 of 118, 76.3%). Conversely, squamous cell carcinoma pathology was three times larger in the sarcopenic group (22 of 118, 18.6%) compared to the non-sarcopenic group (6 of 87, 6.9%).

Table 9 – Local esophagectomy patient demographics by sarcopenia status

		Sarcopenia		
Characteristic	**Overall N = 205**	**No N = 87**	**Yes N = 118**	**p-value[1]**
Age (years)				
Median [IQR]	66 [58-72]	64 [54- 69.5]	67 [61- 75.8]	<0.001[2]
BMI (kg/m^2)				
Median [IQR]	26.5 [23-30.9]	29.8 [26.7- 33.5]	24.4 [21.8- 27.8]	<0.001[2]
Missing data (%)	36 (17.6%)	18 (20.7%)	18 (15.3%)	
Operation duration (mins)				
Median [IQR]	272 [223-334]	272 [218.5-331]	276.5 [230.5-336.2]	0.92[2]
Sex				0.002
Male	170 (82.9%)	64 (73.6%)	106 (89.8%)	
Female	35 (17.1%)	23 (26.4%)	12 (10.2%)	
Pathology				
Adenocarcinoma	168 (82%)	78 (89.7%)	90 (76.3%)	0.014
SCC	28 (13.7%)	6 (6.9%)	22 (18.6%)	0.015
Mixed	6 (2.9%)	1 (1.1%)	5 (4.2%)	
Dysplasia	3 (1.5%)	2 (2.3%)	1 (0.8%)	
ASA Classification				0.20
1	0 (0%)	0 (0%)	0 (0%)	
2	5 (2.4%)	4 (4.6%)	1 (0.8%)	
3	138 (67.3%)	59 (67.8%)	79 (66.9%)	
4	62 (30.2%)	24 (27.6%)	38 (32.2%)	
1-3	143 (69.7%)	63 (72.4%)	80 (67.8%)	0.48
4	62 (30.2%)	24 (27.6%)	38 (32.2%)	
Neoadjuvant Therapy	85 (41.5%)	29 (33.3%)	56 (47.5%)	0.042

[1]Pearson's Chi-squared test; Fisher's exact test
[2]Kruskal-Wallis rank sum test

Overall, neoadjuvant therapy was used in 41.5% (85 of 205) of patients. More patients with sarcopenia had undergone neoadjuvant therapy (56 of 118, 47.5%) compared to non-sarcopenic patients (29 of 87, 33.3%); however, the proportion of patients who underwent neoadjuvant decreased with higher mFI-5 score.

Table 10 – Local esophagectomy patient demographics by mFI-5 score

Characteristic	Overall N = 205	mFI-5 Score 0 N = 91	1 N = 72	2 N = 34	3 N = 8	p-value[1]
Age (years)						
Median [IQR]	66 [58-72]	62.0 [54-70]	67.0 [60.5-73]	67.5 [62.5-71]	70 [66.2-77.2]	0.017[2]
BMI (kg/m^2)						
Median [IQR]	26.5 [23-30.9]	25.8 [22.4-28.8]	26.5 [23.0-31.2]	28.4 [26.2-32.1]	29.2 [24.9-31.9]	0.081[2]
Missing data (%)	36 (17.6%)	18 (19.8%)	11(15.3%)	6(17.6%)	1(12.5%)	
Operation duration (mins)						
Median [IQR]	272 [223-334]	279 [227-337]	264 [220-337]	315 [234.8-357.2]	223.5 [209.8-274]	0.31[2]
Sex						0.41
Male	170 (82.9%)	72 (79.1%)	63 (87.5%)	29 (85.3%)	6 (75%)	
Female	35 (17.1%)	19 (20.9%)	9 (12.5%)	5 (14.7%)	2 (25%)	
Pathology						
Adenocarcinoma	168 (82%)	70 (76.9%)	61 (84.7%)	30 (88.2%)	7 (87.5%)	0.44
SCC	28 (13.7%)	17 (18.7%)	8 (11.1%)	2 (5.9%)	1 (12.5%)	0.24
Mixed	6 (2.9%)	2 (2.2%)	2 (2.8%)	2 (5.9%)	0 (0%)	
Dysplasia	3 (1.5%)	2 (2.2%)	1 (1.4%)	0 (0%)	0 (0%)	
ASA Classification						0.19
1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
2	5 (2.4%)	4 (4.4%)	1 (1.4%)	0 (0%)	0 (0%)	
3	138 (67.3%)	67 (73.6%)	47 (65.3%)	20 (58.8%)	4 (50%)	
4	62 (30.2%)	20 (22%)	24 (33.3%)	14 (41.2%)	4 (50%)	
1-3	143 (69.7%)	71 (78%)	48 (66.7%)	20 (58.8%)	4 (50%)	0.083
4	62 (30.2%)	20 (22%)	24 (33.3%)	14 (41.2%)	4 (50%)	
Neoadjuvant Therapy	85 (41.5%)	44 (48.4%)	29 (40.3%)	10 (29.4%)	2 (25%)	0.20

[1]Pearson's Chi-squared test; Fisher's exact test
[2]Kruskal-Wallis rank sum test

Table 11 – Local esophagectomy patient comorbidities by mFI-5 score

		mFI-5 Score			
Comorbidity	**Overall N = 205**	**0 N = 91**	**1 N = 72**	**2 N = 34**	**3 N = 8**
Hypertension on medication*	80 (39%)	0 (0.0%)	42 (58.3%)	30 (88.2%)	8 (100.0%)
Diabetes*	43 (21%)	0 (0.0%)	12 (16.7%)	23 (67.6%)	8 (100.0%)
Chronic obstructive pulmonary disease*	27 (13.2%)	0 (0.0%)	14 (19.4%)	8 (23.5%)	5 (62.5%)
Functionally dependent*	6 (2.9%)	0 (0.0%)	1 (1.4%)	3 (8.8%)	2 (25.0%)
Congestive heart failure*	3 (1.5%)	0 (0.0%)	1 (1.4%)	2 (5.9%)	0 (0.0%)
Smoking	56 (27.3%)	28 (30.8%)	15 (20.8%)	11 (32.4%)	2 (25.0%)

3.3.2 Outcomes

Outcomes according to sarcopenia status and mFI-5 score are shown in Tables 12 and 13. Overall, unplanned ICU admission occurred in 19% (39 of 205) of patients. Mortality within 30 days, which were all in-hospital, occurred in 3.4% (7 of 205). Mortality within 90 days was 5.4% (11 of 205). Readmission within 30 days occurred in 17.1% (35 of 205). The median length of hospital stay was 11 days (IQR 9-16), with 6.3% (13 of 205) of patients staying over 30 days. Return to the operating room occurred in 22.4% (46 of 205), while 25.4% (52 of 205) of patients experienced an anastomotic leak and 8.3% (17 of 205) experienced a chylothorax.

Patients defined as sarcopenic were more likely to require an ICU admission, 30-day mortality and readmission, 90-day mortality, return to the operating room, anastomotic leak, and chylothorax were all higher in the sarcopenic group (Table 12).

Variables that showed an increasing trend with higher mFI-5 score include: 30-day mortality and readmission, 90-day mortality, median length of stay in hospital, and hospital stay over 30 days. The rate of ICU admission, return to the operating room, and anastomotic leak increased from mFI 0 to 1 and from mFI 1 to 2, but decreased for mFI 3 (Table 13).

Table 12 – Local esophagectomy patient outcomes by sarcopenia status

		Sarcopenia		
Outcome	**Overall N = 205**	**No N = 87**	**Yes N = 118**	**p-value**[1]
ICU admission	39 (19%)	16 (18.4%)	23 (19.5%)	0.84
30-day mortality	7 (3.4%)	2 (2.3%)	5 (4.2%)	0.70
90-day mortality	11 (5.4%)	2 (2.3%)	9 (7.6%)	0.12
30-day readmission	35 (17.1%)	16 (18.4%)	19 (16.1%)	0.67
Length of hospital stay (days)				
Median [IQR]	11 [9-16]	10 [9- 16]	11 [9- 15]	0.40[2]
Length of stay >30 days	13 (6.3%)	6 (6.9%)	7 (5.9%)	0.78
Return to OR	46 (22.4%)	16 (18.4%)	30 (25.4%)	0.23
Anastomotic leak	52 (25.4%)	21 (24.1%)	31 (26.3%)	0.73
Chylothorax	17 (8.3%)	5 (5.7%)	12 (10.2%)	0.26

[1] Pearson's Chi-squared test; Fisher's exact test
[2] Wilcoxon rank sum test

Table 13 – Local esophagectomy patient outcomes according to mFI-5 score

Outcome	Overall N = 205	mFI-5 Score 0 N = 91	1 N = 72	2 N = 34	3 N = 8	p-value[1]
ICU admission	39 (19%)	13 (14.3%)	14 (19.4%)	10 (29.4%)	2 (25%)	0.22
30-day mortality	7 (3.4%)	2 (2.2%)	2 (2.8%)	2 (5.9%)	1 (12.5%)	0.21
90-day mortality	11 (5.4%)	4 (4.4%)	2 (2.8%)	4 (11.8%)	1 (12.5%)	0.14
30-day readmission	35 (17.1%)	12 (13.2%)	14 (19.4%)	7 (20.6%)	2 (25%)	0.50
Length of hospital stay (days)						
Median [IQR]	11 [9-16]	10 [9- 13]	11 [9- 16]	12 [10- 18]	16 [11- 23]	0.012[2]
Length of stay >30 days	13 (6.3%)	3 (3.3%)	4 (5.6%)	4 (11.8%)	2 (25%)	0.045
Return to OR	46 (22.4%)	15 (16.5%)	20 (27.8%)	10 (29.4%)	1 (12.5%)	0.21
Anastomotic leak	52 (25.4%)	19 (20.9%)	18 (25.0%)	13 (38.2%)	2 (25%)	0.26
Chylothorax	17 (8.3%)	11 (12.1%)	4 (5.6%)	2 (5.9%)	0 (0%)	0.45

[1] Pearson's Chi-squared test; Fisher's exact test
[2] Kruskal-Wallis rank sum test

We performed univariate and multivariate regression analyses for sarcopenia and frailty separately, which did not demonstrate significant associations with postoperative ICU admission (Table 13). Notably on univariate analysis, ASA 4 status doubles the odds of ICU admission (OR 2.08, p=0.046; 95% CI 1.01-4.27) while neoadjuvant therapy almost halves the odds of ICU admission (OR 0.49, p=0.065; 95% CI 0.23-1.05). After adjusting for the effects of age, comorbidity (ASA class) and the receipt of neoadjuvant therapy, neither sarcopenia status (OR 1.00, 95% CI 0.47 – 2.15), nor mFI Score (OR 1.18, 95% CI 0.49-2.79 for mFI 1; OR 1.87, 95% CI 0.70 – 4.99 for mFI 2; OR 1.29, 95% CI 0.22 – 7.61 for mFI 3) were significant associated with unplanned ICU admission (Table 14).

Table 14 – Adjusted Odds Ratio of ICU admission accounting for sarcopenia vs mFI-5 and covariates of multivariate logistic regression (P; 95% CI)

Variable	Logistic regression 1	Logistic regression 2
Sarcopenia	1.00 (0.996; 0.47-2.15)	N/A
mFI 1 (vs. 0)	N/A	1.18 (0.706; 0.49-2.79)
mFI 2 (vs. 0)	N/A	1.87 (0.212; 0.70-4.99)
mFI 3 (vs. 0)	N/A	1.29 (0.773; 0.22-7.61)
Age	1.02 (0.246; 0.98-1.06)	1.02 (0.301; 0.98-1.06)
ASA 4 (vs. 2 and 3)	1.91 (0.083; 0.92-3.97)	1.79 (0.124; 0.85-3.79)
Neoadjuvant therapy	0.56 (0.152; 0.25-1.24)	0.59 (0.185; 0.27-1.29)

3.4 Discussion

The aim of this study was to assess two measures of physiologic reserve – sarcopenia and frailty – and their association with surgical morbidity and mortality after esophagectomy for esophageal cancer. This is the first study to describe both metrics in the same cohort of esophagectomy patients.

The prognostic value of these measurements has gained interest in recent years due to the possibility of identifying modifiable risk factors implicated in postoperative complications and survival. Our results did not demonstrate a significant association between either sarcopenia or frailty – as measure by mFI-5 – and major postoperative complications. In our study, the prevalence of sarcopenia and frailty were both high, with more than half of our study population being sarcopenic (57.6%) or having some score of frailty (55.6% scored mFI 1-3). Previous studies that use the same sarcopenia measurement and cut-off values[116] have reported rates of sarcopenia ranging from 15.9%[153] to 80%[154], while the prevalence of frailty in larger database cohorts reported similar levels, with over half the study population having some score of frailty (55.6% scored mFI 1-3)[149]. The prevalence of both conditions in the population of patients presenting for esophagectomy makes these measures of decreased physiologic reserve logical targets for potentially modifiable factors in the pathway to poor postoperative outcomes.

The existing literature examining the impact of sarcopenia on esophagectomy outcomes for cancer patients has demonstrated consistency in the association with respiratory complications[121,122,127,129,154,155], but there is little consensus on anastomotic leak, chylothorax, and complications above Clavien-Dindo grade III[127]. The main difficulties in comparing results of these studies lies in the significant variability in baseline characteristics (e.g. race, tumour stage, histology, type of operation, neoadjuvant therapy) and sarcopenia cut-off values[154]. Since there are no standardize measurements for sarcopenia cut-offs, we chose to use the values put forth by Prado *et al.*[116] for our study, as these appear to the most widely used and well studied set of parameters in existing literature.

Similar issues of heterogeneity exist within the frailty literature, even when the same frailty assessment tool is used. Our previous study using the NSQIP database found higher mFI-5 scores were associated with Clavien-Dindo grade IV complications[149]; however, this finding was not replicated in our current single-center study. Reproducibility is difficult in different study populations because of the disparities in record keeping, data availability, and how outcomes are defined. For example, our local patient cohort had similar age, BMI, and sex distributions compared to the NSQIP patients; however, we had significantly more ASA class 4 patients (30.2%) compared to NSQIP (6.9%), as well as fewer patients who underwent neoadjuvant therapy (41.5%, vs. NSQIP neoadjuvant chemotherapy 69.7% and radiation 59.4%). In the NSQIP study, Clavien-Dindo grade IV was a composite outcome of life-threatening complications that were presumed to be managed in an ICU – it is possible a myocardial infarction or stroke may not have needed to be monitored in the intensive care setting. In the current study, disposition to the ICU was a recorded outcome regardless of the complication, which provides a more useful and clinically relevant level of granularity.

A key factor to consider in using sarcopenia or frailty is the dynamic nature of physiologic reserve. The detrimental effects of neoadjuvant therapy on muscle mass, strength, and function are well documented in literature[115,154,156–158]. This idea that sarcopenia measured at a single point in time does not necessarily predict a poor postoperative outcome in esophageal cancer patients was demonstrated in a study by Järvinen *et al*. which found no statistical difference in 2-year overall survival or recurrence-free survival between the preoperative sarcopenic and non-sarcopenic groups until patients were analyzed based on the amount of change in sarcopenia[154]. This suggests that there is a much more complex interaction that occurs across time between the benefits of neoadjuvant therapy and the resulting harm of sarcopenia in determining adverse surgical outcome. Though the limitations of our imaging capabilities – specifically the inability to calculate sarcopenia score on images obtained outside our institution – prevented us from capturing change in sarcopenia over time, it is possible that this measure may have been more sensitive in demonstrating a relationship between sarcopenia status and unplanned ICU admission.

For mortality specifically, our results were consistent with other studies that looked at 30-day and in-hospital mortality – sarcopenia did not significantly increase the risk of death in the immediate postoperative period. However, we did note that 90-day mortality (OR 3.51, $p = 0.11$; 95% CI 0.74-16.67) was much higher than 30-day mortality (OR 1.88; $p = 0.457$, 95% CI 0.36-9.93). In studies with longer follow-up periods ranging from 1 to 8 years, sarcopenia significantly reduced both overall survival and disease-free survival in esophageal cancer patients who had undergone surgical resection[122,155,158,159]. One possible explanation is that the effects of sarcopenia are cumulative; the loss of muscle mass and function might not be a better marker of risk for short term mortality but a marker of long-term vulnerability to disease- and treatment-related stressors that decrease survival rather than a marker of long-term survival.

Although there are currently no standardized metrics of determining physiologic suitability for an esophagectomy, our results support the hypothesis that surgeons are apt at making decisions about who should proceed to esophagectomy at all. The lack of patients with a frailty score above mFI 3 suggests that patients with higher levels of frailty are not even presenting for surgery, which impacts our understanding of the role of frailty in postoperative outcomes. Furthermore, it is interesting to note that in our study the proportion of patients who underwent neoadjuvant therapy was higher in the sarcopenia group (47.5% vs 33.3% non-sarcopenic group) but showed a decreasing trend with higher frailty scores (48% mFI 0, 40.3% mFI 1, 29.4% mFI 2, 25% mFI 3). This disparity perhaps suggests that sarcopenia and mFI-5 capture different traits of physiologic reserve that were factored into the treatment decision-making process. Our previous study with 2,567 patients from the international NSQIP database did not observe the same trend with frailty[149], possibly indicating a difference in institutional treatment or referral patterns that are not accounted for in this study.

The strengths of this study include being the first to use frailty and sarcopenia measurements in the same esophagectomy cohort where the primary endpoint is measured by a clinically relevant outcome (i.e., admission to ICU). Our study has a few notable limitations. This was a single-center study with a small sample size and an even smaller cohort of patients who had the outcomes of interest. As such, this did not allow us to perform a robust multivariate regression analysis, account for stage of disease or the type of surgery performed. Our patients also did not have the full range of frailty scores, as no one scored higher than 3/5 on the mFI-5. This phenomenon was also observed in our NSQIP study[149], reaffirming that the mFI-5 perhaps does not have the granularity to capture the nuances of frailty assessment specific to patients who undergo an esophagectomy for cancer, or that surgeons are selecting patients with lower frailty scores as appropriate for esophagectomy.

In conclusion, neither sarcopenia nor frailty as measured by mFI-5 demonstrated an association with 30-day morbidity or mortality for esophageal cancer patients in our single-center study. Overall, sarcopenia and frailty can be markers of increased physiologic vulnerability as they reflect the cumulative effects of aging, disease progression, malnutrition, and weight loss. There appears to be both overlap and disparities in these measures of physiologic reserve, but they do not always correspond with statistically and clinically significant outcomes. The interaction between sarcopenia, frailty, and other preoperative factors that affect measures of physiologic reserve may be more nuanced and should be further explored in a prospective manner with a larger patient population.

Chapter 4 – Discussion and Conclusion

4.1 Discussion

The purpose of this thesis was to investigate the association between frailty, sarcopenia, and adverse surgical outcomes in patients who have had an esophagectomy for esophageal cancer. This was approached by first examining mFI-5 using NSQIP, and then local data for mFI-5 and sarcopenia. By the natural course of this disease, it is not surprising that patients with esophageal cancer have a high incidence of unintended weight loss (>70%) and sarcopenia (26–75%) at diagnosis[115]. While modern treatment modalities – surgery, chemotherapy, and radiation therapy – improve survival, they take a significant physiological toll, which often worsen malnutrition, physical deconditioning, and muscle wasting in the preoperative period[115,160]. As we march forward in the era of personalized medicine, we are beginning to understand that pre-treatment physiologic reserve, as measured by metrics such as frailty and sarcopenia, are truly critical determinants of surgical outcomes[161]. An improved understanding of the association between states of decreased physiologic reserve and perioperative morbidity is the first key step in designing interventions to minimize risk and improve patient outcomes.

4.1.1 Literature Review Summary

In Chapter 1, we reviewed the current literature on frailty and sarcopenia, which demonstrated the importance of understanding the impact of physiology reserve on adverse surgical outcomes. In the context of esophageal cancer, however, our review identified a substantial gap in knowledge. Over the last few decades, the concept of frailty has become increasingly recognized as an important determinant of health outcomes. Defining frailty, however, is challenging, with over 50 different tools in existence to capture this metric. These tools range from dichotomous metrics to continuous scales that account for physical, social, and psychosocial domains. Few of these frailty scoring systems have been validated in surgical oncology, and certainly frailty in the context of esophageal cancer surgery has not been well studied. The state of research is such that we apply existing generalized frailty assessments to unique pathologies, not knowing if the metrics are nuanced enough to capture disease- or surgery-specific qualities. There remains substantial room in the literature to explore the use of existing tools in the context of esophagectomy to esophageal cancer.

4.1.2 NSQIP mFI-5 Summary

In Chapter 2, we performed a retrospective cohort study to define the utility of a single frailty measure – the 5-factor mFI – in patients undergoing esophagectomy for esophageal cancer and dysplasia. The National Surgical Quality Improvement Program database for esophagectomy patients who underwent surgery for cancer or pre-cancer was used to investigate the association between the 5-factor mFI and the occurrence of post-operative complications and death within 30 days of surgery. While previous NSQIP studies using the extended 11-factor mFI in patients with esophageal cancer[98], as well as those using the 5-factor mFI in a general population of thoracic surgery patients, demonstrated associations with mortality and morbidity [103], our study demonstrated some conflicting results with respect to the association between the mFI-5 and outcomes in patients undergoing esophagectomy.

Using the mFI-5, we showed that higher frailty scores were indeed associated with a higher incidence of severe complications requiring ICU level care. Our results confirmed our hypothesis that patients with higher scores in frailty have higher rates of severe complications.

In Chapter 2, the lack of patients with frailty scores higher than mFI 3 likely means patients who had four or five of the mFI comorbidities were not offered surgery. Whether it is because these patients never make it to surgery, or because surgeons are simply not offering surgery, there is likely a combination of selection bias and clinical judgement that is unaccounted for in way frailty is measured by the mFI-5. We must consider the possibility that the mFI-5, unlike its 11-factor predecessor, may not be nuanced enough to explore vulnerabilities specific to esophageal cancer and esophagectomies, thereby underestimating the true markers of frailty in these patients. This, perhaps more than any statistical results, serves as the best indictment against relying solely on mFI-5 as a preoperative decision-making tool in this patient population.

4.1.3 Sarcopenia and mFI-5 in Local Cohort Summary

The milestones of Chapter 3 were several folds. First, we aimed to replicate the findings from Chapter 2 by applying mFI-5 to our local patient population. The primary outcome in this study was postoperative ICU admission rather than Clavien-Dindo grade IV complications. ICU admission status was chosen because in Chapter 2 we had to assume grade IV complications would be managed in an intensive care setting, as neither this grading nor ICU status was an outcome assigned by the NSQIP database. ICU admission is not only a more pragmatic outcome in understanding the treatment process of this complex disease, but it also serves as a concrete and important endpoint for decision-making by the patient and their care team. ICU admission is also an immensely useful surrogate for resource intensity – a factor that must be ever salient in a public health care system and particularly relevant during the current pandemic where ICU beds are scarce and intensive care resources have been stretched thinner than ever before.

Second, given that physiologic reserve is multifactorial and multidimensional, we wished to measure frailty and sarcopenia in the first study to describe these two measures of physiologic reserve in the same cohort of esophagectomy patients. Although neither proved to be associated with morbidity or mortality in a significant way, this study did highlight important challenges in the contemporary evaluation of both frailty and sarcopenia.

The concept of sarcopenia – decreased muscle mass and function – is intuitively simple but difficult to standardize. Even when the same objective functions of sex, height, and skeletal muscle area are used, there are crucial components many studies fail to take into account. One important consideration, as mentioned in Chapter 3, is the dynamic nature of physiologic reserve. Our study captured sarcopenia measurements within a 12-week interval between preoperative imaging and surgery since no standardized time cut offs exist. During this period, we did not account for how sarcopenia status may have changed with neoadjuvant therapy, enteral feeding, or disease-related decline. It is therefore difficult to understand how certain temporally important variables impact outcome. This temporal relationship warrants further clarification, especially given that previously studies have shown the amount of change in sarcopenia was associated with 2-year overall survival and recurrence-free survival[154]. Future studies should require not only standardization but also adjustments for nutrition, physical exercise, neoadjuvant therapy, and any factors that are specific to esophageal cancer or institutional differences (e.g., esophageal stenting, feeding tube insertion, pre-habilitation regimens) that could change sarcopenia leading up to surgery.

While the relationship between mFI-5 and adverse outcomes was not statistically significant in Chapter 3, we did note a trend towards increased ICU admissions in patients with mFI scores of 1 and 2. Furthermore, the results in both Chapter 2 and 3 showed a general trend towards increased mortality in patients with higher mFI-5 scores. While we cannot draw any definitive conclusions, the wide confidence intervals of higher frailty scores lead us to believe that a significant limitation to evaluating mFI-5 in our local cohort is the small sample size. While the NSQIP sample size was large, the number of patients with high frailty scores is too small. A larger, multicentered study, ideally conducted in a prospective manner, is the next step to verifying the utility of the mFI-5 in esophagectomy patients. The small sample size of the desired cohort also points to a secondary limitation and highlights the importance of what the mFI-5 does and does not capture. Similar to the NSQIP database, no patients in our local cohort who had undergone an esophagectomy for esophageal cancer had an mFI-5 score above three. As is the nature of retrospective studies, our sample population only captured patients who completed the procedure. The five factors in the mFI-5 are such general metrics of health that presumably those who check more than three boxes are so moribund in unaccounted ways that they may not be offered an esophagectomy or simply do not make it to surgery. As such, the challenge in identifying frail esophageal cancer patients who are more at risk when undergoing an esophagectomy, or indeed any surgical procedure, is tailoring assessment tools specific to the surgery or disease. In this way, perhaps mFI-5 not only requires further investigation in a larger, more adequately powered study, but also the addition of other metrics of physiologic reserve.

With the future of medicine headed increasingly towards individualized therapies, individualization must begin much earlier in the therapeutic process such that modifiable risk factors are identified and mitigated before reaching the treatment step. This requires focusing on disease specific outcomes, which mandates a tailored index that addresses the risks specific to each patient population. While mFI-5 and sarcopenia are useful tools to assess poor physiologic reserve at a glance, their components do not address the risks unique to an esophagectomy. For esophageal cancer patients undergoing an esophagectomy, assessments should occur at multiple points in the timeline of their treatment, taking into account significant events including but not limited to: neoadjuvant treatment, feeding tube insertion, changes to nutritional status, status of social supports, changes to lean muscle mass, and deterioration in mobility or function. A new index tailored for esophagectomy patients should address most, if not all, of these multidimensional aspects; finding the best metrics to quantify these factors will be the next step in the development of an esophagectomy-specific risk assessment tool.

4.3 Conclusions

Esophageal carcinoma is a complex disease, and the perioperative risk management of esophageal resection is more complex still. Patients are at high risk of physical deconditioning, which can lower tolerance to physical stressors and in turn increase the risk for surgical morbidity. Our current understanding of how physiologic reserve impacts esophagectomy outcomes is limited and largely siloed to discrete, static metrics with few considerations for the disease or treatment in question.

By applying the NSQIP 5-factor Modified Frailty Index to this patient population, we identified an association between mFI-5 score and severe 30-day postoperative complications, but not mortality. Further prospective studies with larger sample sizes are warranted to assess specific outcomes of interest. Until then, it is our opinion that this frailty scale has a limited role in aiding preoperative decision-making since it only accounts for non-modifiable risk factors and lacks the nuance specific to esophagectomy patients.

With regards to sarcopenia, despite literature that connects preoperative sarcopenia to adverse post-esophagectomy outcomes, our study did not find any differences in sarcopenia status and 30-day morbidity or mortality. The lack of temporal standardization and consideration for esophageal cancer-specific factors, such as perioperative feeding tube insertion and neoadjuvant therapy, could account for the disparity in our results compared to the existing literature. These considerations could potentially represent substantial changes in sarcopenia measurement. We should therefore avoid dismissing the utility of sarcopenia in this patient population until further studies accounting for these changes can be conducted.

Physiology reserve is dynamic, and much like the multidisciplinary approach to caring for patients with esophageal cancer, the approach to measuring frailty and sarcopenia should be equally multidimensional. Further research is still needed to identify the best metric to quantify physiologic reserve so that we may better individualized management strategies and optimize care for patients undergoing esophagectomies for esophageal cancer.

Appendices

Appendix 1 – REB Approval for Chapter 2

Western Research

Date: 4 September 2020

To: Dr. Richard Malthaner

Project ID: 116514

Study Title: Role of Frailty in Predicting Outcomes after Esophagectomy for Esophageal Cancer – a NSQIP Study

Application Type: HSREB Initial Application

Review Type: Delegated

Full Board Reporting Date: 15September2020

Date Approval Issued: 04/Sep/2020 12:40

REB Approval Expiry Date: 04/Sep/2021

Dear Dr. Richard Malthaner

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals must also be obtained prior to the conduct of the study.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
REB Research Proposal - NSQIP_Role of Frailty in Predicting Outcomes after Esophagectomy for Esophageal Cancer	Protocol	31/Aug/2020	1
Data Collection Spreadsheet - NSQIP	Other Data Collection Instruments	01/Sep/2020	1

No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB , except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Appendix 2 – REB Approval for Chapter 3

Date: 23 September 2020

To: Dr. Richard Malthaner

Project ID: 116608

Study Title: Role of Frailty and Sarcopenia in Predicting Outcomes after Esophagectomy for Esophageal Cancer – a Single Center Study

Application Type: HSREB Initial Application

Review Type: Delegated

Full Board Reporting Date: 06October2020

Date Approval Issued: 23/Sep/2020 11:10

REB Approval Expiry Date: 23/Sep/2021

Dear Dr. Richard Malthaner

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals must also be obtained prior to the conduct of the study.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
REB Research Proposal - LocalData_Role of frailty and sarcopenia in predicting outcomes after esophagectomy	Protocol	31/Aug/2020	1
Data Collection Spreadsheet	Other Data Collection Instruments	22/Sep/2020	3

Documents Acknowledged:

Document Name	Document Type	Document Date	Document Version

No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB , except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Nicola Geoghegan-Mrophet, Ethics Officer on behalf of Dr. Philip Jones, HSREB Vice-Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

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Curriculum Vitae:

NAME

Linda Chang Qu

EDUCATION

Western University
- PGY5 General Surgery 2018 – 2023
- Master of Surgery 2020 – 2022

Queen's University 2014 – 2018
- Doctor of Medicine

University of Toronto 2010 – 2014
- Honours Bachelor of Science

ABSTRACTS AND PRESENTATIONS

1) **Qu LC**, Qiabi M, Nayak R, Malthaner R. NSQIP mFI5 Associated with Morbidity not Mortality After Esophagectomy
   - Dr. Robert Zhong Department of Surgery Research Day, 2022
   - Canadian Surgery Forum, 2021
2) **Qu LC**, Istl AC, Tang JE, Gray DK. Variability in Perioperative Management of Pheochromocytomas in Canada.
   - Canadian Surgery Forum, 2021
3) **Qu LC**, Glass L, Garcia-Ochoa C, Allen L, Roth M, Wiseman D, Yoshy C, Leslie K. Impact of sarcopenia on morbidity and mortality after Whipple procedure for pancreatic ductal adenocarcinoma – a retrospective cohort study.
   - 14th Annual London Imaging Discovery Day, June 2019, London, ON, Canada
   - Canadian Surgery Forum, Sept 2019, Montreal, QC, Canada

ACADEMIC PUBLICATIONS

1) **Qu LC**, Istl AC, Tang JE, Gray DK. Variability in Perioperative Management of Pheochromocytomas in Canada. *European Journal of Endocrinology.* 2021 – Submitted
2) **Qu LC**, Nayak R, Parry NG. (2021). Empyema. In Brown C, Inaba K, Martin MJ, & Sālim A (Eds). *Emergency general surgery: A practical approach*. 2021 – Publication pending
3) Mori Y, Ko E, Furrer R, **Qu LC**, Wiber SC, Fantus IG, Thevis M, Medline A, Giacca A. Effects of insulin and analogues on carcinogen-induced mammary tumours in high-fat-fed rats. *Endocrine Connections*. 2018;7(5):739-748.
4) Allan DS, Kirkham CL, Aguilar OA, **Qu LC**, Chen P, Fine JH, Serra P, Awong G, Gommerman JL, Zúñiga-Pflücker JC, Carlyle JR. (2015). An in vitro model of innate

lymphoid cell function and differentiation. *Mucosal Immunology;* 8 (2), 340-351.

ARTISTIC PUBLICATIONS

The Art of Medicine 2016

- Peterkin, A. (2016). *Staying human during residency training: how to survive and thrive after medical school* (6th ed.) E-book
- Cover art, CFMS Annual Review

ACADEMIC HIGHLIGHTS AND AWARDS

- Accreditation Internal Review Surveyor 2021
- ATLS Instructor Certification 2020
- Bootcamp for Resident Teachers 2020
- White Coat Warm he(Art) Exhibition 2015, 2016
- Gordon Cressy Student Leadership Award, U of T 2014
- Dorothy Helen McRobb Scholarship, U of T 2014
- Department of Immunology Summer Student Award, U of T 2013
- D+H SRI Summer Studentship Award, Sunnybrook Research Institute 2013