Muscle Abnormalities in Colorectal Cancer:

Exploring the Associations of Muscle Abnormalities with Pre-existing Comorbidities, and Adverse Surgical Outcomes in Non-metastatic Colorectal Cancer Patients

by

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Abstract

The aim of this project was to further understand the association of pre-existing comorbidities and adverse surgical outcomes with muscle abnormalities in patients with non-metastatic colorectal cancer (CRC). Computerized tomographpy (CT) imaging was used for body composition assessment, and patients' electronic medical records were searched for demographics, pre-existing comorbidities, and surgical outcomes. Muscle abnormalities were defined as sarcopenia [i.e. low skeletal muscle mass index (SMI)] and/or low skeletal muscle radiodensity (SMD).

In study 1, demographic, clinical variables and body composition measures were obtained for 3,262 patients. Advanced age was a significant predictor for both sarcopenia and low SMD. Compared with patients ⩽50 years, those with 70-80 years had an increased risk for presenting with sarcopenia (OR=5.79, 95% CI 4.45-7.52), and with low SMD (OR=17.29, 95% CI 11.42-26.16). Higher amounts of total adipose tissue predicted a higher likelihood of low SMD (OR=8.52, 95% CI 6.59-11.01), but a lower likelihood of sarcopenia (OR=0.56, 95% CI 0.46-0.67). A significant variability in SMI and SMD across age, sex, body mass index (BMI) and race/ethnicity groups was observed. In study 2, International Classification of Disease-9 diagnostic codes for Charlson's comorbidities were obtained from all inpatient and outpatient encounters in the year prior to CRC diagnosis, in 3,051 patients. Multivariable logistic regressions identified six comorbidities predictive of low SMD, including myocardial infarction (OR=1.77, 95% CI 1.08-2.88), congestive heart failure (OR=3.27, 95% CI 1.97-5.41), peripheral vascular disease (OR=2.15, 95% CI 1.33-3.47), diabetes with (OR=1.61, 95% CI 1.13-2.29) or without (OR=1.46, 95% CI 1.13-1.89) complications, and renal disease (OR=2.21, 95% CI 1.50-3.25), whereas only diabetes with complications predicted a lower likelihood of sarcopenia

(OR=0.64, 95% CI 0.47-0.89). In study 3, data on post-surgical length of hospital stay (LOS), any complication, mortality and readmission up to 30 days post-surgery or post-discharge were obtained for n=1,715 colon cancer patients who underwent resection surgery. Sarcopenia and low SMD were each associated with longer LOS (OR=1.30, 95% CI 1.03-1.63 and OR=1.42, 95% CI 1.08-1.86, respectively). Sarcopenia was additionally associated with a higher risk of postoperative complications (OR=1.26, 95% CI 1.02-1.55) and mortality (OR=3.85, 95% CI 1.14-13.04). The additive effect of sarcopenia and low SMD was even stronger for longer LOS (OR=1.84, 95% CI 1.34-2.54) and 30-day mortality (OR=9.68, 95% CI 2.05-45.72) compared to the independent effects of each muscle abnormality.

These studies demonstrated a high prevalence and great variability of muscle abnormalities among age, sex, BMI and race/ethnicity groups in patients with non-metastatic CRC. The findings of multiple pre-existing comorbidities associating with low SMD suggested a potential shared mechanism between fat infiltration into muscle and each of these comorbidities. The impact of muscle abnormalities on adverse surgical outcomes highlights the need of integrating body composition evaluation for patient risk stratification. These findings can be translated into healthcare improvement for patients with CRC.

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Chapter 1 Introduction

1.1 Thesis Organization

This thesis has been prepared as a paper-format according to specifications provided by the Faculty of Graduate Studies and Research at the University of Alberta. Following the introduction, Chapter 2 is included as a literature review and Chapters 3, 4 and 5 are included as individual manuscripts. A preface precedes Chapters 3, 4 and 5 with a brief description of each study. A version of Chapter 4 has received review comments from the *Journal of Cachexia, Sarcopenia and Muscle* and has been re-submitted. Chapters 3 and 5 are being prepared for submission to *American Journal of Clinical Nutrition* and *Annals of Surgery*, respectively.

1.2 Rationale

According to the American Cancer Society, approximately 856,370 males and 878,980 females will be diagnosed with some types of cancer by the end of 2018 (American Cancer Society, 2018). The estimated deaths related to major cancers (i.e. colon and rectum, lung and bronchus, breast and prostate cancers) are 140,850 and 134,660 for males and females respectively (Siegel, Miller, & Jemal, 2018). Among these, colorectal cancer (CRC) is the second leading cause of cancer related death in males and the third in females (Siegel, Miller, & Jemal, 2018), with 50,630 CRC deaths expected to occur by the end of 2018 in the United States (American Cancer Society, 2018). In Canada, CRC represented 13% of all new cancer cases in 2017, and on average, 73 Canadians will be diagnosed with CRC and 26 will die from this disease every day (Canadian Cancer Society, 2018). The incidence of CRC is influenced by many factors, which often co-occur or interact with each other. These factors include age, male sex, and family history of CRC, inflammatory bowel disease, obesity, diabetes, smoking, alcohol intake, and excess consumption of processed meat (Brenner, Kloor, & Pox, 2014).

In parallel with the shift towards a rapid aging society at population level, median age at CRC diagnosis is about 70 years in developed countries; and the concurrence of medical conditions other than cancer is very common (Brenner et al., 2014). On average, most cancer survivors reported five comorbidities ever diagnosed (Leach et al., 2015). A large body of research investigated the presence of comorbidities as a prognostic factor for survival, and its impact on the effectiveness of cancer treatments. Recently, body composition has been of increasing attention as cancer patients might be at particular risk for abnormal body composition phenotypes, such as sarcopenia and myosteatosis. These two muscle abnormalities are measured as low skeletal muscle mass index (SMI=skeletal muscle cross-sectional area/height^2) and low SMD (skeletal muscle radiodensity, reflective of the amount of fat infiltration in muscle) using computerized tomography (CT) images. However, the associations of comorbidities with these two muscle abnormalities at cancer diagnosis remain largely unknown.

Like most cancers, the cornerstones of treatment for CRC are resection surgery, neoadjuvant radiotherapy, and adjuvant chemotherapy. Surgical procedures are commonly seen during patients' hospital visits with approximately 17.2 million surgical procedures performed per year in the United States alone (Steiner, Karaca, Moore, Imshaug, & Pickens, 2006). Among these, 42.2% were inpatient, and colorectal resection accounted for 302,500 per year (Steiner et al., 2006). Adverse surgical outcomes, such as post-surgical complications and readmission after discharge, occur frequently and incur a significant financial burden to the health-care system (Damle et al., 2014). With the aging population and its associated increase in chronic disease incidence, a growing need for surgical treatment and increasing volume of surgical care are expected to continue (Weiser et al., 2008). For this reason, patient risk stratification becomes a critical component for quality improvement of surgical care, which can in turn identify

prognostic and modifiable factors for unfavourable surgical outcomes. Several studies attempted to examine the prognostic significance of sarcopenia for surgical outcomes in cancer patients. A recent meta-analysis involving 5,267 patients from 24 studies reported a significant increased risk of major postoperative complications and 30-day mortality among sarcopenic patients (K. Jones, Gordon-Weeks, Coleman, & Silva, 2017). However, most of the previous studies were restricted to small sample sizes without sufficient statistical power for certain outcome investigations. Additionally, the impact of low SMD on surgical outcomes remains unknown with a limited number of studies reporting conflicting findings. Despite the emerging prognostic impact of sarcopenia and potentially low SMD in cancer, their characteristics by sex, age, body mass index (BMI), race/ethnicities, as well as the determinants of these two muscle abnormalities has not been described in the context of non-metastatic CRC.

1.3 Purpose

The overall objective of this research was to explore the characteristics of sarcopenia and low SMD and to identify their determinants among patients diagnosed with non-metastatic CRC. Additionally, this research aimed to examine the links of muscle abnormalities with pre-existing comorbidities and short-term post-surgical outcomes.

1.4 Research Questions

1. What is the prevalence of muscle abnormalities (i.e. sarcopenia and low SMD) in non-metastatic CRC patients?
2. Are muscle characteristics (SMI and SMD) different across age, sex, BMI and race/ethnicity groups?
3. What are the determining factors of muscle abnormalities measured at CRC diagnosis?

4. Is there a relationship between the presence of any pre-existing comorbidities and muscle abnormalities?
5. Are specific pre-existing comorbidities associated with muscle abnormalities?
6. Is there an association between muscle abnormalities and adverse outcomes after surgery?

1.5 Objectives and Hypotheses

1.5.1 Characteristics and Predictors of Sarcopenia and Low Skeletal Muscle Radiodensity in Patients with Non-metastatic Colorectal Cancer (Chapter 3)

The objectives of this chapter were as follows:

i) To examine the prevalence of sarcopenia and low SMD among non-metastatic CRC patients.

ii) To investigate demographic and clinical determinants of sarcopenia and low SMD among non-metastatic CRC patients.

iii) To describe body composition characteristics of non-metastatic CRC patients by age, sex, BMI, and race/ethnicity groups.

The primary hypotheses of this chapter were as follows:

i) Sarcopenia and low SMD will be common among non-metastatic CRC patients with prevalence exceeding 30%.

ii) Advanced age will be associated with higher risks of both sarcopenia and low SMD at CRC diagnosis.

iii) Higher total adipose tissue level will be associated with a higher risk of low SMD and a lower risk of sarcopenia.

iv) African Americans will present the lowest risk of having sarcopenia.

v) A wide variability in SMI and SMD will be observed across race/ethnicities with African Americans presenting the highest and Asians presenting the lowest SMI among all race/ethnicities.

1.5.2 Associations of Pre-existing Comorbidities with Skeletal Muscle Mass and Radiodensity in Early Stage Colorectal Cancer (Chapter 4)

The objectives of this chapter were as follows:

i) To investigate the association between Charlson comorbidity score and sarcopenia/low SMD.

ii) To determine whether individual pre-existing comorbidities derived from Charlson comorbidity score are associated with sarcopenia and low SMD.

The primary hypotheses of this chapter were as follows:

i) A higher Charlson comorbidity score will be associated with a higher risk of both sarcopenia and low SMD at CRC diagnosis.

ii) Patients with heart diseases (i.e. myocardial infarction and congestive heart failure), vascular diseases (peripheral vascular disease and cerebrovascular disease), chronic obstructive pulmonary disease, diabetes with or without complications, and renal disease will have greater risks of having sarcopenia and low SMD.

1.5.3 CT-measured Muscle Abnormalities are Associated with Worse Prognosis in Patients Undergoing Colon Resection Surgery (Chapter 5)

The objectives of this chapter were as follows:

i) To examine the independent prognostic effect of sarcopenia and low SMD on short-term outcomes after surgery, including any complications, length of hospital stay (LOS), 30-

day mortality after surgery, and readmission within 30-day after first post-surgical discharge.

ii) To investigate the combined effect of sarcopenia and low SMD on surgical outcomes.

iii) To investigate the associations of muscle abnormalities (i.e. sarcopenia or low SMD) and total adipose tissue with adverse surgical outcomes.

The primary hypotheses of this chapter were as follows:

i) Sarcopenia and low SMD will independently predict higher risks of any complications, prolonged LOS, being readmitted post-discharge, and death within 30-day after resection surgery, after controlling for confounding covariates.

ii) The concurrence of sarcopenia and low SMD will be associated with a higher risk of each adverse outcome after surgery compared to patients without any muscle abnormality.

iii) Patients with any muscle abnormality simultaneously with high total adipose tissue level will be at greater risk of adverse surgical outcomes, compared to patients who had the best body composition profile (lowest total adipose tissue level and normal SMI or normal SMD).

1.6 References

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Chapter 2 Literature Review

2.1 Sarcopenia in Chronic Diseases

Sarcopenia is a condition related to the progressive decrease in muscle mass associated with a decline in muscle strength. Primary (or age-related) sarcopenia has been generally considered as a geriatric syndrome with reported prevalence ranging from 5% to 13% in individuals aged 60 to 70 years, and as high as 50% in those older than 80 years (von Haehling, Morley, & Anker, 2010). Sarcopenia can be considered secondary when it is caused by the presence of diseases, versus normal aging trajectory. The progression of sarcopenia can be accelerated by the co-existence of various chronic illnesses, including obesity, chronic heart failure (CHF), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD) and various types of cancer (Cruz-Jentoft et al., 2010). For this reason, sarcopenia is considered an additional comorbidity, likely occurring concurrently with these diseases. Several common characteristics, metabolic and functional abnormalities associated with sarcopenia have been reported in these diseases, such as older age, insulin resistance, chronic inflammation, and muscle contractile insufficiency (Biolo, Cederholm, & Muscaritoli, 2014). Notably, sarcopenia is different than cachexia, which is a syndrome characterized by the loss of skeletal muscle mass with or without the loss of fat mass, and is often present in the context of advanced diseases with concurrent weight loss, severe hormonal disturbances, and inflammation (K. Fearon et al., 2011; Muscaritoli et al., 2010).

2.1.1 Epidemiology of Sarcopenia in Chronic Diseases

In addition to the elderly population, the prevalence of sarcopenia has been reported among individuals with various types of chronic diseases, such as obesity, CHF, CKD, cirrhosis, COPD and cancer. Abundant literature has investigated sarcopenia in individuals with obesity,

which is also defined as sarcopenic obesity. Various prevalence of sarcopenic obesity have been reported, ranging from 2.1% up to 90%, depending on the diagnostic criteria (Prado, Wells, Smith, Stephan, & Siervo, 2012). Sarcopenia also affects approximately 20% of elderly patients with CHF and exceeds the percentage of sarcopenia observed in individuals with the same age but without CHF (Springer & Anker, 2016). In patients with early stage CKD, sarcopenia is prevalent at about 14% (Androga, Sharma, Amodu, & Abramowitz, 2017), with higher rates towards end stage, ranging from 18% to 75% as previously reviewed (Mak et al., 2011). Several large studies have reported that patients who have diabetes also have lower muscle mass, strength and reduced gait speed (T. N. Kim et al., 2010; Leenders et al., 2013; Park et al., 2007; Sayer et al., 2007). Likewise, sarcopenia is prevalent in patients with cirrhosis, ranging from 25% to 70%, and appears more common in males as reported in a recent systematic review and meta-analysis (G. Kim, Kang, Kim, & Baik, 2017). There are relatively less studies examining sarcopenia in patients with COPD, with a reported prevalence of approximately 15% (von Haehling, Anker, & Anker, 2016). Based on a recent systematic review, the prevalence of sarcopenia in cancer patients is as high as 38.6% at the time of diagnosis (i.e. before any treatment) (Pamoukdjian et al., 2017). The global prevalence of chronic diseases, such as obesity, diabetes, and cancer, is projected to increase exponentially during the next few decades, with the greatest burden among those above 65 years of age (Cowie et al., 2009; Ferlay et al., 2015; Shaw, Sicree, & Zimmet, 2010). This trend suggests that an increasing prevalence of sarcopenia at a population level is expected to continue.

2.1.2 Mechanisms of Sarcopenia in Chronic Diseases

The etiology of sarcopenia in chronic diseases is complex and involves the interplay of multiple factors, including genetic, lifestyle (diet, physical activity, smoking), endocrine (growth

hormone, insulin), vascular (endothelial function, coagulation), and immunological (inflammation, reactive oxygen species) factors (Biolo et al., 2014). Collective alterations in these factors either at the molecular or systemic level ultimately lead to a higher muscle turnover, favoring an increased rate of muscle catabolism over anabolism. The key common molecular and endocrine pathways across multiple diseases leading to muscle loss are hereby discussed.

Skeletal muscle has a strong genetic component, and heritability accounts for a large proportion of muscle mass variations (Roth, 2012) ranging from 50% to 80% based on earlier genetic studies (Arden & Spector, 1997; Bouchard, Savard, Despres, Tremblay, & Leblanc, 1985; Forbes, Sauer, & Weitkamp, 1995; Loos et al., 1997; Seeman et al., 1996; Thomis et al., 1997). Nevertheless, specific genes underlying variations in muscle mass remain largely unknown and the genetic determinants of sarcopenia are even less understood in both normal aging or in the context of chronic diseases. Few studies investigated the associations between genetic variation and muscle mass, identifying potential candidate genes for sarcopenia including alpha actinin 3, androgen receptor CAG-repeat polymorphism, myostatin-related genes, thyrotropin-releasing hormone receptor gene, and Vitamin D receptor gene (Roth, 2012; Tan, Liu, Lei, Papasian, & Deng, 2012). However, these studies either reported conflicting genotype associations with muscle mass (Nielsen et al., 2010; Walsh et al., 2005), or have not been replicated (X. G. Liu et al., 2009). Additionally, none of the genes described above have contributed to greater than 5% of inter-individual variability in muscle mass (Roth, 2012). Gene analysis of muscle traits is at an early stage and more genotype research is needed to identify individuals with genetic susceptibility to sarcopenia, and whether the associated genes are similar in normal aging versus disease-related muscle wasting.

A large body of evidence supports increased muscle proteolysis as a main driver for muscle loss, particularly through the activation of ubiquitin-mediated proteasome degradation pathway (Lecker, Goldberg, & Mitch, 2006; Lecker et al., 2004). Proteins from the intracellular compartment are mainly degraded by proteasome, which acts as a multicatalytic protease complex that specifically degrades ubiquitin-conjugated proteins (Lecker et al., 2006). Specifically, the ubiquitin proteasome system is upregulated by skeletal muscle during muscle loss in disease models by promoting ubiquitin-ligase MurF1 and Atrogin-1 expression (Sacheck, Ohtsuka, McLary, & Goldberg, 2004). For this reason, MurF1 and Atrogin-1 could serve as biomarkers for increased rates of protein breakdown and muscle loss (Sacheck et al., 2004). FoxO3a and NF-kB are the two transcription factors mainly responsible for the expression of these ubiquitin ligases (Porporato, 2016). The catabolic actions related to ubiquitin proteasome proteolytic system have been demonstrated in patients with a spectrum of clinical conditions, including CHF (Farges et al., 2002), CKD (Bailey et al., 1996), sepsis (Garcia-Martinez, Llovera, Agell, Lopez-Soriano, & Argiles, 1995), COPD (Sakuma & Yamaguchi, 2012) and cancer (A. Williams, Sun, Fischer, & Hasselgren, 1999).

Although the development of muscle wasting involves multiple contributors, the presence of inflammatory process represents the primary requirement for the alterations in muscle protein synthesis and breakdown. A plethora of studies have investigated the role of the main inflammatory players in muscle wasting, such as tumor necrosis factor-a (TNF-a), interleukin-6 (IL-6), interleukin-1 and interferon-γ. These pro-inflammatory cytokines are thought to act on two key metabolic control points: the activation of the ubiquitin-proteasome system (Khal, Wyke, Russell, Hine, & Tisdale, 2005) and inhibition of Akt/mTOR pathways (Frost & Lang, 2007). Alterations of these pathways promote protein degradation as well as muscle resistance to

anabolic signals, ultimately leading to muscle loss. An association of muscle loss with elevated circulating concentrations of pro-inflammatory cytokines or loss of anti-inflammatory activity has been evident in diseases such as CHF (Sente et al., 2016), obesity (Cesari et al., 2005), COPD (Joppa et al., 2016), CKD (Honda et al., 2007) and cancer (Cespedes Feliciano et al., 2017).

Insulin resistance is another common feature in sarcopenic individuals, and its association with muscle loss is implicated in several highly prevalent disorders, such as type 2 diabetes (T2D) (Mordarska & Godziejewska-Zawada, 2017), obesity (Cleasby, Jamieson, & Atherton, 2016), CHF (Doehner, Frenneaux, & Anker, 2014), and cancer (Argilés, Busquets, Orpi, Serpe, & López-Soriano, 2011). In healthy individuals, insulin signaling activates the mTOR pathway and inhibits autophagy, both of which are crucial for maintaining muscle protein balance (Lawrence, 2001). However, insulin resistance leads to increased stimulation of protein degradation pathways and concurrent decreased activation of protein synthesis, ultimately resulting in an accelerated rate of muscle loss (Morley, 2017; X. Wang, Hu, Hu, Du, & Mitch, 2006). The dysfunction of other anabolic hormones such as circulating growth hormone (GH) and insulin-like growth factor-1 (IGF-1) is seen in patients with CHF or cancer (Cicoira, Kalra, & Anker, 2003; J. M. Garcia et al., 2005). The effect of GH on muscle protein metabolism is complex partly due to its indirect effects via IGF-1, which has glucose-lowering effects similar to insulin (Grounds, 2002). Overall, GH seems beneficial and its downstream signaling through IGF-1 promotes delivery of amino acids to skeletal muscle and inhibits proteolysis. Nevertheless, high levels of GH can cause hyperinsulinemia or insulin resistance (S. H. Kim & Park, 2017). A GH resistance status accompanied with low levels of IGF-1 has been found in patients who had CHF (Anker et al., 2001; Cicoira et al., 2003; Hambrecht et al., 2002). In addition, the

stimulation of GH and IGF-1 secretion has shown to improve muscle mass in cancer patients (Currow & Skipworth, 2017).

Loss of skeletal muscle oxidative capacity is commonly observed among various chronic diseases, which accelerates muscle loss through the disturbance of mitochondrial homeostasis (Romanello & Sandri, 2015). Mitochondrial homeostasis is altered in such a way that mitochondrial degradation is favored above biogenesis, resulting in reduced mitochondrial quantity and quality (Marzetti et al., 2013). Smaller size and number of muscle mitochondria can be related to low glucose disposal rate, insulin insensitivity and decreased exercise capacity (Kelley, He, Menshikova, & Ritov, 2002; Leermakers & Gosker, 2016). Additionally, chronic or intermittent hypoxia could also affect mitochondrial function and lead to oxidative stress, decreased energy availability, and reduced protein synthesis (Leermakers & Gosker, 2016). The link between impaired mitochondrial function and its subsequent decline in muscle oxidative capacity have been suggested in CHF (Guzman Mentesana et al., 2014), T2D (Kelley et al., 2002) and cancer (Julienne et al., 2012; Leermakers & Gosker, 2016). In addition to the pathways discussed above, poor nutrition and physical inactivity also play a role in the development of sarcopenia for patients with one or more chronic diseases.

2.1.3 Health Consequences of Sarcopenia

Muscle loss directly impacts patients' functional performance and quality of life. Exercise intolerance or functional impairment related to low muscle mass is seen in patients with chronic diseases, such as cancer and CHF (Fulster et al., 2013; Mauricio, Xiao, Prado, Gonzalez, & Correia, 2017). For example, low handgrip and quadriceps strength are common in cancer patients and can be associated with fatigue and decreased functional performance (Kilgour et al., 2010). Additionally, the impact of muscle loss can also be regional and certain organs may be

more vulnerable to muscle loss, such as heart muscles (Kazemi-Bajestani, Becher, Fassbender, Chu, & Baracos, 2014; Kazemi-Bajestani, Becher, Ghosh, Montano-Loza, & Baracos, 2016). Muscle loss can directly impact patients' prognosis during treatment. For example, cancer patients who have low muscle mass often experience an increased risk of having post-operative complications, chemotherapy toxicity, and shortened survival (Prado, Birdsell, & Baracos, 2009). Cirrhotic patients with low muscle mass are at higher risk of post-transplant infection, prolonged hospitalization, and shorter survival after liver transplant (G. Kim et al., 2017). From an economic perspective, sarcopenia has been associated with a significant increase in healthcare cost (Janssen, Shepard, Katzmarzyk, & Roubenoff, 2004). A recent study investigated the financial impact of sarcopenia among a cohort of patients undergoing major abdominal operations and reported that the presence of sarcopenia was associated with a $14,322 increase in total hospital costs (Gani et al., 2016). A significant higher healthcare cost has also been recently reported in sarcopenic patients with cirrhosis, compared to those without sarcopenia (J. L. A. van Vugt et al., 2017).

In summary, the prevalence of sarcopenia is expected to increase over the next decade parallel with an increase in the incidence of chronic diseases. Sarcopenia is a major factor of reduced quality of life, as well as in the progression to frailty and cachexia in patients with chronic diseases.

2.2 Definition of Myosteatosis

In addition to loss of muscle mass, the ectopic fat infiltration in skeletal muscle (i.e. myosteatosis) represents another type of muscle abnormality. Myosteatosis includes two modalities of fat depots with varying health implications (Correa-de-Araujo et al., 2017). The storage of lipids in adipocytes located beneath the deep fascia of muscle, and between and within

muscle groups constitutes the first type of fat depots, also termed intermuscular fat (Correa-de-Araujo et al., 2017). At the cellular level, myofibers are surrounded by several stem cell populations, including muscle satellite cells, fibro/adipogenic progenitors as well as multipotent mesenchymal stem cells, which all have adipogenic potentials (Hamrick, McGee-Lawrence, & Frechette, 2016). In patients with muscle injury or glucocorticoid treatment, fibro/adipogenic progenitors have shown to contribute to the accumulation of intermuscular fat by differentiating into adipocytes (Agley, Rowlerson, Velloso, Lazarus, & Harridge, 2013; Dong, Silva, Dong, & Zhang, 2014) . The fat infiltration that directly accumulates within myocytes represents the microscopic lipid droplets (also known as intramyocellular lipid droplets) and is utilized as a source of energy within muscle (Correa-de-Araujo et al., 2017).

2.2.1 Myosteatosis in Chronic Diseases

Fat infiltration into muscle is considered as a normal physiological phenomena associated with aging. In a longitudinal study of 1678 elderly individuals (aged 70 to 79 years), Delmonico et al. reported increased myosteatosis ranging from 35.5% to 74.6% in men and from 16.8% to 50.0% in women (Delmonico et al., 2009). This was the first study demonstrating that fat infiltration in skeletal muscle was a consistent characteristic of aging regardless of weight change (i.e. weight gain, loss or stable) or baseline obesity status. In addition, myosteatosis has been shown in several pathological conditions such as T2D (Goodpaster et al., 2003), obesity (Goodpaster, Theriault, Watkins, & Kelley, 2000), and cancer (Stephens et al., 2011).

2.2.2 Mechanism of Myosteatosis in Chronic Diseases

Despite the growing clinical relevance of myosteatosis, the biological mechanisms underlying its increase with aging or under pathological conditions remain considerably unknown. Several pathways have been hypothesized to act as origins of this condition.

The direct contribution of excess adipose tissue to myosteatosis has been well documented in individuals with obesity. One of the most apparent causes is a level of energy intake exceeding energy expenditure (Shulman, 2014), leading to oversupply of energy and subsequent storage from adipose tissue to skeletal muscle or other organs. Several processes have been suggested to link energy imbalance to myosteatosis, including excess lipid availability from high-fat diet, a reduction in the utilization of fatty acids (i.e. reduced lipolysis and lipid oxidation), increased fatty acid transport and uptake into muscle (Roden, 2005), or impaired adipogenesis (Moro, Bajpeyi, & Smith, 2008). Nevertheless, an inverse association between body mass index (BMI) and lipid droplets has also been reported, suggesting the underlying causes of shifts in energy balance might play a more important role than a specific positive or negative energy balance in inducing increased lipids in muscle (Perseghin et al., 2002; Schrauwen-Hinderling, Hesselink, Schrauwen, & Kooi, 2006). The exact mechanism through which energy imbalance contributes to fat infiltration warrants further investigation.

Age-related fat redistribution and ectopic fat accumulation occur throughout life (Cartwright, Tchkonia, & Kirkland, 2007). Compared with young individuals, older adults have shown larger intramyocellular lipid droplets and higher intramyocellular lipid content (Crane, Devries, Safdar, Hamadeh, & Tarnopolsky, 2010). However, the mitochondria number is fewer and the proportion of intramyocellular lipid in contact with mitochondria is lower in older adults (Crane et al., 2010). These age-related changes collectively contribute to decreased oxidative capacity and thus an increase in fat deposition into muscle. Additionally, an 80% increase in intramyocellular lipid content, concurrent with 30% reduction in mitochondrial oxidative phosphorylation in the muscle of non-obese, insulin-resistant offsprings of T2D patients has been reported, compared to insulin-sensitive controls (Befroy et al., 2007; Petersen, Dufour, Befroy,

Garcia, & Shulman, 2004). In individuals with obesity, mitochondrial concentration has been found to be lower, whereas fat accumulation in skeletal muscle greater in the central region of muscle fibers (Malenfant et al., 2001). These data suggest a potential important link among mitochondrial dysfunction and fat accumulation in muscle across patients with diabetes and obesity.

Additionally, alterations in muscle fiber development might directly contribute to fat deposition in muscle (Hausman, Basu, Du, Fernyhough-Culver, & Dodson, 2014; Sinanan, Buxton, & Lewis, 2006). A change in the differentiation of mesenchymal stem cells or muscle satellite cells favoring the formation of adipocytes (i.e. adipogenesis) over the formation of muscle fibers (i.e. myogenesis) have been found during aging process and in well-defined pathological conditions, including obesity, T2D, primary myopathies (Vettor et al., 2009). This alteration could enhance the conversion of multipotent cells and muscle satellite cells to mature adipocytes, thus increasing fat depots in muscle in the form of either intermuscular fat or intramyocellular lipid droplets (Vettor et al., 2009). Inflammation is also suggested to play a role in the differentiation of mesenchymal stem cells, as well as preadipocytes into mature adipocytes (L. Liu, Mei, Yang, & Li, 2014). Certain critical transcription factors and enzymes could be inhibited by inflammatory cytokines, such as peroxisome proliferator-activated receptor gamma (PPARr) and cytosine-cytosine-adenosine-adenosine-thymidine enhancer binding protein (C/EBPa) (L. Liu et al., 2014). IL-6 and TNF-a have both been associated with decreased expression of PPARr2 and C/EBPa (Gustafson & Smith, 2006). Inhibition of the expression of PPARr and C/EBPa prevents the normal development of preadipocytes to fully differentiated adipose cells, which decreases the storage of lipid in adipose tissue and results in higher probability of lipid accumulation in non-adipose tissues (Gustafson & Smith, 2006).

Some previous studies hypothesized that in addition to impaired cellular mechanisms regulating lipid storage and utilization, myosteatosis might be due to limited capability of subcutaneous adipose tissues to store excess lipids (Correa-de-Araujo et al., 2017; Gan et al., 2002). Physical inactivity and muscle injury are also factors contributing to myosteatosis (Marcus, Addison, Kidde, Dibble, & Lastayo, 2010). An increased accumulation of intermuscular fat has been found only after four weeks of immobilization among healthy young individuals (Manini et al., 2007). In has been reported that in patients with muscular dystrophy, prolonged cycle of muscle injury and regeneration could lead to a marked accumulation of myosteatosis (Hamrick et al., 2016).

2.2.3 Health Consequences of Myosteatosis

Myosteatosis impacts host health through interfering metabolism or impairing muscle functionality. The association between myosteatosis and insulin resistance has been well documented. Insulin acts as an anabolic factor for skeletal muscle protein synthesis, and almost 80% of glucose disposal take place in skeletal muscle (Kelley, Mokan, Simoneau, & Mandarino, 1993). The accumulation of fat into muscle, either in the form of intermuscular fat or intramyocellular lipids decreases insulin sensitivity and impairs the capacity for normal muscle protein synthesis (Rivas et al., 2016). A positive association between intramyocellular lipids and insulin resistance has been reported among individuals with various characteristics, such as older age, obesity, diabetes, or sedentary lifestyle (Miljkovic-Gacic, Wang, et al., 2008). A landmark study was conducted by Goodpaster et al. (Goodpaster et al., 2003) among 2964 elderly individuals with diverse race/ethnicities. In this study, intermuscular fat was higher in individuals with T2D or impaired glucose tolerance than in individuals with normal glucose tolerance (Goodpaster et al., 2003). Of note, this association was independent of obesity. The authors

concluded that elevated fat accumulation in muscle may be a risk factor for metabolic abnormalities such as T2D (Goodpaster et al., 2003). Similar findings have been found in other cohorts of middle-aged or older individuals with African American or Caucasian ancestry (Boettcher et al., 2009; Miljkovic-Gacic, Gordon, et al., 2008). However, it remains unclear whether myosteatosis acts merely as a biomarker of metabolic dysfunction or directly intermediates or modifies insulin signaling pathways.

Earlier cross-sectional studies have shown a negative association between the amount of fat infiltration in muscle and muscle strength or mobility performance. Using 3,075 elderly individuals from the Health, Aging and Body Composition (ABC) study, Visser et al. (Visser et al., 2002) reported that fat infiltration into muscle was associated with poorer lower extremity performance (i.e. walking 6 meters at a usual pace, and stand up and sit down five times from a chair as quickly as possible), even after adjustment for lifestyle factors and health status. Using the same cohort data, the authors further demonstrated that greater fat infiltration into muscle was associated with an increased risk of mobility limitations as assessed by self-reported level of difficulty walking one-quarter mile and climbing 10 steps without resting (Visser et al., 2005). A further analysis of 2,627 individuals from the Health ABC study has revealed that higher muscle attenuation values were associated with greater voluntary isokinetic knee extensor strength and this association was independent of mid-thigh muscle mass and adipose tissue (Goodpaster et al., 2001). More recently, reduced muscle attenuation was associated with higher risk of physical function impairments, longer Timed Up and Go, limitations in instrumental activities of daily living, climbing stairs and walking 1 block in a cohort of 185 cancer patients aged $\geq$ 65 years, whereas skeletal muscle mass was not associated with these outcomes (G. R. Williams et al., 2017).

Research clearly demonstrates links between myosteatosis and physical function impairments. However, the implications of myosteatosis have not been well documented in chronic diseases other than obesity and T2D. Additionally, it is unclear whether myosteatosis is simply a marker for muscle function or whether it has a direct effect on muscle dysfunction.

2.3 Computerized Tomography (CT) Imaging

Muscle abnormalities, both sarcopenia and myosteatosis, can be assessed using sophisticated imaging techniques, such as CT imaging. In a typical cancer center, approximately 30,000 CT images are acquired per year (V. Baracos et al., 2012). Over the past decade, these images have been proposed as an accurate and reliable tool for body composition studies across patients' cancer trajectory. A two-dimensional CT image consists of a map of pixels that corresponds to the volume elements in a three-dimensional section within a patient (Goodpaster, Thaete, & Kelley, 2000a).

2.3.1 Rationale for Body Composition Assessment using CT Imaging

Each pixel has a numerical value in Hounsfield Unit (HU), which corresponds to tissue attenuation. Tissue attenuation depends on the physical properties of tissue within the voxel and relate to tissue density. Higher tissue density is associated with higher linear attenuation coefficient and therefore higher HU values, with water (0 HU) and air (-1000 HU) as the references (Sjostrom, 1991). This variation in attenuation is directly visualized as the level of white and gray within the image. As for skeletal muscle, it has been originally quantified within a specific range of attenuation values from 0 to 100 HU (Mitsiopoulos et al., 1998). A more commonly used range in cancer research is from -29 HU to 150 HU (Aubrey et al., 2014). Within this range, the mean attenuation value for muscle can be measured. Adipose tissues are less dense compared with muscle and therefore correspond to lower HU radiation attenuation

ranges: -150 to -50 for visceral adipose tissue (VAT), and -190 to -30 for intermuscular adipose tissue (IMAT) and subcutaneous adipose tissue (SAT). The unique and specific HU ranges of different tissues allow for their identification in cross-sectional images. Cross-sectional areas of each tissue are subsequently calculated by multiplying the number of pixels by the surface area of the pixel for a given tissue (Heymsfield, Wang, Baumgartner, & Ross, 1997).

A milestone study conducted by Mitsiopoulos et al. validated CT-measured tissues with cadaver estimates in 1998 (Mitsiopoulos et al., 1998). This study compared arm and leg skeletal muscle cross-sectional area measured on CT images with corresponding cadaver estimates, and demonstrated their high correlation ($r=0.99$, SEE=3.8 cm^2, $p<0.001$). Different locations of cross-sectional CT images have been used for body composition measurement, such as thigh and abdominal images. Among these, the third lumbar vertebra (L3) has been the landmark of interest for body composition research. Shen and colleagues were the first group conducted a methodological study in search for a single abdominal image at which tissue cross-sectional areas best correlate with whole-body tissue volumes (Shen et al., 2004). In this study, 328 individuals without malignancy were included and their whole body magnetic resonance images (MRI) obtained. Among these images, six locations were chosen around the fourth and fifth lumbar vertebra (L4-L5): -10 cm below L4-L5, -5 cm below L4-L5, L4-L5, and 5 cm, 10 cm, and 15 cm above L4-L5 (Shen et al., 2004). Overall, abdominal skeletal muscle area on a single slice was highly correlated with whole-body muscle volume with correlation coefficients ranging from 0.712 to 0.924 (Shen et al., 2004). Among these six sites, muscle cross-sectional areas at 5 cm above L4-L5, which corresponds to a location of L3, demonstrated the highest correlation with whole-body muscle volume ($r=0.924$) (Shen et al., 2004). Additionally, a predictive equation was established for whole-body muscle estimates from L3 measurement in this study.

Therefore, L3 has been considered as the landmark of interest for body composition using CT scans. Because of the emerging importance of body composition assessment in cancer research domains, a subsequent methodological study was conducted by Mourtzakis et al. among patients with advanced cancer (Mourtzakis et al., 2008). In this study, equations were developed to predict whole-body fat-free mass from the muscle measures of a single cross-sectional CT image at L3 (Mourtzakis et al., 2008).

2.3.2 Advantages and Limitations

CT imaging method has several advantages. It is regarded as the gold-standard imaging methodology for body composition analysis with high level of accuracy, reliability and availability as discussed above. The intra-observer and inter-observer coefficient of variation are both low for this technique and the results are highly reproducible (Prado & Heymsfield, 2014). Additionally, CT imaging method does not require extra burden on radiologists. Personnel who are trained to use the software and have knowledge of anatomy are qualified for image analysis. Several image analysis software are available. Among these, Slice-O-Matic software developed by Tomovision is one of the most commonly used in research settings. Other analysis software (free-of-charge or paid) that have been used include MeVislab, MeVis Medical Solutions AG, UltraVisual, UltraVisual Medical Systems Inc; ImageJ, National Institutes of Health; OsiriX, Pixmeo; analyzer Synapse Vincent 3D image analysis system, Fujifilm Medical (Prado CM, 2015). CT imaging has been increasingly used for body composition research in cancer due to its availability for cancer diagnosis or disease surveillance purposes; however, its use is not restricted to cancer. Studies in several clinical disorders have highlighted the use of CT imaging method, such as cirrhosis, COPD, human immunodeficiency virus, Crohn's disease, Alzheimer disease and traumatic injuries, as recently reviewed (Prado & Heymsfield, 2014).

A few considerations regarding CT imaging method are worthy of discussion. Firstly, the radiation dose generated by CT is high and therefore it is unethical to expose individuals merely to assess body composition. Current investigations are mostly cross-sectional and have used readily available CT images obtained from the medical record. Secondly, if a patient's body size exceeds the range of a CT machine's field of view, tissues such as subcutaneous adipose tissue or even muscle may not be fully captured on cross-sectional images, resulting in an underestimation of these tissues. Additionally, muscle attenuation value varies depending on the phase of the scan, with the lowest attenuation values being observed in the non-contrast phase compared to arterial and portovenous phases (Rollins et al., 2017). Although the difference is not substantial, a standardized phase of CT for body composition analysis should be used to minimize measurement error.

2.4 Sarcopenia and Myosteatosis in Surgical Oncology

According to the Healthcare Cost and Utilization Project report, approximately 17.2 million hospital visits involve some type of surgical procedures in the United States alone (Steiner et al., 2006). Among these, 42.2% were inpatient, and colorectal resection accounted for 302,500 per year (Steiner et al., 2006). Unfavourable surgical outcomes, such as post-surgical complications and readmission after discharge, occur frequently and incur a significant financial burden to the health-care system (Damle et al., 2014). An increasing need for surgical treatment and increasing volume of surgical care are expected to continue with the aging population (Weiser et al., 2008). Therefore, identifying prognostic and modifiable factors for adverse outcomes after surgery is critical for patient risk stratification and an essential component of surgery care quality.

2.4.1 Prognostic Significance of Sarcopenia for Surgical Outcomes

The relationship between sarcopenia and prognosis during the surgical period has emerged as a hot topic during the past few years. The majority of this research was conducted in cancer patients, including colorectal, pancreatic, gastric, and oesophageal, head and neck cancers and hepatocellular carcinoma (HCC). Short-term outcomes hereby reviewed mainly consist of complications, mortality, length of hospital stay (LOS) post-surgery, and readmission post-discharge.

2.4.1.1 Colorectal cancer

Among colorectal cancer (CRC) investigations, ten studies reported the prognostic significance of sarcopenia or sarcopenic obesity for overall or major complications. Eight of these studies reported an increased risk of having overall or major complications in sarcopenic patients compared with their non-sarcopenic counterparts (Boer et al., 2016; Huang et al., 2015; K. I. Jones, Doleman, Scott, Lund, & Williams, 2015; Lieffers, Bathe, Fassbender, Winget, & Baracos, 2012; Malietzis, Currie, et al., 2016; Nakanishi et al., 2017; P. D. Peng et al., 2011), as shown in Table 1. Peng et al. (P. D. Peng et al., 2011) was the first to investigate the effect of sarcopenia among 259 metastatic CRC patients. In this study, sarcopenia was quantified as low psoas muscle mass using CT images and major complications were defined as a Clavien–Dindo classification score ≥ 3. Sarcopenia was present in 16% of patients. The authors reported a 2-fold increased risk of having any complications for sarcopenic patients; and their risk of having major complications was even higher [odds ratio (OR)=3.12, 95% CI 1.14-8.49] compared to patients without sarcopenia. In a cohort with similar sample size, Lieffers and colleagues (Lieffers et al., 2012) found that 39% patients were sarcopenic out of 234 stage II-IV CRC patients. The risk of infections associated with sarcopenia was influenced by age. Sarcopenia was associated with a

higher risk of infectious complications in the subgroup of patients older than 65 years, while no relationship between sarcopenia and infections was noted in patients younger than 65 years. In multivariate analysis adjusted for age, sex, cancer stage and tumor site, sarcopenia was associated with a more than four-fold increased risk of having infectious complications (OR=4.60, 95% CI 1.50-13.90), whereas no associations were found with age (Lieffers et al., 2012). A study by Jones et al. (K. I. Jones et al., 2015) involved 100 patients who underwent colorectal resection; and approximately 15% of these patients were identified as having sarcopenia. Sarcopenia was strongly associated with an increased risk of major post-operative complications (OR=5.41, 95% CI 1.45-20.15) (K. I. Jones et al., 2015).

Consistent with the findings from the three above-mentioned studies, several other investigations identified sarcopenia as an independent predictor of any/major complication(s) with different effect sizes. Huang et al. (Huang et al., 2015) reported that sarcopenia was associated with a higher risk of major complications (OR=4.52, 95% CI 1.58-12.92) among 142 CRC patients with stage I-III disease. Additionally, an increased risk of having infectious complications was also noted for sarcopenic patients (OR=3.28, 95% CI 1.12-9.55) compared to non-sarcopenic patients in this cohort. Likewise, Nakanishi and colleagues (Nakanishi et al., 2017) found that sarcopenia was an independent predictor of major postoperative complications (OR=1.82, 95% CI 1.13-3.00) in 494 stage I-IV CRC patients. In both these studies, Clavien-Dindo classification score ≥2 was used to define major complications.

The study by Boer et al. (Boer et al., 2016) reported sarcopenia using two different measures, psoas muscle area or total abdominal muscle area. Regardless of the measurement difference, sarcopenia was independently predictive of a higher risk of severe complications. Nevertheless, the prognostic significance of sarcopenia was only evident in the subgroup of

patients with obesity (Boer et al., 2016). Malietzis and colleagues (Malietzis, Currie, et al., 2016) compared the incidence of major complications by sarcopenia status and did not find a difference; nonetheless, similar to the finding by Boer et al., patients who had sarcopenic obesity presented with higher incidence of major complications. In contrast, Lodewick et al. (Lodewick et al., 2015) did not find sarcopenia associated with complication rates in patients who underwent liver resection for metastatic CRC regardless of the presence of obesity.

A common feature of the above eight studies is defining sarcopenia as a dichotomous variable using cutoff values. van Vugt et al. (J. L. van Vugt et al., 2015) used the measure of muscle mass as a continuous variable and reported an increasing skeletal muscle index (SMI=skeletal muscle cross-sectional area/height^2, cm^2/m^2) protected against the occurrence of severe post-operative complications independent of other covariates (OR=0.93; 95 % CI 0.87-0.99). The study by Reisinger et al. (Reisinger et al., 2015) specifically investigated the relationship between sarcopenia and two individual postoperative complications (i.e. anastomotic leakage and sepsis). In this study, sarcopenia was associated with neither complication; nevertheless, a combined functional assessment, including a nutritional questionnaire, a frailty questionnaire and sarcopenia measurement, predicted postoperative sepsis after colorectal resection (Reisinger et al., 2015).

Eight studies reported the associations between sarcopenia with LOS outcomes in CRC patients. Three studies reported that patients who had sarcopenia were more likely to have a prolonged overall LOS evaluated as the mean value of days (Lieffers et al., 2012; Nakanishi et al., 2017; P. D. Peng et al., 2011). Peng et al. (P. D. Peng et al., 2011) found that the postoperative LOS of sarcopenic patients were significantly longer compared to non-sarcopenic patients (6.6±6.1 days versus 5.4±3.2 days, p=0.03), although absolute days of LOS were similar

between groups. Similarly, the overall LOS was relatively longer in other two studies. Lieffers et al. (Lieffers et al., 2012) found an almost seven-day longer LOS for sarcopenic patients compared to patients without sarcopenia (20.2±16.9 days versus 13.1±8.3 days, p=0.008) in the subgroup of those older than 65 years. Likewise, sarcopenic patients were more likely to have a longer LOS compared with non-sarcopenic patients (19.4±17.8 days versus 16.3±12.0 days, p=0.01) in the study conducted by Nakanishi et al (Nakanishi et al., 2017). LOS was not different in five studies, where one study compared the mean LOS value (K. I. Jones et al., 2015), and four compared the median values of LOS postoperatively (Huang et al., 2015; Lodewick et al., 2015; Malietzis, Currie, et al., 2016; J. L. van Vugt et al., 2015).

Only four studies reported mortality outcomes after surgery in CRC (Malietzis, Currie, et al., 2016; P. D. Peng et al., 2011; Reisinger et al., 2015; J. L. van Vugt et al., 2015). Overall, post-operative mortality rate was low in these studies. Peng et al. (P. D. Peng et al., 2011) found that only two events occurred (mortality rate 0.8%) with one patient having sarcopenia. Similarly, death within 30 days post-surgery was equally common in sarcopenic and non-sarcopenic patients in the study by Malietzis et al. (Malietzis, Currie, et al., 2016). Despite the non-significant association between sarcopenia and mortality, seven patients who had sarcopenic obesity died versus three deaths in the rest of patients (i.e. patients who were non-sarcopenic and non-obese, or only sarcopenic or only obese, p<0.001) (Malietzis, Mughal, et al., 2015). Van Vugt et al. (J. L. van Vugt et al., 2015) reported five death events and two patients were sarcopenic (mortality rate 2.2%), which was not different from the mortality rate of those non-sarcopenic patients (2.6%). In contrast, Reisinger et al. (Reisinger et al., 2015) reported a higher 30-day in-hospital mortality risk in sarcopenic patients compared to the non-sarcopenic group. Out of the 14 death events (mortality rate 4.5%), 13 patients had sarcopenia, which was

predictive of a greater than 15-fold increased risk of mortality in univariate analysis (OR=15.5, 95% CI 2.0-120.0) (Reisinger et al., 2015). In multivariable model adjusting demographic and clinical covariates, sarcopenia was an even stronger predictor of short term mortality (OR=43.3, 95% CI 2.7-685.2) (Reisinger et al., 2015). However, these results must be interpreted with caution due to the insufficient statistical power and wide confidence intervals reported.

In addition to overall/major complication, LOS and short-term mortality, other outcomes being explored in CRC studies include readmission rate, intensive care unit (ICU) admission or stay, use of inpatient rehabilitation care, and time to mobilization after surgery. Three studies reported readmission rate and the overall readmission rate ranged from 4.2% to 13.5%. Lieffers et al. (Lieffers et al., 2012) defined readmission as any admission to hospital within 30 days of discharge from the surgical admission, which was 6% in their study. Sarcopenic and non-sarcopenic patients were equally readmitted post-surgery (Lieffers et al., 2012). A similar readmission rate (4.2%) was reported by Huang et al. (Huang et al., 2015) and no difference by sarcopenia status was found. Lodewick et al. (Lodewick et al., 2015) also found no association between sarcopenia and readmission rate, but reported a significantly higher readmission rate in patients with sarcopenic obesity compared to the rest of the patients.

Two studies investigated the relationship between sarcopenia and ICU stay. Peng et al. (P. D. Peng et al., 2011) found patients with sarcopenia were more likely to have an ICU stay ≥ 2 days (15% versus 4% in patients without sarcopenia, p=0.004). In contrast, Jones et al. (K. I. Jones et al., 2015) compared admission to critical care unit by sarcopenia status and found no associations. The authors additionally measured the time interval to initial mobilization after surgery as the patients' functional endpoint, but found no association between sarcopenia and an increased interval to initial mobilization (Urquhart et al., 2011). Only one study in CRC

investigated patients' use of rehabilitation care following surgery. In this study, patients who had sarcopenia were more likely to request inpatient rehabilitation care than those who did not have sarcopenia, and sarcopenia remained a significant predictor of requesting rehabilitation care after controlling for confounding factors (Lieffers et al., 2012).

2.4.1.2 Pancreatic cancer

Similar morphological assessment method was applied to assess sarcopenia pre-operatively among patients with various tumor types, including a relatively larger number of studies in pancreatic cancer patients who underwent pancreatectomy or pancreaticoduodenectomy. In contrast to the prevailing association between sarcopenia and an increased risk of overall or major complications observed in most CRC studies (eight out of ten), the majority of studies conducted in pancreatic cancer did not find a relationship between sarcopenia and complications. Only four studies reported a relationship between sarcopenia and major/overall complications (Amini et al., 2015; Jaap et al., 2016; Joglekar et al., 2015; Nishida et al., 2016).

Amini et al. (Amini et al., 2015) evaluated preoperative sarcopenia by measuring both psoas muscle area and volume in 763 patients undergoing curative resection for pancreatic adenocarcinoma. The authors reported that patients with sarcopenia had a 69% increased risk of experiencing postoperative complications compared to those without sarcopenia (OR=1.69, 95% CI 1.16-2.46). Of note, this association was observed when sarcopenia was evaluated using muscle volume (i.e. less than the lowest sex-specific quartile of total psoas volume), instead of muscle area (Amini et al., 2015). In the study of 180 pancreatic cancer patients conducted by Jaap et al., (Jaap et al., 2016) the impact of sarcopenia on surgical complications was even stronger. Patients who had sarcopenia presented with almost four times higher risk of having

complications (OR=3.52, 95% CI 1.47-8.47) after pancreatectomy compared to patients without sarcopenia. Joglekar et al. (Joglekar et al., 2015) employed a different parameter named HU average calculation (i.e. multiplication of psoas muscle area and mean attenuation divided by total psoas muscle area) to assess sarcopenia in 118 pancreatic cancer patients. The authors defined sarcopenia as having a HU average calculation below the lowest sex-specific quartiles. In this study, sarcopenia predicted major complications (OR=3.45, 95% CI 1.82-6.67) with a similar effect size as reported by Jaap et al. Among 266 consecutive patients who underwent a pancreaticoduodenectomy, Nishida et al. (Nishida et al., 2016) reported that the rate of major complications was significantly higher in the sarcopenic patient group compared to the group without sarcopenia. In particular, sarcopenia was a predictor of postoperative pancreatic fistula, which is considered a serious surgical complication (Nishida et al., 2016). Although these four studies all reported a negative effect of sarcopenia on surgical complications, it is worth to note that the indices (shown in Table 1) used to evaluate sarcopenia were different among these studies.

Different from the above findings, six studies in pancreatic cancer did not find that sarcopenia predicted an increased risk of having major/overall complications or that the rates of complications were different by sarcopenia status (Namm et al., 2017; Ninomiya et al., 2017; Okumura et al., 2015; Onesti et al., 2016; P. Peng et al., 2012; Sandini et al., 2016). Nonetheless, among these six studies, Namm et al., (Namm et al., 2017) found a protective effect of sarcopenia for surgical site infection among 116 patients undergoing pancreaticoduodenectomy. The rationale for this unexpected association was not clear despite the authors' attribution to a high proportion of firm glands and large ducts in sarcopenic patients (Namm et al., 2017). Sandini et al. (Sandini et al., 2016) reported that a high ratio between visceral adipose tissue and

muscle mass was the only determinant of major complications among conventional demographic and clinical indicators (i.e. age and sex), whereas sarcopenia per se was not a predictor. The authors concluded that patients under the dual burden of low muscle mass and high visceral adipose tissue might be particularly vulnerable to have complications after surgery.

Among the six studies reporting LOS, two did not find an association with sarcopenia (Namm et al., 2017; P. D. Peng et al., 2011). Three other studies reported a longer median LOS in sarcopenic patients compared to patients without sarcopenia (Amini et al., 2015; Jaap et al., 2016; Nishida et al., 2016). Joglekar et al. (Joglekar et al., 2015) used psoas muscle index (i.e. muscle mass area adjusted by height squared) as a continuous variable and found that this value was associated with a lower risk of prolonged LOS (OR=1.75, 95%CI 1.10-2.78).

Short-term mortality data was reported in nine studies (Amini et al., 2015; Jaap et al., 2016; Namm et al., 2017; Ninomiya et al., 2017; Nishida et al., 2016; Pecorelli et al., 2016; P. Peng et al., 2012; Sandini et al., 2016; van Dijk et al., 2017). These investigations either did not find an association between sarcopenia and short-term mortality or reported a low incidence of death events, which was not powered for statistical analysis. Only one study by Pecorelli et al. (Pecorelli et al., 2016) found that the ratio between visceral adipose tissue and muscle area was a significant predictor of 60-day mortality (OR=6.76, 95% CI 2.41-18.99) whereas muscle mass was not a predictor.

Five studies reported readmission rate after surgery and four of them found that the readmission rate was not different between patients who had sarcopenia and who did not; neither did sarcopenia predict readmission rate (Jaap et al., 2016; Joglekar et al., 2015; Namm et al., 2017; Nishida et al., 2016). Only one study in pancreatic cancer reported that male patients who had sarcopenia were less likely to be readmitted (OR=0.30, 95% CI 0.1-0.9) (Onesti et al., 2016).

Notably, this study evaluated readmission within six months after discharge whereas the majority of other studies examined readmission rate within 30 days post-discharge, which may partially explain the different findings.

2.4.1.3 Gastric cancer

Six studies assessed the impact of sarcopenia on postoperative complications in patients undergoing gastrectomy for gastric cancer, Table 1. Wang et al. (S. L. Wang et al., 2016) reported a prevalence of 12.5% for sarcopenia, which was defined as a combination of low muscle mass and low muscle strength/physical performance among 255 patients who underwent gastrectomy. Sarcopenic patients had a substantially higher risk of having major post-surgical complications (OR=4.64, 95% CI 2.10-10.25) compared to patients who did not have sarcopenia (S. L. Wang et al., 2016). Likewise, in a cohort of 937 patients with gastric cancer, sarcopenia independently predicted higher risk of severe postoperative complications after gastrectomy (OR=3.01, 95% CI 1.73-5.23) (Zhuang et al., 2016). Huang et al. (Huang et al., 2017) classified sarcopenia into three groups based on the presence of low muscle mass, low muscle strength and low physical performance. Patients who had severe sarcopenia (i.e. concurrence of low muscle mass, strength and physical performance) showed an almost 9-fold higher risk of overall postoperative complications (OR=8.96, 95% CI 3.88-20.70) after radical gastrectomy, compared to patients without any of the three abnormalities (Huang et al., 2017). The study conducted by Nishigori et al. (Nishigori et al., 2016) stratified patients into four groups by sarcopenia (yes or no) and obesity (yes or no) and found that only patients with sarcopenic obesity had an increased risk of surgical site infection after total gastrectomy (OR=4.59, 95% 1.18, 17.78) compared to patients who were in the non-sarcopenic and non-obese group. Similarly, in a cohort of 206 overweight and obese patients, Lou et al. (Lou et al., 2017) reported that sarcopenic obesity was

an independent predictor of post-operative complications after radical gastrectomy (OR=6.01, 95% 1.90-19.36). Only one out of the six studies in gastric cancer failed to find an association between sarcopenia and post-operative complications (Tegels et al., 2015).

Huang et al. (Huang et al., 2017) found a gradual increase in the duration of LOS as patients' sarcopenia level increase from presarcopenia (i.e. low muscle mass without the reduction of muscle strength or physical performance) to severe sarcopenia (i.e. concurrent low muscle mass, low muscle strength and low physical performance). Wang et al. (S. L. Wang et al., 2016) reported that patients with low muscle mass but without decline in muscle function had shorter postoperative LOS compared with patients with both low muscle mass and low muscle strength/physical performance. Zhuang et al. (Zhuang et al., 2016) also found that sarcopenic patients stayed longer in hospital after surgery compared to non-sarcopenic patients. In contrast, Lou et al. (Lou et al., 2017) and Tegels et al. (Tegels et al., 2015) found that the mean values of postoperative LOS were not different between sarcopenic and non-sarcopenic groups. Only two studies reported short-term mortality outcomes and did not find an association of sarcopenia with mortality (Tegels et al., 2015; Zhuang et al., 2016). As for readmission rate, two studies did not find a difference between sarcopenic and non-sarcopenic patients (Huang et al., 2017; S. L. Wang et al., 2016), while another study found sarcopenic patients experienced a higher rate of being readmitted after discharge compared with those without sarcopenia (Lou et al., 2017). In addition, three studies investigated sarcopenia-associated healthcare cost and consistently found that the cost was higher among sarcopenic patients compared to non-sarcopenic patients (Huang et al., 2017; Lou et al., 2017; S. L. Wang et al., 2016).

2.4.1.4 Other cancer types

The value of sarcopenia for preoperative risk assessment has also been examined in cancers with relatively low incidence. In a cohort of 230 patients undergoing esophagectomy for esophageal cancer, psoas muscle area was not different between patients who presented with and without complications/anastomotic leak (Sheetz et al., 2013). Nevertheless, two recent studies in esophageal cancer patients reported an association between sarcopenia and complications. One study found that sarcopenia predicted higher risks of major complications, postoperative pulmonary complications, pneumonia, and prolonged intubation (Elliott et al., 2017). The other study found sarcopenia was predictive of anastomotic leaks in the subgroup of those older than 65 years (Nakashima et al., 2017). Neither of these two esophageal cancer studies found a relationship between sarcopenia and short-term mortality. Similarly, no difference in complications or short-term mortality rate between sarcopenic and non-sarcopenic patients were reported among those who underwent hepatectomy for hepatocellular carcinoma (Voron et al., 2015) and those with periampullary cancer who underwent pancreatoduodenectomy (Van Rijssen et al., 2017). In contrast, in a cohort of 70 head and neck cancer patients, sarcopenia was a significant predictor for overall complications (OR=7.96, 95% CI 1.39-45.29) (Achim et al., 2017).

1.4.2 Prognostic Significance of Myosteatosis for Surgical Outcomes

The prognostic value of myosteatosis, evaluated as the mean attenuation values (or SMD) measured using CT images has only recently been examined. A total of nine studies reported the association between myosteatosis and short-term outcomes post-surgery in different types of cancer, including CRC, pancreatic cancer, breast cancer and HCC as shown in Table 1. Due to the limited available evidence, this discussion is not separated by cancer type.

In the four CRC studies, Sabel et al, (Sabel et al., 2013) investigated SMD (measured from psoas muscle) as a continuous variable and reported a 5% decreased risk of infectious complications for every one unit increase in SMD (OR=0.95, 95% CI 0.93-0.98) among 302 patients undergoing colectomy for colon cancer. Similarly, two other recent studies by Boer et al. (Boer et al., 2016) and Margadant et al. (Margadant et al., 2016) both reported that low SMD was associated with a greater risk of major complications. Of note, while Boer et al. used SMD as a continuous variable, Margadant and colleagues defined low SMD as Housfield unit calculation (i.e. multiplication of psoas muscle area and mean attenuation), which might reflect the dual effect of sarcopenia and myosteatosis. In contrast to these studies, Malietzis et al. (Malietzis, Currie, et al., 2016) did not find patients with myosteatosis more likely to have major complications compared to patients without this condition. However, 30-day mortality and median LOS was higher in patients with myosteatosis in this study (Malietzis, Currie, et al., 2016).

In a prospective cohort of 199 patients undergoing pancreatic surgery, post-operative surgical site infection rates and mortality rates were similar between patients with and without low SMD (van Dijk et al., 2017). In another study of 116 pancreatic cancer patients, low SMD was an independent predictor of surgical site infection and discharge to a nursing facility after surgery, although it was not predictive of major complications, prolonged LOS or readmission (Namm et al., 2017).

Among 281 periampullary cancer patients, Van Rijssen et al. (Van Rijssen et al., 2017) found that low SMD, but not sarcopenia was the only risk factor for major complications in multivariate analysis (OR=2.40, 95%CI 1.30-4.50). The study by Shachar et al. (Shachar et al., 2017) investigated the impact of low SMD on treatment outcomes among 44 metastatic breast

cancer patients. In addition to SMD, the authors also generated a skeletal muscle gauge (SMG) by multiplying muscle mass and SMD values. The only short-term outcome reported in this study was hospitalization related to either infection, or gastrointestinal toxicity and neutropenic fever. Both SMD and SMG were lower in patients who had any hospitalization in this study (Shachar et al., 2017).

The research on the prognostic value of myosteatosis for short-term outcomes is still at an early phase. Within the limited number of studies available, a lack of standardized methods for evaluating myosteatosis with various terminologies and muscle groups being measured was noted (Table 1). Specifically, most studies measured a single muscle group, which constitutes only a small proportion of the entire muscle cross-sectional area at the abdominal region and may not reflect systematic muscle change (V. E. Baracos, 2017). Two studies used different mathematical inference to combine the effect of muscle mass and radiodensity to represent overall muscle "quality", while other studies simply assessed the mean attenuation value (Joglekar et al., 2015; Margadant et al., 2016). The definition of myosteatosis also varied due to heterogeneity in cutoffs to define low SMD. Threshold values have been set as lowest sex-specific quartiles, values below the median or derived from optimal stratification, precluding comparison of findings across studies. While the majority of studies investigated the effect of sarcopenia or myosteatosis as a binary categorical variable, few studies examined SMI or SMD as a continuous variable. Standard evaluation criteria for myosteatosis need to be established before definite conclusions on the impact of this condition on short-term post-operative outcomes are made.

Table 2.1 Muscle Abnormalities and Surgical Outcomes in Cancer Patients

Author, year	Sample size	Including metastasis	Muscle abnormality definition	Sarcopenia %	Myosteatosis %	Short-term outcome measures	Complications	LOS	Mortality/readmission/other outcomes
Colorectal cancer									
Peng et al, 2011[P. D. Peng et al., 2011]	259	Yes	Optimal stratification (psoas muscle area≤500mm^2/m^2)	17%	N/A	Overall and major complication; mean LOS; peri-operative mortality; ICU stay.	Sarcopenia predicted overall (OR=2.22, p=0.02) and major complications (OR=3.12, 95%CI 1.14-8.49).	Sarcopenic patients, longer LOS.	2 death events after surgery with 1 sarcopenic patient. Sarcopenic patients, more likely to use ICU.
Lieffer et al. 2012[Lieffers et al., 2012]	234	Yes	Prado et al. 2008 Definition	38.9%	N/A	Infections complications; mean LOS; 30-day readmission; inpatient rehabilitation care.	Sarcopenia predicted infectious complications (OR=4.60, 95%CI 1.50-13.90).	Sarcopenic patients, longer LOS.	No difference in readmission rate by sarcopenia. Sarcopenia predicted use rehabilitation care.
Jones et al, 2014[K. I. Jones et al., 2015]	100	Yes	Fearon et al. 2011 definition (psoas muscle index)	15%	N/A	Major complication; mean LOS; admission to ICU; time to mobilization.	Sarcopenia predicted major complications (OR=5.41, 95%CI 1.45-20.15).	No difference in LOS by sarcopenia.	No association with ICU admission or time to mobilization.
Huang et al., 2015[Huang et al., 2015]	142	No	EWGSOP and AWGS consensus	12%	N/A	Major complication; infectious complication; median LOS; readmission.	Sarcopenia predicted major complications (OR=4.52, 95%CI 1.58-12.92) and infectious complications (OR=3.28, 95%CI 1.12-9.55).	No difference in LOS by sarcopenia.	No difference in readmission by sarcopenia.
Nakanishi et al., 2017[Nakanishi et al., 2017]	494	Yes	Prado et al, 2008 definition	60%	N/A	Overall and major complications; mean LOS.	Sarcopenia predicted major complications (OR=1.82, 95% 1.13-3.00).	Sarcopenic patients, longer LOS (19 versus 16 days, p=0.01)	N/A
Boer et al., 2016[Boer et al., 2016]	91	Yes	Psoas muscle mass<sex-specific median values, psoas muscle density as a continuous variable	50%	N/A (reported as a continuous variable)	Overall and severe complication.	Every 1 unit decrease in HU, 8.8% increased risk of overall complications. Sarcopenic obesity predicted severe complications (OR=6.4, 95% 1.9-21.3).	N/A	N/A

Malietzis et al., 2015[Malietzis, Currie, et al., 2016]	805	Yes	Martin et al. 2013 definition	60.2%	77.6%	Major compilations; median LOS; 30-day mortality.	Sarcopenic obese patients, more likely to have major complications.	No difference in LOS by sarcopenia. Low SMD, longer median LOS (7 versus 6 days).	Sarcopenic obese patients, more likely to die after surgery.
Lodewick et al, 2014[Lodewick et al., 2015]	171	Yes	Martin et al., 2013 definition	47%	N/A	90-day complications; median LOS; readmission.	Sarcopenia or sarcopenic obesity, no association with complications.	No difference in LOS by sarcopenia or sarcopenic obesity.	No difference in readmission rate by sarcopenia. Sarcopenic obese patients, more likely to be readmitted.
van Vugt et al. 2015[J. L. van Vugt et al., 2015]	206	Yes	Prado et al, 2008 definition	43.7%	N/A	Overall and severe complications; median LOS; 30-day mortality.	Every 1 unit decrease in SMI, 7% increased risk of having severe complications (OR=0.93, 95%CI 0.87-0.99).	No difference in LOS by sarcopenia.	No difference in 30-day mortality by sarcopenia.
Reisinger et al., 2015[Reisinger et al., 2015]	310	Yes	Prado et al, 2008 definition	47.7%	N/A	Anastomotic leak and sepsis; 30-day mortality.	A combined indicator including sarcopenia predicted sepsis (OR=25.1, 95%CI 5.11-123.00).	N/A	Sarcopenia predicted 30-day mortality (OR=15.50, 95%CI 2.00-120.00).
Sabel et al., 2013[Sabel et al., 2013]	302	Yes	Psoas muscle density as a continuous variable.	N/A	N/A	Overall complications.	Every 1 unit increase in SMD, 5% decreased risk of infectious complications (OR=0.95, 95%CI 0.93-0.98).	N/A	N/A

Margadant et al., 2016[Margadant et al., 2016]	373	Yes	Psoas muscle density (HU average calculation)<sex-specific quartiles	24.7%	24.7%	Major complications; median LOS; 30-day mortality; 30-day readmission; ICU admission.	Patients with low psoas muscle density (categorical variable), more likely to have major complications. HU calculation (continuous variable) predicted major complication risk (OR=1.09, 95%CI 1.04-1.14). Low psoas muscle density (categorical variable) predicted major complications (OR=1.80, 95%CI 1.11-2.97).	Patients with low muscle density, longer LOS (13 versus 10 days, p=0.025)	No difference in mortality rate by HU calculation. Patients with low muscle density, higher readmission and ICU admission rates.
Pancreatic cancer									
Amini et al., 2015 [Amini et al., 2015]	763	No	Psoas muscle index or volume<the lowest sex-specific quartiles	25%	N/A	Overall/major complication; median LOS; 30-day or 90-day mortality.	Sarcopenic patients, more likely to have overall or major complications. Sarcopenia predicted complications (OR=1.69, 95%CI 1.16-2.46). The above associations were present when sarcopenia defined by muscle volume.	Sarcopenic patients, longer median LOS (9 versus 8 days with sarcopenia defined by muscle area; 10 versus 8 with sarcopenia defined by muscle volume).	No difference in mortality rate by sarcopenia.
Jaap et al., 2016 [Jaap et al., 2016]	180	Yes	Psoas muscle area< sex-specific lowest quartile	24.4%	N/A	Overall complications; median LOS; mortality; 30-day readmission; discharge to home versus rehabilitation facility.	Sarcopenia predicted overall complications (OR=3.52, 95%CI 1.47-8.47).	Sarcopenic patients, longer median LOS (9 versus 7 days, p=0.09).	No difference in readmission by sarcopenia. Neither did sarcopenia predict readmission. 3 death events, no analysis.

Joglekar et al., 2015[Joglekar et al., 2015]	118	No	Psoas muscle index or HU average calculation<sex-specific lowest quartile	24.6% by HU average calculation, 26.3% by psoas muscle index	N/A	Overall and major complications; LOS; 30-day readmission; ICU admission; delayed gastric emptying.	HU average calculation predicted major complications (OR=3.45, 95%CI 1.82-6.67), infectious (OR=1.69, 95%CI 1.08-2.70), gastrointestinal (OR=1.75, 95%CI 1.06-2.94), pulmonary (OR=2.56, 95%CI 1.43-4.76) and cardiac complications (OR=2.70, 95%CI 1.54-4.76).	Psoas muscle index (OR=1.75, 95%CI 1.10-2.78) and HU average (OR=2.00, 95%CI 1.22-3.33) predicted longer LOS.	HU average calculation predicted longer ICU stay (OR=2.33, 95%CI 1.32-4.00) and delayed gastric emptying (OR=2.33, 95%CI 1.19-4.35). No association with readmission.
Nishida et al., 2016[Nishida et al., 2016]	266	Yes	Martin et al., 2013 definition	49.6%	N/A	Major complications and post-operative pancreatic fistula; median LOS; mortality; 30-day readmission.	Sarcopenia predicted post-operative pancreatic fistula (OR=2.87, 95%CI 1.33-6.20). Sarcopenic patients, more likely to have major complications.	Sarcopenic patients, longer median LOS (15 versus 13 days, p=0.01).	No difference in readmission rate by sarcopenia. 1 death event in cohort (sarcopenic patient).
Peng et al., 2012[P. Peng et al., 2012]	557	Yes	Psoas muscle index<the lowest sex-specific quartiles	25%	N/A	Overall and major complications; mean LOS; 30-day and 90-day mortality; mean ICU stay.	No difference in overall or major complications by sarcopenia.	No differences in mean LOS or ICU stay by sarcopenia.	Sarcopenia did not predict mortality.
Okumura et al. 2015[Okumura et al., 2015]	230	Yes	Psoas muscle area (males<5.896 cm^2/m^2, females<4.067cm^2/m^2)	27.8%	N/A	Major complication.	No difference in major complication rate by sarcopenia.	N/A	N/A
Pecorelli et al., 2016[Pecorelli et al., 2016]	202	Yes	Prado et al., 2008 definition or SMI as a continuous variable	65%	N/A	Major complications and postoperative pancreatic fistula; 60-day mortality.	Sarcopenia did not predict postoperative pancreatic fistula. No correlation between major complication and muscle area.	N/A	SMI did not predict mortality. Visceral adipose tissue area/muscle area ratio predicted mortality (OR=6.76, 95%CI 2.41-18.99).

Onesti et al., 2016[Onesti et al., 2016]	270	No	Psoas muscle area< the lowest tertile	33%	N/A	Major complications; readmission within 6 month; rehabilitation discharge.	Sarcopenia did not predict major complications.	N/A	Sarcopenic patients, more likely to be discharged to rehabilitation care compared to patients in the upper tertile (OR=2.7, 95%CI 1.1-6.9), but less likely to be readmitted (OR=0.3, 95%CI 0.1-0.9).
Ninomiya et al., 2017[Ninomiya et al., 2017]	265	Yes	SMI: males<43.75 cm^2/m^2, females<38.50 cm^2/m^2	64.2%	N/A	Major complications and surgical site infection; 90-day mortality.	No difference in major complication rate by sarcopenia.	N/A	No death events in cohort.
Van Dijk et al., 2016[van Dijk et al., 2017]	199	Yes	SMI <lowest tertile; SMD <lowest tertile	33%	33%	Major complications and surgical site infection; 90-day operative mortality.	No difference in surgical site infection by SMI or SMD group.	N/A	No difference in mortality rate by SMI or SMD group.
Namm et al., 2017[Namm et al., 2017]	166	Yes	Psoas muscle area and HU as continuous variables	N/A	N/A	Major complications; LOS; 30-day mortality; 90-day readmission; ICU admission; discharge to skilled nursing facility.	Psoas muscle index not predicting major complications. Higher psoas muscle index and HU predicted higher risk of concurrence of surgical site infection pancreatic fistula.	No association with LOS.	No association with readmission, ICU admission. Higher psoas muscle index or HU, lower risk of discharge to skilled nursing facility. 1 death event in cohort, no analysis.

Sandini et al., 2016[Sandini et al., 2016]	124	No	Martin et al., 2013 definition	24.2%	N/A	Major complications; in-hospital or 30-day after discharge mortality.	No difference in major complication rate by sarcopenia and sarcopenia not predicting complications. Pulmonary complication rate was different by sarcopenic obesity. Visceral adipose tissue area/muscle area ratio predicted major complications (OR=3.2, 95%CI 1.35-7.60).	N/A	No difference in mortality rate by sarcopenia.
Gastric Cancer									
Wang et al., 2016[S. L. Wang et al., 2016]	255	No	EWGSOP and AWGS consensus	12.5%	N/A	Overall/major complications; median LOS; 30-day readmission; healthcare cost.	Sarcopenic patients, higher overall complication rate.	Sarcopenic patients, longer LOS (16 versus 13 days).	No difference in readmission rate by sarcopenia. Sarcopenic patients, higher healthcare costs.
Zhuang et al., 2016[Zhuang et al., 2016]	937	No	Optimal stratification (SMI: males 40.8 cm^2/m^2, females 34.9 cm^2/m^2)	41.5%	N/A	Overall/major complications; median LOS; 30-day mortality.	Sarcopenic patients, higher overall complication rate. Sarcopenia predicted severe complications (OR=3.01, 95%CI 1.73-5.23).	Sarcopenic patients, longer LOS (11 versus 10 days).	Not difference in mortality rate by sarcopenia.
Huang et al., 2017[Huang et al., 2017]	470	No	Optimal stratification (SMI: males 40.8 cm^2/m^2, females 34.9 cm^2/m^2)	20.6% (pre-sarcopenia), 10% (sarcopenia), 6.8% (severe sarcopenia).	N/A	Overall/major complications; median LOS; 30-day readmission; healthcare cost.	Severe sarcopenia predicted overall complications (OR=8.96, 95%CI 3.88-20.70). Visceral adipose tissue area/muscle area predicted overall complications (OR=2.93, 95%CI 1.76-4.89).	Sarcopenic patients, longer LOS (20 versus 14 versus 11 days for severe sarcopenia, sarcopenia, presarcopenia).	No difference in readmission rate by sarcopenia. Sarcopenic patients, higher healthcare costs.
Nishigori et al., 2016[Nishigori et al., 2016]	157	Yes	Prado et al., 2008 definition	57%	N/A	Major complications.	Sarcopenic obesity predicted surgical site infection (OR=4.59, 95%CI 1.18-17.78).	N/A	N/A

Lou et al., 2017[Lou et al., 2017]	206	No	Optimal stratification (SMI: males 40.8 cm^2/m^2, females 34.9 cm^2/m^2)	6.8%	N/A	Overall complications; mean LOS; 30-day readmission; healthc are cost.	Sarcopenia predicted overall complications (OR=6.07, 95%CI 1.90-19.36).	No differences in LOS by sarcopenia.	Sarcopenic patients, higher healthcare costs. Sarcopenic patients, higher readmission rate.
Tegels et al., 2015[Tegels et al., 2015]	180	Yes	Martin et al., 2013 definition	57.7%	N/A	Severe complications; mean LOS; in-hospital/30-day mortality.	No difference in severe complication rate by sarcopenia.	No differences in LOS by sarcopenia.	No difference in mortality rate by sarcopenia.
Other Cancers									
Sheetz et al., 2013[Sheetz et al., 2013]	230 esophageal cancer	Yes	Psoas muscle area as a continuous variable	N/A	N/A	Overall complications.	Psoas muscle area, not related to overall complications.	N/A	N/A
Voron et al., 2015[Voron et al., 2015]	109 hepatocellular carcinoma	N/A	Prado et al., 2008 definition	54.1%	N/A	Overall and severe complications; 60-day mortality.	No difference in major complication rate by sarcopenia.	N/A	No difference in mortality rate by sarcopenia.
Van Rijssen et al., 2017[Van Rijssen et al., 2017]	281 periampullary cancer	No	Optimal stratification (for SMI males: 53.5 cm^2/m^2, females 46.6 cm^2/m^2; for SMD, males <36.3 HU, females<36 HU)	78%	49%	Major complications.	No difference in major complication rate by sarcopenia. Patients with low SMD, higher major/overall complication rate, higher rate of postoperative hemorrhage, delayed gastric emptying. Sarcopenia did not predict, but low SMD predicted major complications (OR=2.4, 95%CI 1.3-4.5).	N/A	N/A
Achim et al., 2017[Achim et al., 2017]	70 head and neck cancer	N/A	Prado et al., 2008 definition	77.1%	N/A	Overall complications.	Sarcopenia predicted overall complications (OR=7.96, 95%CI 1.39-45.29).	N/A	N/A

Shachar et al., 2017[Shachar et al., 2017]	40 breast cancer	Yes	SMD and SMG as continuous variables	58.0%	N/A	Hospitalization as a binary variable.	N/A	Lower SMD and SMG in patients who were hospitalized. No difference in SMI by hospitalization.	N/A

Prado et al., 2008 definition (Prado et al., 2008): SMI, males <52.4 cm^2/m^2, females<38.5 cm^2/m^2. Fearon et al. 2011 definition (K. Fearon et al., 2011): psoas muscle index (i.e. psoas muscle area/height^2), females<385 mm^2/m^2, males <545 mm^2/m^2. Martin et al. 2013 definition (Martin et al., 2013): SMI, females<41 cm^2/m^2; males <43 cm^2/m^2 for BMI<25kg/m^2, males<53 $cm^2/m^2$for BMI≥25kg/m^2. EWGSOP (Cruz-Jentoft et al., 2010) and AWGS (Chen et al., 2014) consensus (SMI, males<36 cm^2/m^2, females<29 cm^2/m^2). HU average calculation=[(right HU*right psoas area)/total psoas area + (left HU*left psoas area)/total psoas area]/2. SMI=skeletal muscle index (skeletal muscle cross-sectional area/height^2). LOS=length of hospital stay, EWGSOP=European Working Group on Sarcopenia in Older People, AWGS=Asian Working Group for Sarcopenia, SMG=skeletal muscle gauge, SMI=skeletal muscle index, SMD=skeletal muscle radiodensity

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Chapter 3 Characteristics and Predictors of Sarcopenia and Low Muscle Radiodensity in Patients with Non-metastatic Colorectal Cancer

3.1 Preface

The following chapter is based on data from a population-based study of 3,262 patients with non-metastatic colorectal cancer (CRC) diagnosed at Kaiser Permanente Northern California, an integrated healthcare system. This study aimed to describe the prevalence and predictors of muscle abnormalities among these patients. Ms. Jingjie Xiao was responsible for measuring body composition using computerized tomography (CT) images. She additionally performed statistical analysis and interpretation, and wrote the first draft of the manuscript with ongoing discussions with Dr. Carla Prado. Ms. Erin Weltzien contributed to compiling the clinical and demographic data, and data analysis. Drs. Vickie Baracos and Elizabeth Cespedes Feliciano contributed to interpretation and critically review of the manuscript. Dr. Marilyn L. Kwan contributed to data interpretation and manuscript review. Drs. Bette Caan, Jeffrey Meyerhardt, Candyce Kroenke and Carla Prado contributed to concept formation, study design , interpretation, and editing of the final manuscript. This manuscript is being submitted to the American Journal of Clinical Nutrition.

3.2 Introduction

Skeletal muscle constitutes the largest fraction of the lean soft tissue compartment and is the primary site of body protein storage (Prado & Heymsfield, 2014). In addition, approximately 80% of glucose disposal in the human body occurs in skeletal muscle (Kelley et al., 1993). Therefore, skeletal muscle is crucial for maintaining glucose homeostasis and represents a patient's physiological reserve and overall health status. The term sarcopenia was originally used to describe age-associated decline in muscle mass (primary sarcopenia) (Cruz-Jentoft et al., 2010). Secondary sarcopenia, however, is the loss of muscle mass observed in multiple pathological and physiological disorders, such as illnesses requiring critical care, end-stage renal disease and malignant disease (Cruz-Jentoft et al., 2010).

Colorectal cancer (CRC) is the third leading cause of cancer-related death in women and second in men in the United States (Siegel, Miller, & Jemal, 2018). Upward of 71% patients with CRC are affected by sarcopenia (Malietzis, Aziz, et al., 2015). CRC patients with sarcopenia have poor functional capacity, increased postoperative morbidity, greater chemotherapy toxicity, shorter time to cancer progression and decreased life expectancy (Prado CM, 2015). Moreover, sarcopenia has been associated with a higher rate of major complications after CRC resection, longer recovery time and greater need for rehabilitation care (K. Jones et al., 2017).

Computerized tomography (CT) allows precise quantification of muscle mass, and hence, sarcopenia. Additionally, this technique allows the assessment of low skeletal muscle radio-density (SMD), reflective of a higher level of fat infiltration in muscle. Low SMD is an emerging prognostic factor in CRC and in other cancers (Martin et al., 2013). Little is known about risk factors for sarcopenia and low SMD in cancer. Recognizing these factors may aid in the prediction of overall patient prognosis. Additionally, attempts could be made to improve

modifiable risk factors related to these conditions, thus improving short and long term prognosis. The aim of this study was to assess the prevalence and major determinants of sarcopenia and low SMD in a large cohort of 3,262 non-metastatic CRC patients.

3.3 Methods

3.3.1 Study Population and Setting

We included patients aged 18 to 80 years at Kaiser Permanente Northern California (KPNC) diagnosed with stage I-III invasive CRC between 2006 and 2011. Patients who had abdominal CT scans around diagnosis with sufficient image quality for body composition assessment were included as described elsewhere (Caan et al., 2017). This study was approved by the KPNC Institutional Review Board and the University of Alberta Health Research Ethics Board.

3.3.2 Body Mass Index and Body Composition Variables

We selected patients' height and weight closest to cancer diagnosis measured by KPNC medical assistants and computed "at-diagnosis" BMI (body weight kg/height in meters^2) and classified patients according to World Health Organization guidelines: underweight (<18.5 kg/m^2), normal weight (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2), Class I obesity (30 to <35kg/m^2), and Class II/III obesity (≥35 kg/m^2).

Body composition was measured from diagnostic CT scans taken before any chemotherapy or radiation treatment (83% pre-surgical). The median time between diagnosis and scan was 0.2 months, ranging from -2.0 to 3.8 months. A single image at the third lumbar vertebra (L3) was selected for body composition quantification, including skeletal muscle mass, inter-muscular adipose tissue (IMAT), visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) cross-sectional areas (cm^2). A single L3 image strongly correlates with whole-body

muscle and total adipose tissue (TAT) volumes (Shen et al., 2004). Tissue areas were measured according to the standard Hounsfield unit (HU) range of -29 to 150 for muscle (Heymsfield et al., 1990), -150 to -50 for VAT (Miller et al., 1998), -190 to -30 for IMAT and SAT (Mourtzakis et al., 2008) using SliceOmatic Software version 5.0 (TomoVision, Montreal, Quebec, Canada). SMD in HU was generated by the software as the mean radiation attenuation value of the measured muscle groups at L3. The inter-observer coefficient variations were 1.2% for skeletal muscle, 0.7% for SMD, and 1% for total adipose tissue (TAT). Skeletal muscle index (SMI) was calculated from skeletal muscle cross-sectional area divided by height squared (cm^2/m^2). TAT was calculated as the sum of VAT, IMAT, and SAT.

3.3.3 Definitions of Sarcopenia and Low Skeletal Muscle Radiodensity

Threshold values of muscle abnormalities (i.e. sarcopenia and/or low SMD) were developed using the optimal stratification approach (Martin et al., 2013; Prado et al., 2008). This method identifies cut points that best separate patients' risk with respect to time to death, which has been increasingly accepted as a clinically relevant approach for patient risk stratification. Accordingly, sarcopenia was defined as SMI < 52.3 cm^2/m^2 for men and < 38.6 cm^2/m^2 for women in underweight/normal/overweight categories (BMI<30 kg/m^2), and SMI < 54.3 cm^2/m^2 for men and < 46.6 cm^2/m^2 for women in obese category (BMI≥30 kg/m^2) (Caan et al. 2017). Similarly, low SMD was defined as SMD < 35.5 HU for men and < 32.5 HU for women for all BMI categories (Kroenke et al. 2018). We further classified patients into four phenotype groups: non-sarcopenic, normal SMD; non-sarcopenic, low SMD; sarcopenic, normal SMD; and sarcopenic, low SMD.

3.3.4 Demographic and Clinical Variables

We reviewed all patients' electronic medical records and the KPNC Cancer Registry for information on demographics, lifestyle, and medical history. Age at diagnosis, sex, disease stage, race/ethnicity, comorbidities (1 year before cancer diagnosis), pre-diagnostic weight change (i.e. the subtraction of diagnosis weight from the weight taken 18 months prior to diagnosis), smoking history and alcohol use (any time prior to and closest to cancer diagnosis) were obtained.

3.3.5 Statistical Analysis

Differences in descriptive statistics by muscle abnormalities and differences in body composition variables by patient subgroups defined by age, BMI, and sex were analyzed using one-way analysis of variance or Pearson's Chi-square tests, where appropriate. Mean difference and marginal means of body composition components by race/ethnicity were estimated from generalized linear models. Logistic regression models were applied to determine clinical and demographic predictors of outcome variables (i.e. sarcopenia and/or low SMD) in univariate and multivariable analysis. All statistical analyses were performed using STATA (version 14.2; StataCorp LP), with statistical significance established with 2-sided tests with $p=0.05$.

3.4 Results

3.4.1 Patient Characteristics

A total of 3,262 patients was included. Patient demographic, clinical and body composition characteristics are given in Table 1. Males presented with both higher SMI and SMD than females. Prevalence of sarcopenia and low SMD were 45.3% and 28.4% in males, 39.5% and 30.9% in females, respectively. Although sarcopenia and/or low SMD were more common in older patients, both conditions occurred across the age spectrum: for example, 114

(6.7%) of patients younger than 65 years at diagnosis had both sarcopenia and low SMD (data not shown). Figure 1 shows the percentage of patients who had sarcopenia and/or low SMD across the TAT distribution. The majority of patients who only had sarcopenia were more likely to be at the lower end of the TAT distribution, whereas patients with only low SMD were more likely to be at the other extreme of the distribution (Figure 1).

3.4.2 Body Composition Features and Predictors of Muscle Abnormalities

Variations in body composition components by age and sex are shown in Table 2. Mean SMI and SMD were lower in the higher age categories for both sexes. In contrast, VAT, SAT and TAT were higher with older age except in those 70-80 years of age. In multivariable regression analysis, older age was associated with higher risks of sarcopenia and low SMD in a dose-response manner. Compared with patients younger than 50 years, the odds ratios (ORs) for sarcopenia were higher in older age groups (Table 3); patients aged 70-80 years had the highest risk of sarcopenia (OR=5.79, 95% CI 4.45, 7.52). The dose-response effect of age on SMD was more pronounced (Table 3). Of note, patients who were older than 70 years had a substantially higher risk of low SMD compared to those younger than 50 years (OR=17.29, 95% CI 11.42, 26.16).

Within each age group, there was a direct, dose-response relationship between BMI and SMI in both sexes (Supplementary Tables 1 and 2). In contrast, SMD was lower in those in in the higher BMI categories, which was consistent with the overall linear trend shown in Figure 2. Patients with higher BMI had more of each type of adipose tissue (Supplementary Tables 1 and 2). Multivariable regression analysis showed different associations between adiposity level and sarcopenia or low SMD. Similar to the distribution shown in Figure 1, those in the highest TAT

tertile had a lower risk of sarcopenia but higher risk of low SMD, after adjusting for confounding factors (Table 3).

Substantial differences in muscle abnormalities (Figures 3 and 4) and adipose tissue components (Supplementary Figures 1 and 2) by race/ethnicity were noted. In males, African Americans presented with the highest SMI and SAT. Male White/Caucasians had the lowest SMI and SMD, but the highest VAT and TAT. The highest SMD was found in male Asians. Among females, African Americans had the highest SMI, SMD and SAT, while Caucasians had the lowest SMI. Consistent with males, African American females had both the lowest VAT and TAT. In contrast, Hispanic/Latino females had the highest levels of VAT and TAT.

In multivariable logistic regression analysis, race/ethnicity predicted muscle abnormities. Compared to Whites/Caucasians as a reference group, African Americans had a 50% lower risk of sarcopenia and a 65% lower risk of low SMD. Hispanics/Latinos were 35% less likely to have sarcopenia, while Asians were 62% less likely to have low SMD (Table 3).

Patients with stage II and III CRC had a higher likelihood of sarcopenia, while patients with stage III had a higher risk of low SMD, compared with those who had stage I cancer. In addition, compared to those with proximal colon cancer patients as a reference group, those with distal colon cancer were more likely to have sarcopenia, and those who had rectal cancer were less likely to have low SMD. Regarding lifestyle and clinical factors, alcohol use did not predict either muscle abnormality in the univariate analysis and was dropped in further analyses. Current and former smokers were more likely to have low SMD, but not sarcopenia, compared with non-smokers. Likewise, patients with a Charlson comorbidity score ≥1 were more likely to have low SMD, but not sarcopenia compared to patients without any comorbidity. Further adjustment for pre-diagnostic weight change history did not alter the ORs for sarcopenia or low SMD in

sensitivity analysis; and was therefore excluded from models. In a sensitive analysis, ORs of age, TAT, race/ethnicity, smoking was not different in patients who had their CT scans taken prior to surgery (n=2,701).

3.5 Discussion

To our knowledge, this is the largest study to describe body composition characteristics of non-metastatic CRC patients, and the first to examine predictors of sarcopenia and low SMD. Sarcopenia was found in 42% and low SMD in 30% of patients, despite the wide BMI range. Older age was a strong predictor of both sarcopenia and low SMD with a more pronounced effect on low SMD. Higher TAT was associated with a lower risk of sarcopenia but a higher risk of low SMD. Compared with Caucasians, African American and Hispanic/Latino patients had lower risks of sarcopenia, whereas African American and Asian patients had lower risks of low SMD.

Muscle mass generally constitutes 50% of total body weight in young adults, but progressive muscle loss, particularly in the lower body extremities, can begin as early as 25 years of age (Keller & Engelhardt, 2013; Porter, Vandervoort, & Lexell, 1995). The rate of loss accelerates after 50 years of age, and muscle mass decreases to 25% of total body weight by 75-80 years (Kalyani, Corriere, & Ferrucci, 2014). Concomitant with a decline in muscle mass, higher adipose tissue accumulation within or between skeletal muscle occurs with aging (Borkan, Hults, Gerzof, Robbins, & Silbert, 1983; Miljkovic & Zmuda, 2010) and has been related to reduced oxidative enzyme capacity and insulin resistance in muscle (Goodpaster, Thaete, Simoneau, & Kelley, 1997; Simoneau, Colberg, Thaete, & Kelley, 1995). The mean age in our cohort was ≥ 60 years; as expected, age remained a significant predictor of both sarcopenia and low SMD, and the likelihood of each condition increased with age. Compared to patients ≤ 50 years, those aged

≥ 70 years were at particularly higher risk of having any muscle abnormality. Mean values for SMI and SMD across age categories in the current study were relatively higher than those in another large-scale investigation of patients (n=1,473) including non-metastatic and metastatic lung and gastrointestinal cancer (Kazemi-Bajestani, Mazurak, & Baracos, 2016; Martin et al., 2013). This is likely due to a lower level of disease severity in our cohort as these patients were at earlier stages of disease trajectory. Catabolic processes related to the tumor itself might be of lower burden compared with patients with advanced disease. Regardless of stage, sarcopenia was highly prevalent among CRC patients in both this and prior studies.

We found that BMI and TAT were positively related to SMI, which is consistent with previous studies in different cancer types (Martin et al., 2013; P. D. Peng et al., 2011). The prevalence of overweight/obesity was 67.3% in the current cohort. Physiological increases in lean mass with increasing adipose tissue has been previously reported (Bosy-Westphal & Muller, 2015), which may partially explain the lower risk of sarcopenia in patients with higher TAT. Despite the lower risk of sarcopenia associated with higher TAT, our previous report demonstrated that sarcopenia was predictive of higher risk of mortality, independent of adipose tissue levels (Caan et al., 2017). Even among obese patients, relatively lower SMI (known as sarcopenic obesity) increased mortality risk, even if their absolute amount of SMI in obese patients is higher compared to non-obese individuals. Since BMI cannot distinguish muscle from fat, patients with sarcopenic obesity or other body composition phenotypes that increase risk of poor oncological outcomes often go undetected.

The negative relationship between TAT/BMI and SMD was similar to previous findings reported in a large group of metastatic lung and gastrointestinal cancer patients, and patients with diabetes or obesity (Esfandiari et al., 2014; Goodpaster, Kelley, Thaete, He, & Ross, 2000). Of

note, diabetes could lead to up to 15.3 HU decrease of SMD (Goodpaster, Kelley, et al., 2000; Goodpaster, Thaete, & Kelley, 2000b; Kelley, McKolanis, Hegazi, Kuller, & Kalhan, 2003; Lee et al., 2005). The precise mechanism leading to SMD decline in cancer has not been determined. Nevertheless, it is reasonable to speculate that the ectopic fat infiltrates into surrounding organs, in this case skeletal muscle, resulting in the radiologic manifestation of low SMD (Miljkovic & Zmuda, 2010). Additionally, high circulating free fatty acids levels or disuse of muscle have also been suggested to impair mitochondria oxidation and lipid metabolism within muscle, both leading to fat accumulation into muscle (Miljkovic & Zmuda, 2010; Stein & Wade, 2005). Future studies are warranted to investigate the precise relationship between these metabolic disturbances and SMD decline in cancer patients.

We also observed race/ethnicity differences in body composition. African Americans presented the highest mean SMI (age and BMI adjusted) among all race/ethnicities for both sexes, which is consistent with a previous large-scale multi-ethnic study where body composition was also measured by CT images (Shah et al., 2016). In a large cohort of healthy elderly individuals, African American men and women both presented higher lean mass (measured by dual X-ray absorptiometry) than Caucasian (Taaffe et al., 2001). Similar to our findings, African Americans were less likely to have sarcopenia than other race/ethnicities in a cohort of advanced cancer patients who were referred to a phase I oncology service (Parsons, Baracos, Dhillon, Hong, & Kurzrock, 2012).

Race difference in SMD is less understood. We found African Americans and Asians had higher mean SMD and were less likely to have low SMD compared with Caucasians. Nevertheless, earlier studies in non-cancer individuals suggested greater amounts of intramuscular fat among individuals with African heritage compared with Caucasians (Gallagher

et al., 2005; Munoz & Gower, 2003; Ryan, Nicklas, & Berman, 2002). More research is needed to elucidate differences in muscle fat infiltration across race/ethnicities and the determining factors/underlying mechanism of this variability (Miljkovic-Gacic, Wang, et al., 2008).

Regarding lifestyle risk factors, those who smoke or had smoking history also had higher level of TAT ($p<0.001$, data not shown); it is possible that smoking impacted the risk of SMD through high TAT. Other studies have suggested that smoking induces insulin resistance and oxidative stress in skeletal muscle (Barreiro et al., 2012; Chiolero, Faeh, Paccaud, & Cornuz, 2008). These alterations could lead to impaired lipid metabolism and therefore the accumulation of intramuscular adipose tissue. Likewise, the Charlson comorbidity score was associated with low SMD, but not sarcopenia. This is consistent with our previous analysis in this cohort reporting that six (out of eleven) pre-existing comorbidities (i.e. myocardial infarction, congestive heart failure, peripheral vascular disease, diabetes with or without complications, and renal disease) were associated with a higher likelihood of low SMD at diagnosis, while most of them were not associated with sarcopenia (Xiao et al. under review).

Limitations of this study include the cross-sectional design, precluding causal inferences. It is unknown whether the predictors identified in this study lead to muscle abnormalities or vice versa. Although all CT scans were obtained within the same healthcare system (KPNC), the collection time frame was relatively wide, likely impacting protocol-related variation. Furthermore, socioeconomic status, dietary intake, and physical activity were not captured and could possibly influence body composition (Hojan, Milecki, Molinska-Glura, Roszak, & Leszczynski, 2013; Klement & Sweeney, 2016). Further investigations are needed to evaluate longitudinal changes in muscle mass and SMD during cancer trajectory. In addition, whether the rate and magnitude of muscle mass and SMD decline in CRC are the same as those occurring in

the normal aging process needs to be investigated. Although anthropometric and clinical risk factors (i.e. age, race/ethnicity, stage, cancer site) associated with muscle abnormalities cannot be changed, other risk factors (i.e. smoking, TAT, and comorbidities) are modifiable. These factors should be explored in pre-treatment rehabilitation programs (Glance, Osler, & Neuman, 2014).

3.6 Conclusions

This is the largest study to provide data on associations between demographics, clinical variables and body composition at the time of cancer diagnosis, and to demonstrate the determinants of sarcopenia and/or low SMD among non-metastatic CRC patients. Different determinants of these two abnormalities suggest diverse pathophysiological mechanisms between muscle depletion and fat infiltration, which may explain why sarcopenia and low SMD uniquely impact short and long-term prognosis (Sjoblom et al., 2016). Clinically-acquired CT images produce accurate, reliable estimates of muscle and adipose tissue without exposing the patient to additional ionizing radiation. Since CT images are routinely collected for diagnostic and surveillance purposes, CT-assessed body composition can easily be implemented in oncology practice.

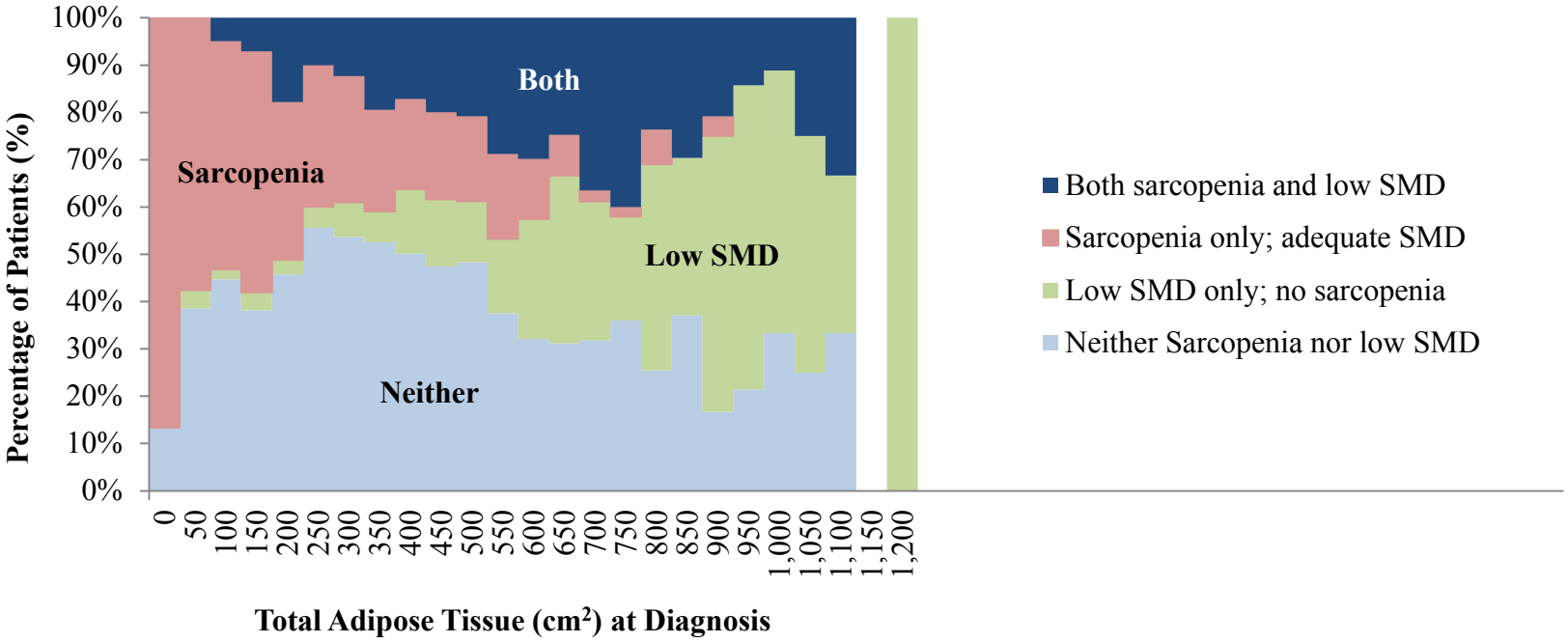


Figure 3.1 Percentage of Patients with Sarcopenia and/or Low Skeletal Muscle Radiodensity across the Spectrum of Total Adipose Tissue

SMD=skeletal muscle radiodensity

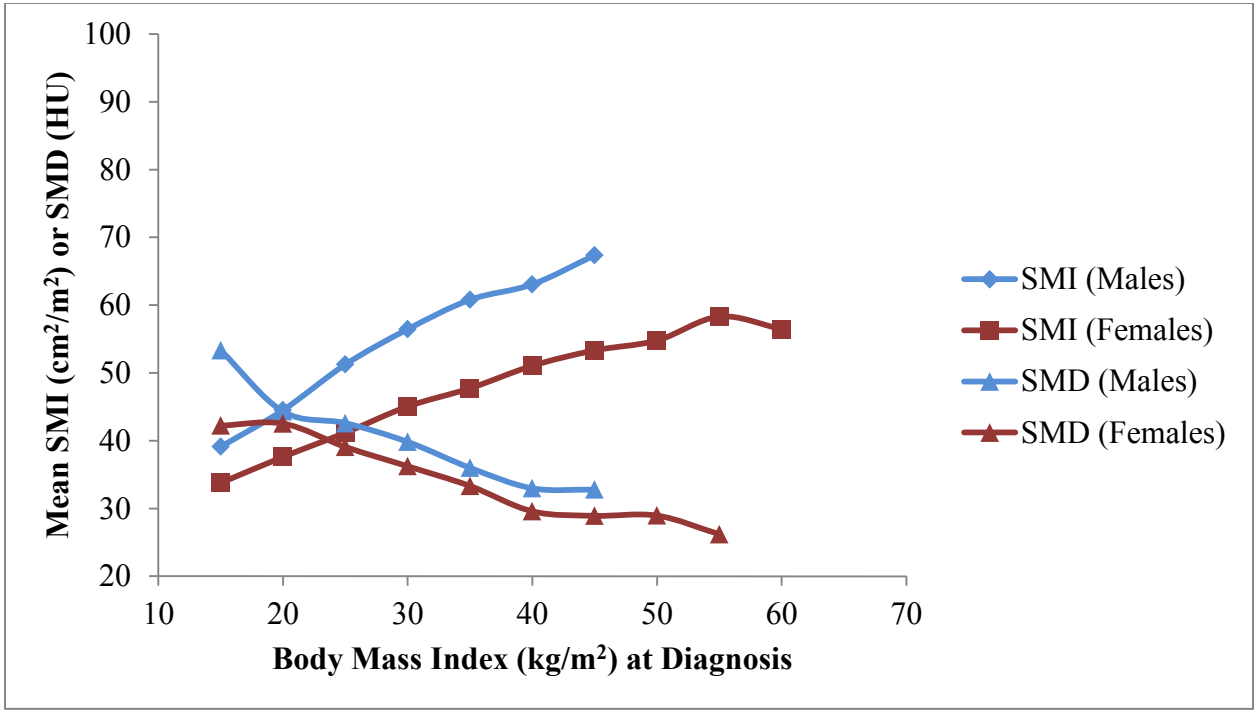


Figure 3.2 Mean Skeletal Muscle Index and Radiodensity by Body Mass Index and Sex at Diagnosis among Non-metastatic Colorectal Cancer Patients

HU=Hounsfield unit, SMI=skeletal muscle index; SMD=skeletal muscle radiodensity

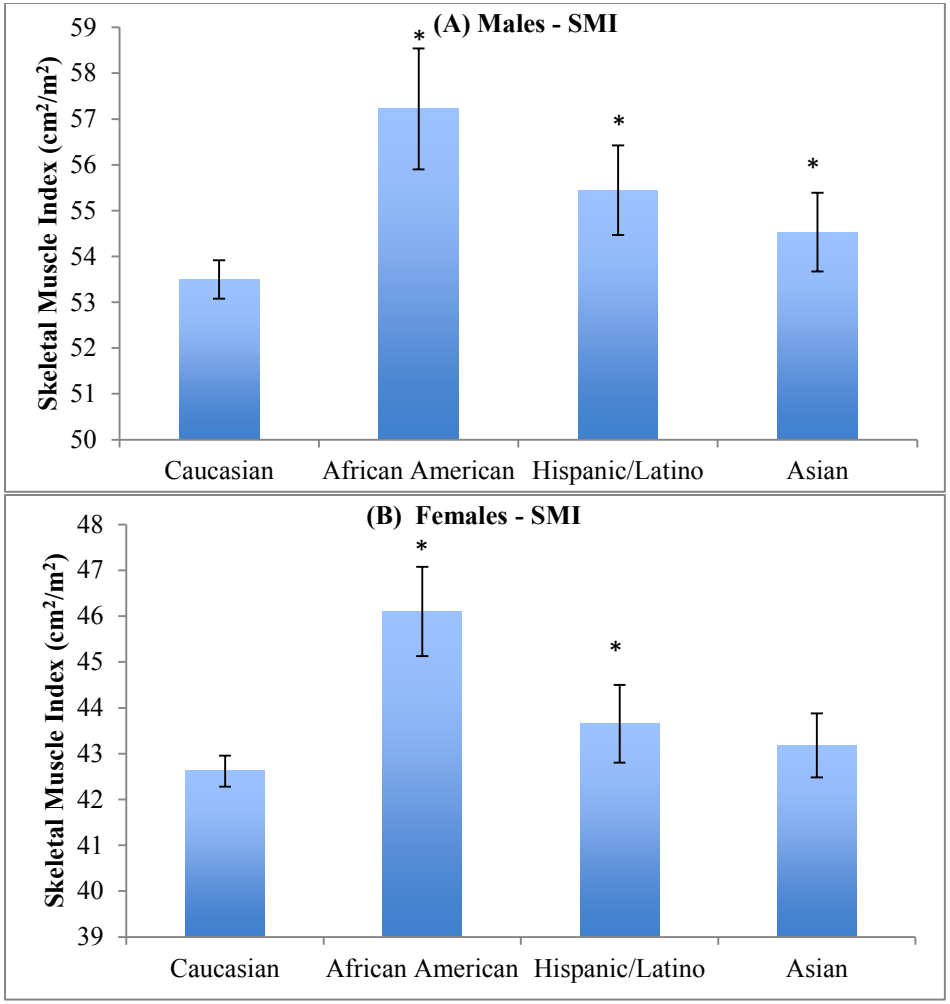


Figure 3.3 Mean Skeletal Muscle Index (SMI) by Race/Ethnicities for Non-metastatic Colorectal Cancer Patients
(A) Male and (B) Female. Mean values are adjusted by age and body mass index. *P value of mean difference <0.05 using Caucasians as the reference group

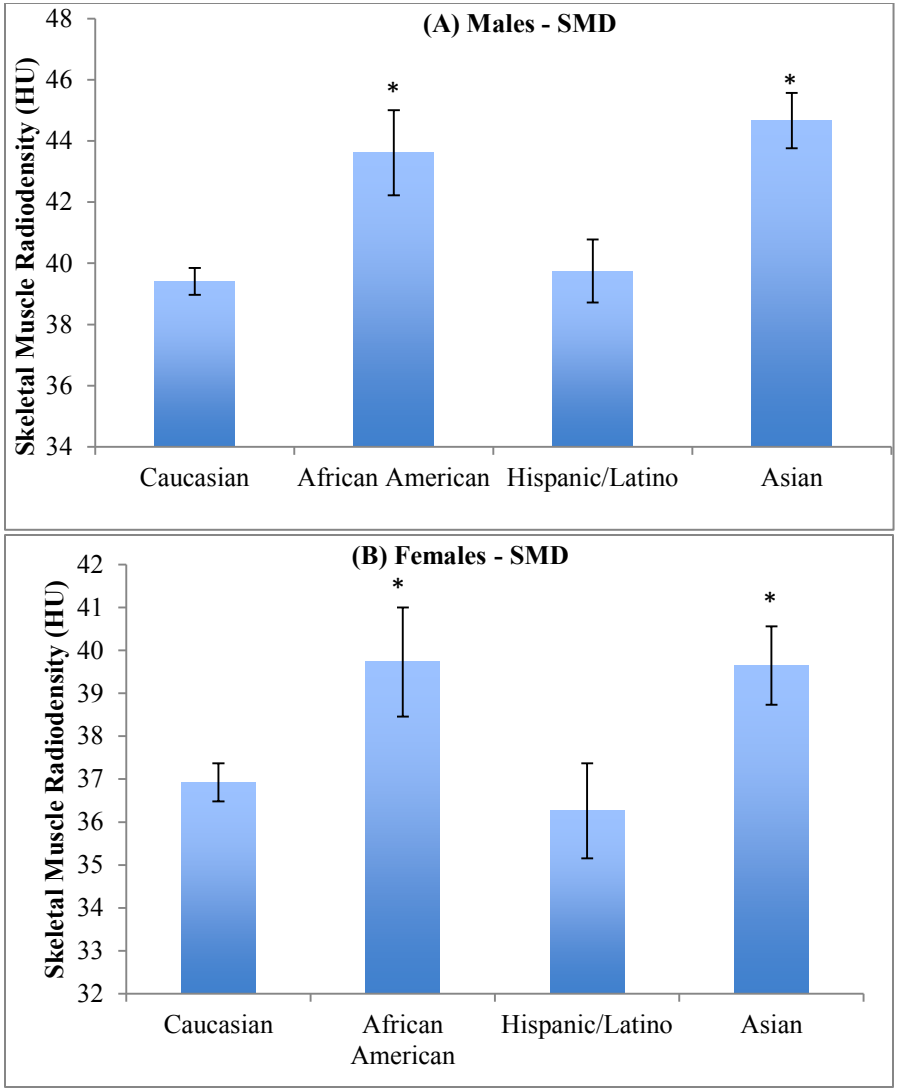
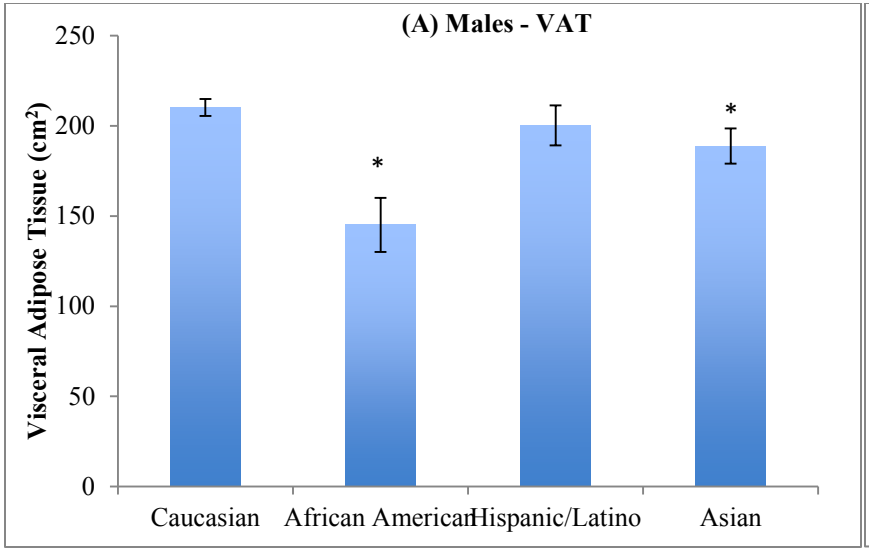
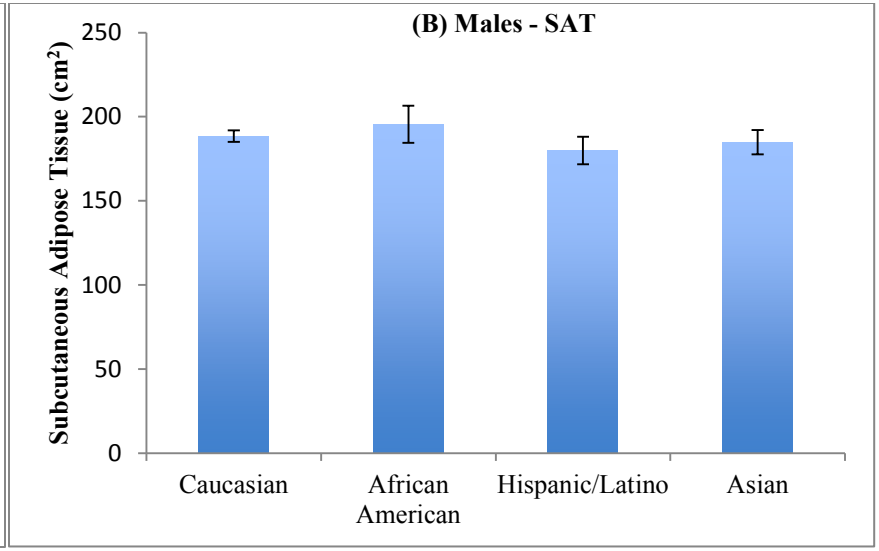
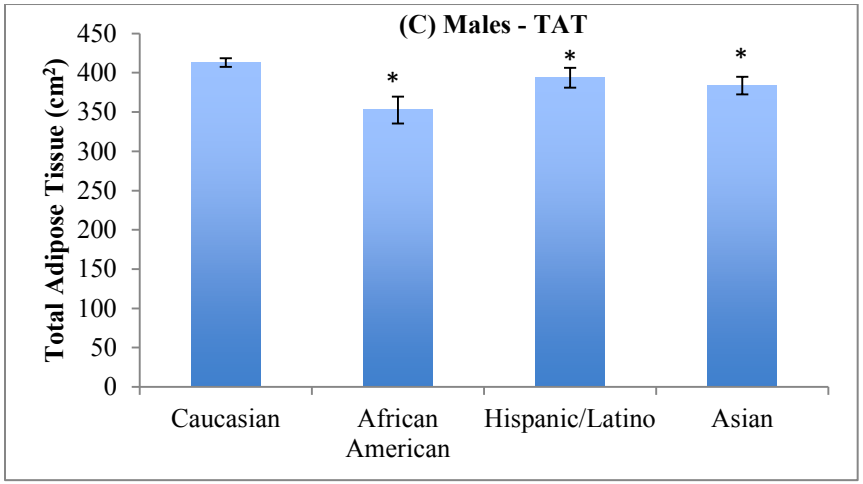


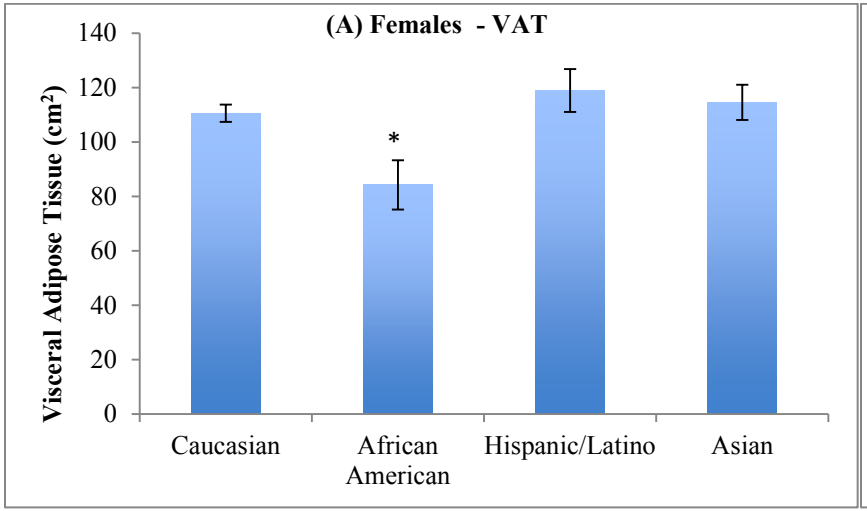
Figure 3.4 Mean Skeletal Muscle Radiodensity (SMD) by Race/ethnicities for Non-metastatic Colorectal Cancer Patients
(A) Male and (B) Female. Mean values are adjusted by age and body mass index. *P value of mean difference <0.05 using Caucasians as the reference group. HU=Hounsfield unit

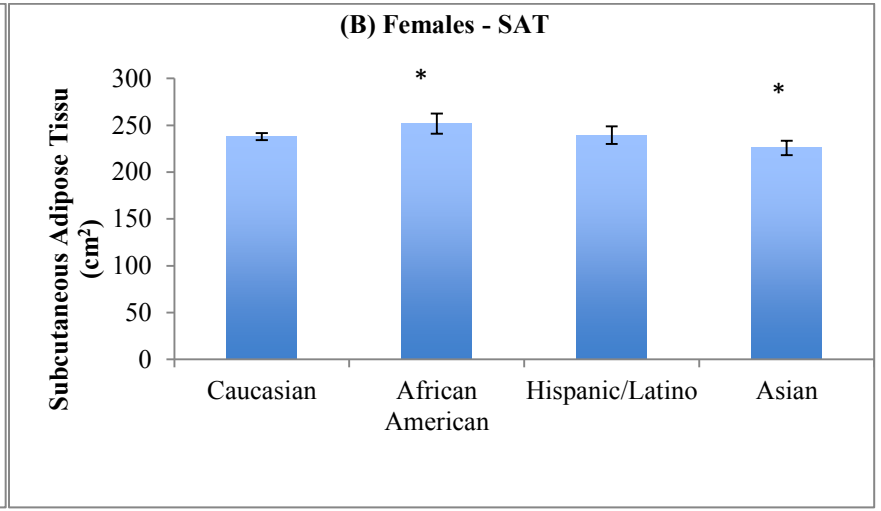


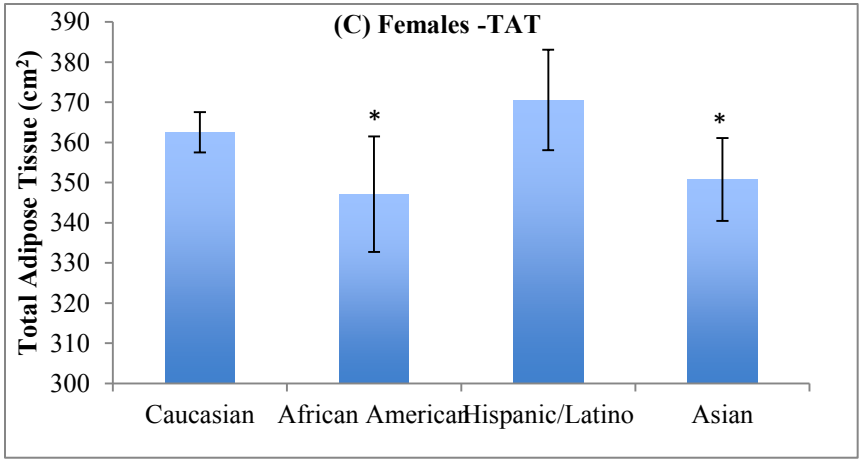




Supplementary Figure 3.1 Mean Adipose Tissues by Race/ethnicities for Male Non-metastatic Colorectal Cancer Patients
(A) VAT, (B) SAT, (C) TAT. Mean values are adjusted by age and body mass index. *P value of mean difference <0.05 using Caucasians as the reference group
VAT=visceral adipose tissue, SAT=subcutaneous adipose tissue, TAT=total adipose tissue







Supplementary Figure 3.2 Mean Adipose Tissues by Race/ethnicities for Female Non-metastatic Colorectal Cancer Patients
(A) VAT, (B) SAT and (C) TAT. Mean values are adjusted by age and body mass index. *P value of mean difference <0.05 using Caucasians as the reference group. VAT=visceral adipose tissue, SAT=subcutaneous adipose tissue, TAT=total adipose tissue

Table 3.1 Characteristics of Patients with Non-metastatic Colorectal Cancer

	Overall (n=3,262)	Males (n=1,634)	Females (n=1,628)	P-values
	Mean±SD or N(%)			
Demographics				
Age, years	62.6±11.4	62.0±11.3	63.2±11.5	0.002
BMI, kg/m^2	28.1±6.0	28.3±5.2	27.9±6.7	0.088
BMI Categories				
Underweight	61(1.9)	14(0.9)	47(2.9)	<0.001
Normal Weight	1,007(30.9)	416(25.5)	591(36.3)	
Overweight	1,164(35.7)	687(42.0)	477(29.3)	
Class I Obesity	645(19.8)	360(22.0)	285(17.5)	
Class II/III Obesity	385(11.8)	157(9.6)	228(14.0)	
Race/Ethnicity				
White/Caucasian	2,118(65.0)	1,063(65.1)	1,055(64.9)	0.442
African Americans	234(7.2)	105(6.4)	129(7.9)	
Hispanic/Latino	365(11.2)	193(11.8)	172(10.6)	
Asian/Pacific Islander	520(16.0)	261(16.0)	259(15.9)	
Other	21(0.6)	10(0.6)	11(0.7)	
Clinical variables				
Site of Cancer				
Proximal	1,436(44.0)	644(39.4)	792(48.7)	<0.001
Distal	879(27.0)	438(26.8)	441(27.1)	
Rectal	947(29.0)	552(33.8)	395(24.3)	
Cancer Stage				
I	979(30.0)	501(30.7)	478(29.4)	0.179
II	1,030(31.6)	531(32.5)	499(30.7)	
III	1,253(38.4)	602(36.8)	651(40.0)	
Smoking History				
Never	1,516(46.5)	634(38.9)	882(54.2)	<0.001
Former	1,347(41.3)	771(47.3)	576(35.4)	
Current	396(12.2)	226(13.9)	170(10.4)	
Alcohol Use				

Never	797(24.4)	276(16.9)	521(32.0)	< 0.001
Former	38(1.2)	16(1.0)	22(1.4)	
Current	928(28.5)	509(31.2)	419(25.8)	
Missing	1,499(46.0)	833(51.0)	666(40.9)	
Charlson Comorbidity Score				
0	1,770(54.3)	867(53.1)	903(55.5)	0.479
1-2	946(29.0)	482(29.5)	464(28.5)	
≥3	321(9.8)	171(10.5)	150(9.2)	
Missing	225(6.9)	114(7.0)	111(6.8)	
Body Composition				
SMI, cm^2/m^2	48.6±10.1	54.2±9.2	43.1±7.5	<0.001
SMD, HU	39.0±9.9	40.6±9.6	37.5±10.0	<0.001
VAT, cm^2	155.7±109.9	201.2±116.2	109.9±80.6	<0.001
SAT, cm^2	212.5±120.3	187.4±105.3	237.8±129.0	<0.001
TAT, cm^2	381.4±196.0	401.9±195.6	360.8±194.3	<0.001
Sarcopenia	1,383(42.4)	740(45.3)	643(39.5)	0.001
Low SMD	967(29.6)	464(28.4)	503(30.9)	0.118

BMI=body mass index, SMI=skeletal muscle index, SMD=skeletal muscle radiodensity, VAT=visceral adipose tissue, SAT=subcutaneous adipose tissue, TAT=total adipose tissue, HU=Hounsfield unit

Table 3.2 Variation of Body Composition by Age and Sex in Patients with Non-metastatic Colorectal Cancer

Age (years)	SMM (cm^2)	SMI (cm^2/m^2)	SMD (HU)	VAT(cm^2)	SAT(cm^2)	TAT(cm^2)
	Mean±SD					
Males						
<50 (n=273)	185.7±30.6	59.2±8.9	48.6±8.0	153.9±100.5	207.2±130.3	369.3±212.3
50-60 (n=422)	176.1±28.4	56.6±8.6	43.0±8.1	188.2±104.8	199.4±117.3	399.0±198.8
60-70 (n=498)	167.8±28.6	53.5±8.7	39.0±8.5	224.1±123.0	188.0±96.2	426.4±195.3
70-80 (n=441)	151.8±26.2	49.4±8.3	35.0±9.0	217.2±117.8	163.0±77.6	397.2±178.3
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	0.001
Females						
<50 (n=250)	121.1±20.7	45.6±7.5	46.2±8.6	72.9±63.2	244.4±136.6	324.5±187.6
50-60 (n=388)	119.4±20.1	45.4±7.9	40.7±8.6	111.1±78.1	267.2±140.2	388.9±206.3
60-70 (n=451)	111.4±19.8	42.5±6.9	36.2±8.8	121.9±83.9	244.7±127.0	380.9±198.0
70-80 (n=539)	105.0±17.5	40.8±6.7	32.3±8.9	116.2±82.0	207.7±111.5	340.6±180.4
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

SMM=skeletal muscle mass, SMI=skeletal muscle index, SMD=skeletal muscle radiodensity, VAT=visceral adipose tissue, SAT=subcutaneous adipose tissue, TAT=total adipose tissue, HU=Hounsfield unit

Table 3.3 Predictors of Sarcopenia and Low Skeletal Muscle Radiodensity among Non-metastatic Colorectal Cancer Patients

	Odds Ratio (95%CI) for sarcopenia		Odds Ratio (95%CI) for low SMD	
Characteristics	**Univariate**	**Multivariate[1]**	**Univariate**	**Multivariate[2]**
Age, per 5 years	1.06(1.05,1.06)	1.06(1.05,1.07)	1.09(1.08,1.10)	1.09(1.08,1.10)
Age				
≤50 years	Reference	Reference	Reference	Reference
50 to 60 years	1.72(1.33,2.22)	1.85(1.42,2.40)	2.83(1.90,4.19)	2.47(1.62,3.75)
60 to 70 years	3.21(2.51,4.10)	3.55(2.75,4.60)	6.20(4.27,9.02)	5.00(3.34,7.49)
70 to 80 years	5.29(4.14,6.76)	5.79(4.45,7.52)	15.86(10.96,22.96)	17.29(11.42,26.16)
TAT Tertiles				
Tertile 1	Reference	Reference	Reference	Reference
Tertile 2	0.56(0.47,0.67)	0.50(0.41,0.60)	2.58(2.06,3.23)	2.48(1.93,3.19)
Tertile 3	0.59(0.50,0.70)	0.56(0.46,0.67)	6.87(5.54,8.52)	8.52(6.59,11.01)
Race/Ethnicity				
Caucasian	Reference	Reference	Reference	Reference
African American	0.47(0.35,0.64)	0.50(0.36,0.68)	0.38(0.27,0.54)	0.35(0.23,0.52)
Hispanic/Latino	0.53(0.42,0.68)	0.65(0.50,0.83)	0.88(0.70,1.12)	1.13(0.85,1.50)
Asian/ Pacific Islander	1.03(0.85,1.24)	1.04(0.84,1.28)	0.24(0.18,0.31)	0.38(0.27,0.53)
Weight Change History				
Stable, <5% change	Reference	-	Reference	-
>=5% loss	1.20(0.98,1.47)		1.02(0.82,1.27)	
>= 5% gain	1.07(0.75,1.53)		1.33(0.92,1.92)	
Stage				
Stage I	Reference	Reference	Reference	Reference
Stage II	1.42(1.19,1.69)	1.39(1.15,1.68)	1.16(0.96,1.41)	1.19(0.95,1.50)
Stage III	1.14(0.96,1.35)	1.26(1.05,1.51)	1.02(0.85,1.23)	1.26(1.01,1.58)
Site				
Proximal	Reference	Reference	Reference	Reference
Distal	0.88(0.74,1.04)	1.21(1.01,1.46)	0.60(0.50,0.72)	0.88(0.71,1.10)
Rectal	0.71(0.60,0.84)	0.95(0.79,1.15)	0.44(0.36,0.53)	0.66(0.53,0.84)
Charlson Comorbidity Score				

0	Reference	-	Reference	Reference
1 or 2	1.08(0.92,1.27)		2.18(1.83,2.59)	1.43(1.17,1.76)
≥3	1.12(0.88,1.43)		4.83(3.77,6.20)	2.49(1.84,3.35)
Smoking history				
Never smoker	Reference	Reference	Reference	Reference
Former smoker	1.25(1.08,1.45)	1.06(0.90,1.25)	1.98(1.68,2.33)	1.45(1.19,1.77)
Current smoker	1.18(0.94,1.47)	1.18(0.93,1.51)	1.63(1.28,2.07)	2.03(1.52,2.72)
Alcohol				
Never	Reference	-	Reference	-
Former	1.15(0.60,2.20)		1.43(0.73,2.78)	
Current	1.03(0.85,1.25)		0.91(0.74,1.12)	

[1]Sarcopenia model was adjusted for age at diagnosis (either categorical or continuous), race/ethnicity, cancer stage, cancer site, smoking history, TAT at diagnosis.[2]SMD model adjusted for age (either categorical or continuous), race/ethnicity, cancer stage, cancer site, smoking history, comorbidities, TAT at diagnosis. SMD=skeletal muscle radiodensity, TAT=total adipose tissue

Supplementary Table 3.1 Variation of Body Composition in Male Patients with Non-metastatic Colorectal Cancer Patients by age, and Body Mass Index

Age, years	BMI groups	SMM, cm^2	SMI, cm^2/m^2	SMD, HU	VAT,cm^2	SAT,cm^2	TAT,cm^2
		Mean±SD					
<50 (n=273)	Underweight(n=0)	-	-	-	-	-	-
	Normal weight(n=67)	160.1±20.4	52.0±5.7	54.3±5.9	53.7±42.0	89.3±40.0	146.5±70.9
	Overweight(n=110)	183.0±23.0	58.6±6.9	50.1±6.9	139.6±67.0	171.0±52.4	317.1±96.1
	Class I obesity(n=57)	199.8±28.7	63.2±8.4	44.6±5.3	216.4±76.1	258.2±73.5	485.3±94.0
	Class II/III obesity(n=39)	216.5±28.1	67.1±9.3	40.3±8.2	275.2±92.5	437.0±128.4	730.0±159.1
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
50-60 (n=422)	Underweight(n=1)	108.1	38.5	49.3	5.9	51.5	61.5
	Normal weight(n=90)	151.2±21.2	58.6±5.8	46.9±7.2	91.7±63.6	104.2±43.1	202.9±93.4
	Overweight(n=180)	173.7±20.5	56.6±6.9	44.8±7.1	172.6±74.7	162.4±53.2	344.5±99.3
	Class I obesity(n=102)	189.6±25.7	60.3±7.5	40.3±7.2	241.2±91.1	245.0±75.6	500.2±110.7
	Class II/III obesity(n=49)	204.0±28.4	64.1±8.5	35.1±7.8	315.7±94.7	418.1±137.1	755.5±175.6
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
60-70 (n=498)	Underweight(n=5)	116.1±15.3	38.4±5.1	46.4±11.0	9.2±9.9	11.0±11.4	23.2±20.9
	Normal weight(n=114)	144.0±19.8	46.4±5.7	41.7±7.3	107.6±67.7	116.2±46.4	233.9±96.7
	Overweight(n=215)	164.9±19.7	53.0±6.2	40.9±7.7	210.9±77.8	163.6±49.9	385.9±98.1
	Class I obesity(n=114)	184.0±23.2	58.2±7.6	36.2±7.4	306.2±105.7	232.5±63.7	555.7±109.0
	Class II/III obesity(n=50)	202.7±31.0	63.0±9.7	30.5±8.6	381.1±112.8	373.3±106.4	784.3±128.0
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
70-80 (n=441)	Underweight(n=8)	103.8±28.1	36.3±7.6	41.1±14.8	60.3±57.8	40.5±27.9	106.9±86.4
	Normal weight(n=145)	136.5±18.3	45.1±6.5	38.2±8.2	123.6±72.9	110.2±38.9	245.7±97.4
	Overweight(n=182)	155.6±21.9	50.2±6.7	34.7±8.8	233.5±85.3	163.2±44.9	414.2±101.3
	Class I obesity(n=87)	169.3±25.8	54.7±8.5	31.4±7.9	319.7±106.3	228.0±73.6	570.8±140.0
	Class II/III obesity(n=19)	171.8±29.9	56.1±10.2	27.2±7.8	372.1±88.8	317.0±119.1	717.6±150.7
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

SMM=skeletal muscle mass, SMI=skeletal muscle index, SMD=skeletal muscle radiodensity, VAT=visceral adipose tissue, SAT=subcutaneous adipose tissue, TAT=total adipose tissue

Supplementary Table 3.2 Variation of Body Composition in Female Patients with Non-metastatic Colorectal Cancer Patients by age, Body Mass Index

Age,years	BMI groups	SMM, cm^2	SMI, cm^2/m^2	SMD, HU	VAT,cm^2	SAT,cm^2	TAT,cm^2
		Mean±SD					
<50 (n=250)	Underweight(n=10)	89.8±12.4	34.7±5.7	53.0±11.2	15.3±19.7	78.7±42.6	98.1±58.0
	Normal weight(n=99)	111.2±14.1	41.9±4.4	50.5±6.3	32.3±27.0	151.6±59.6	187.6±78.9
	Overweight(n=65)	119.8±13.6	45.8±5.5	45.2±7.7	69.3±38.1	237.3±61.6	314.2±81.4
	Class I obesity(n=42)	135.2±19.8	50.0±7.0	43.0±7.2	110.8±45.4	337.4±78.8	456.9±87.2
	Class II/III obesity(n=34)	144.3±19.1	53.9±8.2	37.1±7.4	171.2±67.3	461.9±143.5	645.8±152.7
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
50-60 (n=388)	Underweight(n=7)	82.8±11.8	32.8±4.1	49.5±13.4	14.8±23.6	63.2±32.6	82.4±50.1
	Normal weight(n=111)	106.8±13.5	40.5±5.1	45.3±6.9	44.3±34.2	140.7±54.0	191.2±78.8
	Overweight(n=114)	116.4±15.9	44.0±5.8	41.7±7.1	101.0±51.4	236.6±54.2	347.0±80.2
	Class I obesity(n=82)	126.9±13.4	48.3±5.6	39.5±7.0	140.9±58.5	318.2±68.2	470.9±96.2
	Class II/III obesity(n=74)	138.3±21.1	53.0±8.9	32.9±8.2	202.7±72.8	467.0±130.1	688.0±162.9
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
60-70 (n=451)	Underweight(n=13)	93.3±11.4	35.3±3.9	43.0±8.5	8.2±5.8	58.8±45.7	72.8±53.3
	Normal weight(n=157)	99.6±15.1	38.4±5.3	41.1±7.0	61.9±44.7	146.7±52.2	217.8±83.7
	Overweight(n=132)	111.0±13.6	42.2±4.7	36.0±7.9	120.6±61.4	230.7±62.4	364.9±97.2
	Class I obesity(n=82)	120.7±18.0	45.7±5.7	33.4±7.3	175.3±60.2	324.1±69.4	515.5±88.2
	Class II/III obesity(n=67)	131.9±20.3	50.1±7.2	27.6±7.5	222.0±80.5	441.1±111.4	689.8±142.0
	p-value		<0.001	<0.001	<0.001	<0.001	<0.001
70-80 (n=539)	Underweight(n=17)	93.8±11.6	35.9±3.8	36.4±8.4	19.6±18.7	57.9±32.6	88.2±52.5
	Normal weight(n=224)	97.5±12.8	37.6±4.9	35.7±8.0	62.8±44.2	138.7±54.1	213.4±86.1
	Overweight(n=166)	106.5±14.4	41.8±5.8	32.0±8.1	126.3±58.8	207.1±61.6	349.8±87.9
	Class I obesity(n=79)	112.3±18.5	43.8±7.0	27.6±8.1	186.1±71.1	295.6±67.3	505.1±91.4
	Class II/III obesity(n=53)	124.8±22.0	48.1±7.7	24.3±8.2	237.5±66.9	418.0±110.7	684.7±119.3
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

SMM=skeletal muscle mass, SMI=skeletal muscle index, SMD=skeletal muscle radiodensity, VAT=visceral adipose tissue, SAT=subcutaneous adipose tissue, TAT=total adipose tissue

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Chapter 4 Associations of Pre-existing Comorbidities with Skeletal Muscle Mass and Radiodensity in Patients with Non-metastatic Colorectal Cancer

4.1 Preface

The following chapter is derived from patients diagnosed with non-metastatic colorectal cancer (CRC) at Kaiser Permanente Northern California and had Kaiser healthcare membership for one year prior to cancer diagnosis (n=3,051). This is the first study to examine the association between comorbidities and muscle abnormalities in patients with CRC. In addition to body composition analysis, Ms. Jingjie Xiao contributed to concept formation, analysis and interpretation of findings, and manuscript writing. Ms. Erin Weltzien contributed to data analysis. Drs. Bette Caan, Elizabeth Cespedes Feliciano, Candyce Kroenke, Jeffery Meyerhardt, Vickie Baracos, Marilyn Kwan and Carla Prado contributed to concept formation, data interpretation, and manuscript revision. Ms. Adrienne Castillo contributed to study organizational procedures and editing. Dr. Carla Prado supervised and contributed to all aspects of this study. All authors of this research paper have approved the final version submitted. This manuscript has been submitted to the Journal of Cachexia, Sarcopenia and Muscle.

4.2 Introduction

Colorectal cancer (CRC) is a leading cause of cancer death in the United States (Siegel, Miller, & Jemal, 2018). As such, understanding the predictors of survival in CRC patients can aid the development of targeted interventions to decrease mortality, beyond cancer-specific care.

Comorbidities are highly prevalent and adversely influence survival outcomes in patients with CRC and other cancer types (De Marco, Janssen-Heijnen, van der Heijden, & Coebergh, 2000; Jorgensen, Hallas, Friis, & Herrstedt, 2012). Muscle abnormalities, including low skeletal mass index (SMI, quantified as muscle cross-sectional area adjusted by height squared, cm^2/m^2) and low skeletal muscle radiodensity (SMD, quantified in Hounsfield units, HU) can be measured using computerized tomography (CT) images. Both these muscle abnormalities have been associated with the presence of specific comorbid conditions as well as cancer prognosis, and thus are potential mechanisms explaining why certain comorbid conditions are associated with worse cancer prognosis (Lieffers et al., 2012; Voutsadakis, 2016; Wu, Hsu, Chang, Yu, & Lee, 2015). Low SMI, also termed sarcopenia, is highly prevalent and has been shown as a strong prognostic factor in CRC patients and in many other types of cancer (Kazemi-Bajestani, Mazurak, et al., 2016). Additionally, a recent meta-analysis of 7843 patients with solid tumors found a 44% higher risk of death for patients with low SMI versus those with normal amount of muscle mass (Shachar, Williams, Muss, & Nishijima, 2016). Furthermore, low SMI predicts clinical endpoints, such as a higher risk of surgical complications after resection, longer hospitalization and/or higher risk of chemotherapy toxicity in various cancers (Kazemi-Bajestani, Mazurak, et al., 2016; Prado, 2013; Prado, Cushen, Orsso, & Ryan, 2016).

Skeletal muscle radiodensity reflects fat infiltration into muscle (Dahya et al., 2016). To date, the largest study investigating SMD included 1,473 patients with lung or gastrointestinal tract cancer, showing this abnormality as an independent predictor of shorter survival (Martin et

al., 2013). Additional studies have reported that low SMD was associated with complications and short-term mortality after surgery in CRC and in other types of cancer (Boer et al., 2016; Hamaguchi et al., 2016).

As CT-measured muscle abnormalities and comorbidities both strongly predict cancer prognosis, there is good reason to believe they are inter-related. Colorectal cancer patients with any pre-existing comorbidity might be at higher risk for muscle abnormalities, the dual burden of which might negatively impact prognosis. Nevertheless, little in known on whether patients with comorbidities are at higher risk of having muscle abnormalities compared to those without comorbidities, and on how different comorbidities contribute to the presence of muscle abnormalities in CRC. Therefore, our goal was to investigate the prevalence of pre-existing comorbidities by muscle abnormalities, and evaluate which pre-existing comorbidities predicted muscle abnormalities among newly diagnosed CRC patients.

4.3 Methods

4.3.1 Study Cohort

The present cross-sectional study identified patients diagnosed with stage I-III invasive CRC at Kaiser Permanente Northern California (KPNC, n=3,262) from 2006-2011 as described elsewhere (Caan et al., 2017). For this analysis, we restricted the cohort to patients who were members of KPNC for at least one year prior to CRC diagnosis (n=3,051). This study was approved by the KPNC and University of Alberta Institutional Review Boards.

4.3.2 Comorbidities

Pre-existing comorbidities were recorded using an adapted version of Charlson comorbidities derived from International Classification of Disease (ICD)-9 diagnostic codes (Quan et al., 2005). Relevant ICD-9 codes for all comorbidities were obtained from all inpatient

and outpatient encounters in the year prior to CRC diagnosis. To be confirmed as having a comorbid condition, we required two diagnostic codes of the same condition for each patient at least 30 days apart in the one-year period prior to CRC diagnosis. We examined each component of the Charlson comorbidities separately as a binary variable (presence or absence), including myocardial infarction (MI), congestive heart failure (CHF), peripheral vascular disease (PVD), cerebrovascular disease (CVD), dementia, chronic obstructive pulmonary disease (COPD), rheumatic disease (RD), peptic ulcer disease, mild liver disease, diabetes without chronic complication, diabetes with chronic complication, hemiplegia or paraplegia, renal disease, moderate or severe liver disease, any malignancy, metastatic solid tumor and acquired immune deficiency syndrome and human immunodeficiency virus infection and (AIDS/HIV). Cancer-related categories (i.e. any malignancy and metastatic solid tumor) were excluded, and comorbidities with less than three cases (i.e. dementia, n=1; hemiplegia/paraplegia, n=3; moderate or severe liver disease, n=2; and AIDS/HIV, n=3) were omitted for statistical reasons, leaving eleven comorbidities included in the final analysis.

4.3.3 Body Composition Measurement

Abdominal CT images within four months of CRC diagnosis and before any chemotherapy or radiation treatment were obtained from the patients' electronic medical record (EMR). A single image at the third lumbar vertebra (L3) was selected for muscle mass and adipose tissue quantification, as skeletal muscle and adipose tissue cross-sectional areas at this landmark strongly correlate with muscle volume at the whole body level (Mourtzakis et al., 2008; Shen et al., 2004). According to the standard HU range for muscle (-29 to 150) , visceral adipose tissue (VAT, -150 to -50), inter-muscular adipose tissue (IMAT, -190 to -30) and subcutaneous adipose tissue (SAT, -190 to -30) (Heymsfield et al., 1990; Miller et al., 1998;

Mourtzakis et al., 2008), cross-sectional areas of muscle and adipose tissue at L3 were analyzed by a single, trained researcher (JX) using SliceOmatic Software version 5.0 (TomoVision, Montreal, Quebec, Canada). Total adiposity was calculated as the sum of VAT, IMAT and SAT. Intra-observer coefficient variations of muscle mass, radiodensity and total adiposity measurements at least one month apart were 0.7%, 1.2% and 0.3%, respectively. Muscle mass was calculated as SMI from total muscle cross-sectional area divided by height square (cm^2/m^2) (Mourtzakis et al., 2008; Prado et al., 2008). SMD was generated by the software as the mean radiation attenuation value of the whole muscle group at L3. The optimal stratification method was used to determine the cohort specific threshold values of SMI and SMD as described elsewhere for this cohort (Caan et al., 2017). This method identifies cut points that best separate patients' risk with respect to time to death based on the maximum absolute value of the log-rank statistic test (Berthold Lausen, 1992). For normal/overweight patients [body mass index (BMI)<30 kg/m^2], the threshold values of SMI were 52.3 cm^2/m^2 for men and 38.6 cm^2/m^2 for women, while for obese patients (BMI>30 kg/m^2) these were 54.3 cm^2/m^2 for men and <46.6 cm^2/m^2 for women (Caan et al., 2017). Similarly, threshold values of SMD were 35.5 HU for men and 32.5 for women (Kroenke et al. 2018). Patients presenting below these threshold values were classified as having either low SMI or low SMD. Four muscle phenotypes were further defined according to the presence or absence of low SMI and low SMD: normal SMI, normal SMD; normal SMI, low SMD; low SMI, normal SMD; low SMI, low SMD.

4.3.4 Covariate Assessment

Data sources of patients' EMR and the Cancer Registry were reviewed for information on disease stage, tumor characteristics and demographics, including age, height, weight, weight change history prior to CRC diagnosis, sex, race/ethnicity and smoking history. Height and

weight measured at the clinical visit closest to the diagnostic CT scan were used to calculate BMI at CRC diagnosis. Weight change history was computed by subtracting the diagnostic weight from the weight taken 18 months prior to diagnosis. Cancer stage was defined according to the American Joint Committee on Cancer (Compton, Fenoglio-Preiser, Pettigrew, & Fielding, 2000).

4.3.5 Statistical Analysis

Differences in patient characteristics by presence or absence of muscle abnormalities were analyzed using independent t-tests or Pearson's Chi-square tests, where appropriate. Prevalence of comorbidities was compared by muscle abnormalities (categorical variables) using Pearson's Chi-square tests. Logistic regression models were used to evaluate associations between comorbid condition(s) and dichotomous muscle abnormality outcomes. Multiple comparison tests were performed using Bonferroni correction method for each logistic regression model to account for the likelihood that findings could be due to chance. Multinominal logistic regression models were conducted to further explore the associations between comorbidities and four muscle phenotypes (i.e. phenotype analysis). In this analysis, the muscle phenotype was computed as the outcome variable, with normal SMI/normal SMD group as the reference. Covariates included age, sex, BMI at CRC diagnosis, weight change history, ethnicity/race, and smoking history. In a sensitivity analysis, we compared models with and without adjustment for weight change history, as well as with adjustment of total adiposity instead of BMI. All statistical analyses were performed using STATA (version 14.2; StataCorp LP). Statistical significance was established with 2-sided tests with α of 0.05.

4.4 Results

4.4.1 Low Skeletal Muscle Index

Demographic and clinical parameters are shown in Table 1. Low SMI was highly prevalent at 43.1%. Among males the prevalence of low SMI was 46.0%, and among females the prevalence was 40.2% (p=0.001). SMI was higher in males compared to females (Figure 1A). Total adiposity was lower for patients with low SMI compared to those with normal SMI in both sex. Patients with low SMI were approximately six years older, and their mean muscle attenuation was five HU lower compared to their counterparts (36.1 HU versus 40.9 HU, p<0.001). Differences by race/ethnicity and BMI distribution were also observed. Caucasians and Asian/Pacific Islanders were more likely to have low SMI than were African Americans or Hispanics. Patients with low SMI had lower BMI, which was consistent with the higher percentage of underweight/normal weight patients in the low SMI group. The correlation coefficient between SMI and BMI was 0.50. Patients with stage II or colon cancer were more likely to present with low SMI than those with other stages or those with rectal cancer. Patients who were former or current smokers were more likely to have low SMI compared to those who never smoked.

4.4.2 Low Skeletal Muscle Radiodensity

Approximately one third (30.2%) of the patients had low SMD with a prevalence of 28.8% and 31.6% in males and females respectively. Women had a slightly lower SMD than that of their male counterparts (Figure 1B). Mean SMI was lower while total adiposity was higher in the low SMD group than in the normal SMD group for both males and females. Compared to patients with normal SMD, those with low SMD were on average nine years older, had a higher BMI and consequently, a greater prevalence of obesity. Mean muscle attenuation was moderately

correlated with BMI (r=0.35). More Caucasians and Hispanics were in the low SMD group. Patients with stable weight or who had any weight fluctuation (gaining or losing ≥5% body weight) prior to CRC diagnosis were more likely to have low SMD. There were no differences in cancer stage between SMD groups. The findings for other clinical parameters by SMD, including cancer type and smoking history, were similar to those reported above by SMI groups (Table 1).

4.4.3 Comorbidities and Muscle Abnormalities

No difference in Charlson index score was observed between SMI groups (Table 1). When analyzing the prevalence of comorbidities by SMI group, those with low SMI were more likely to have PVD (4.9% versus 2.1% respectively, compared to those with normal SMI, $p<0.001$), but not other comorbidities. In contrast, patients with low SMD were more likely to have a Charlson comorbidity index score equal or greater than one compared to those with normal SMD (Table 1), and those with low SMD had a higher prevalence of 9 of 11 comorbidities (Figure 2).

Mean values of SMI and SMD were computed and compared for those with and without comorbidities. Patients with PVD had lower SMI than those without PVD. In contrast, those who had diabetes had higher SMI compared to those without diabetes ($p=0.048$ for complicated diabetes and $p<0.001$ for non-complicated diabetes). We noted similar results stratified by sex. PVD was associated with lower SMI only in males, while diabetes with or without complications were related to higher SMI only in females (data not shown). SMD was much more consistently associated with comorbidities with or without stratification by sex. Mean SMD was lower in patients with MI, CHF, PVD, CVD, COPD, RD, diabetes with/without complications, or renal disease than in patients without these conditions (data not shown).

4.4.4 Univariate and Multivariate Regression Models

In logistic regression analysis, patients who had diabetes with complication were less likely to have low SMI in multivariate analysis (OR=0.64, 95% CI 0.47-0.88). No other comorbidities or Charlson index were associated with low SMI after controlling for confounding factors (Table 2).

In similar regression models, cardiovascular conditions, diabetes and renal disease were associated with low SMD (Table 3). After adjusting for confounding factors, patients with MI or PVD were more likely to have low SMD. Patients who had pre-existing CHF were at particularly high risk of low SMD (OR=3.27, 95% CI 1.97-5.41). Similarly, diabetes with or without complications both showed an association with low SMD; patients with pre-existing diabetes were more likely to have low SMD at CRC diagnosis. Likewise, patients with renal disease were more likely to have low SMD. A higher Charlson index score was associated with greater risks of having low SMD compared to patients without any comorbid condition.

In a sensitivity analysis for these regression models, results remained similar with or without adjustment for weight change history prior to diagnosis. We also adjusted by level of total adiposity (versus BMI) with similar findings for SMD models. However, in addition to the six comorbidities that predicted low SMD, in this sensitivity analysis, patients with COPD were more likely to have low SMD (OR=1.37, 95% CI 1.03-1.82). As for low SMI, after adjustment for total adiposity, diabetes with complications lost association with low SMI.

In multiple comparison tests, a Bonferroni critical p-value of 0.0045 was calculated using 0.05 divided by 11 (the number of investigated comorbidities). According to the Bonferroni critical p-value, no comorbidities were associated with low SMI, while CHF, PVD, diabetes without complications and renal disease remained independent predictors of low SMD.

We further examined comorbidities predicting concurrent muscle abnormalities using patients with both normal SMI and normal SMD as the reference group. In multinomial logistic regression models, patients who had CHF or renal diseases were more likely to present with low SMD, regardless of concurrent low SMI, while patients with PVD were more likely to have both low SMI and low SMD. Patients who had diabetes were more likely to present with normal SMI and low SMD (Supplementary Table 1).

4.5 Discussion

We investigated the prevalence of comorbidities and their associations with low SMI, and/or low SMD in 3051 newly diagnosed CRC patients. This is the first study to evaluate associations between comorbidities and CT-assessed muscle abnormalities in a large sample of patients with CRC. Two important clinical findings emerged. First, nine out of eleven comorbidities were more prevalent in patients with low SMD, whereas only one comorbidity had higher prevalence in patients with low SMI, compared to those with normal SMD or SMI. Second, most comorbidities were associated with low SMD, with only one being associated with low SMI, independent of age, sex, BMI at diagnosis, ethnicity/race, cancer stage, cancer site, pre-diagnostic weight change and smoking history.

We found males presented higher SMI and higher SMD compared to females. This finding is consistent with previously reported data from a large cohort (n=1,473) of patients with lung or gastrointestinal cancer (Martin et al., 2013). In subgroup analysis, the effects of MI, PVD and renal diseases on low SMD were only observed in men, while the effect of diabetes with complications was only evident in women (data not shown). Rheumatic disease and COPD additionally predicted higher risk of low SMD in men (data not shown). Despite these sex differences, none of the comorbidities predicted low SMI in men, and only diabetes was

associated with low SMI in women. The latter might be attributed to better health and medical care for these patients or well-controlled blood glucose level (e.g. use of insulin or metformin) potentially decreasing the risk of muscle loss (Chevalier & Farsijani, 2014). Additionally, 76.6% female diabetic patients were overweight or obese, and the prevalence of low SMI is known to decrease with increasing BMI for most patients (Prado et al., 2016). The higher observed prevalence of low SMI and low SMD in patients with colon and stage II cancer is likely confounded by age. The prevalence of patients with ≥ 65 years was higher among those with colon cancer (54.1% versus 36.7% rectal cancer, $p<0.001$), and among those with stage II cancer (53.9% versus 47.1% other stages, $p<0.001$).

Few studies have examined the relationship between presence of comorbidities and muscle abnormalities in the context of cancer. Using a cohort of 234 patients with CRC, Lieffers et al. found a higher prevalence of cardiac arrhythmias, COPD, diabetes, and other disorders among individuals with lower SMI (Lieffers et al., 2012). Although age, BMI and SMI of their cohort were comparable to ours, we found PVD as the only condition more prevalent in patients with lower SMI. In Lieffers et al., the prevalence of low SMI was 38.9% (versus 43.1% in the present study) while the majority of patients with low SMI had stage IV CRC (37.4%). It is likely that the dual burden of tumor progression and comorbidities may increase the risk for low SMI. No studies have investigated the association between comorbidities and low SMD in CRC.

Evidence outside the oncology setting shows that low SMI is present in multiple disease states, including diabetes, COPD, arthritis, PVD, CHF, advanced renal disease, cirrhosis (Costa et al., 2015; de Oliveira Nunes Teixeira, Filippin, Viacava, de Oliveira, & Xavier, 2013; Dos Santos et al., 2017; Johansen & Lee, 2015; McDermott et al., 2004; Park et al., 2009; Tessari, 2003). Reduced SMD has been reported in elderly individuals and individuals with diverse types

of diseases, such as diabetes, obesity and cirrhosis (Goodpaster et al., 2001; Goodpaster, Kelley, et al., 2000; Montano-Loza et al., 2016).

The pathogenesis of low SMI and low SMD in chronic diseases is not completely understood. Low SMI is likely a result of a complex network involving chronic inflammation, elevated protein catabolism, and disturbed hormonal balance (K. C. Fearon, Glass, & Guttridge, 2012). These processes result in chronic imbalance in muscle protein turnover favoring protein breakdown and a shift in fiber distribution from type II to type I fiber, ultimately leading to morphological muscle depletion (V. E. Baracos, 2000; Miljkovic & Zmuda, 2010). Among these mechanisms, inflammation-mediated muscle proteolysis through ubiquitin-proteasome pathway has been commonly recognized in cancer, CHF, COPD, diabetes and chronic renal diseases (Rom & Reznick, 2016). As such, Anker et al. proposed the use of the term "muscle wasting" to represent the common physiological process related to low muscularity across a spectrum of disorders, including cancer, CHF, CKD, COPD, neuromuscular disease, and chronic infection (Anker et al., 2014). Comprehensive and detailed reviews regarding the mechanism of low SMI in cancer can be found elsewhere (K. C. Fearon et al., 2012; Porporato, 2016).

Our previous findings from this cohort and other studies have shown that both low SMI and low SMD to be independently associated with systematic inflammatory response in CRC (Malietzis, Johns, et al., 2016; McSorley, Black, Horgan, & McMillan, 2017). Inflammatory networks have also been suggested to play a pathophysiological role in the development of comorbidities, including cardiovascular diseases, renal disease and diabetes (Cheung, Paik, & Mak, 2010; C. Garcia et al., 2010; Zauli, Tisato, Raffetto, & Vaccarezza, 2017). Although inflammation might be a common pathway through which comorbidities impact both SMI and SMD, we found a clear association of low SMD with six comorbidities (i.e. MI, CHF, PVD,

diabetes with or without complications, and renal disease), but the same was not true in regards to low SMI. Of note, most of the comorbidities we identified predicting low SMD were cardiovascular and metabolic disorders, suggesting metabolic inefficiency at either local or systemic levels, such as myocardial energy deficiency and insulin resistance, could contribute to the decline in SMD. Physiological mechanisms of fat infiltration has only been investigated in diabetes and obesity, including alterations of mitochondrial structure and function, impaired fatty acid metabolism and a defect in the ability of adipose tissue to store excess fatty acids, and consequently an overflow of adipose tissue into muscle (Miljkovic & Zmuda, 2010). Disuse of muscle might also impair the capacity of muscle cells to oxidize lipids, resulting in an accumulation of lipids within muscles (Stein & Wade, 2005). Additionally, adipose tissue has been characterized as an active endocrine organ and upregulates the activity of macrophage and T-cell expression, thus the secretion of pro-inflammatory cytokines, potentially creating a locally chronic low inflammatory status within muscle (Khan et al., 2015; Lehr, Hartwig, & Sell, 2012). Collectively, these alterations related to fat infiltrated into muscle cells may explain the different findings of low SMI or low SMD in association with comorbidities in this study. We also speculate that different findings between muscle abnormalities are possibly due to a higher rate of SMD decrease than that of SMI loss under certain chronic disorders, which makes SMD more likely to decline at the time point of CRC diagnosis. Although we cannot determine the exact time point of low SMD occurrence and the cause-effect associations of metabolic dysregulation, local/systematic inflammation and low SMD, it is reasonable to assume that their impacts are bi-directional.

Our findings also suggest that fat infiltration into muscle might be a shared mechanism among these comorbidities leading to low SMD, as discussed previously. The phenotype analysis

in this study illustrates that patients with pre-existing comorbidities are likely to have low SMD with or without compromised SMI. Rarely considered and even more occult than low SMI, low SMD may be a pathway through which comorbidities influence cancer survival. Future examinations are warranted to evaluate whether patients with the concurrence of low SMD and pre-existing comorbidities identified in this study were at higher risk for poorer prognosis. Of note, our findings of the associations between comorbidities and low SMD were independent of BMI or total adiposity at diagnosis. Although obesity was not included as a comorbidity in the Charlson's comorbidity index, obesity itself (BMI≥30 kg/m^2), as well as total adiposity (in quintiles, with the lowest quintile as the reference) were independent predictors of low SMD. Patients who were obese had 4-fold higher risk of having low SMD (data not shown). A decrease in SMD in association with obesity (defined using either BMI or total adiposity) has been illustrated in patients with or without cancer (Esfandiari et al., 2014; Goodpaster, Kelley, et al., 2000). Importantly, low SMD is potentially modifiable through resistance training or n-3 fatty acid supplementation (Ewaschuk, Almasud, & Mazurak, 2014). Therefore, patients with comorbidities may warrant evaluation for muscle abnormalities, as this may be a particularly vulnerable group of early-stage patients with a high mortality risk. Stratification of patients with comorbidities and muscle abnormalities into different risk groups and individualized treatment strategies at early stages of cancer could represent a significant progress into the personalized medicine era.

Several limitations to our study should be acknowledged including our convenient sample and cross-sectional approach where causality cannot be inferred. Furthermore, we do not know whether comorbidities lead to low SMI and low SMD or vice versa because the timing of the onset of muscle abnormalities could not be determined. Finally, while we were able to

control for key confounders including smoking status, information on physical activity and dietary intake was not available in this study. Nonetheless, our study had several strengths. It is the first large CRC cohort examining the association of comorbidities and muscle abnormalities. Additionally, we applied a state-of-the-art, highly precise and clinically-relevant tool, CT imaging, to assess muscle abnormalities (Prado & Heymsfield, 2014). The findings of muscle abnormalities, particularly low SMD, observed with certain comorbidities among non-metastatic CRC patients have important clinical implications, as low SMD may be a parameter for screening at risk patients. This study also opens a new avenue of investigating the underlying pathological and physiological mechanism of low SMD, which may be shared across multiple chronic conditions.

4.6 Conclusion

In summary, our findings indicate an association of multiple comorbidities, i.e. MI, CHF, PVD, diabetes and renal disease, with low SMD rather than with low SMI in patients with non-metastatic CRC, suggesting fat infiltration into muscle is a shared mechanism across these diseases. Our results also highlight the clinical relevance of incorporating CT-assessed muscle abnormalities, particularly SMD, into future screening in order to guide patient risk stratification and individualized interventions.

Future mechanistic studies should seek to clarify whether the pathways that augment the breakdown of muscle mass and that promote fat infiltration into muscle overlap or are distinct from each other, and to what extent these pathways vary among different diseases. Clinical trials are also needed to demonstrate the feasibility and efficacy of modifying muscle abnormalities in cancer patients.

Table 4.1 Characteristics of Colorectal Cancer Patients with Respect to the Presence and Absence of Muscle Abnormalities

	Overall (n=3,051)	**Normal SMI** (n=1,736)	**Low SMI** (n=1,315)	p-value	**Normal SMD** (n=2,130)	**Low SMD** (n=921)	p-value
	Mean (Standard Deviation) or %						
Demographic characteristics							
Age, years	63.2 (11.2)	60.4 (11.1)	66.8 (10.1)	<0.001	60.5 (11.1)	69.4 (8.5)	<0.001
Males	50.1	47.5	53.5	0.001	51.1	47.8	0.09
Females	49.9	52.5	46.5		48.9	52.2	
Race/Ethnicity, %							
Caucasian	65.9	62.2	70.7	<0.001	60.9	77.3	<0.001
African American	7.3	9.2	4.7		8.6	4.1	
Hispanic	10.7	12.9	7.8		10.2	11.9	
Asian/Pacific Islander	15.6	15.0	16.4		19.8	6.1	
Others	0.6	0.8	0.3		0.6	0.5	
Body weight and composition							
Body mass index, kg/m^2	28.1 (6.0)	29.9 (6.2)	25.0 (4.3)	<0.001	27.1 (5.4)	30.6 (6.8)	<0.001
Body mass index, %							
Underweight,$<18.5 kg/m^2$	1.7	0.4	3.9	<0.001	1.9	1.2	<0.001
Normal,18.5 to $25 kg/m^2$	31.3	19.8	51.2		36.4	19.7	
Overweight,25 to $30 kg/m^2$	35.6	37.3	32.7		37.5	31.2	
Obese Class I,30 to $35 kg/m^2$	19.7	25.5	9.8		17.4	25.2	
Obese Class II/III,$\geq 35 kg/m^2$	11.6	17.0	2.4		6.8	22.8	
Weight change prior to diagnosis							
Stable, <5% change	37.0	37.9	35.5	0.07	35.9	39.7	<0.001
>=5% loss	17.7	16.3	20.0		17.0	19.2	
>= 5% gain	4.5	4.6	4.2		3.9	5.8	
SMI, cm^2/m^2, men	54.1 (9.3)	60.7 (6.5)	46.3 (4.9)	<0.001	55.4 (8.9)	50.9 (9.4)	<0.001
SMI, cm^2/m^2, women	43.0 (7.4)	46.8 (6.4)	37.3 (4.5)	<0.001	43.4 (7.2)	42.1 (7.6)	0.001
SMM, cm^2, men	168.5 (30.7)	187.4 (25.2)	146.3 (19.7)	<0.001	171.1 (30.2)	162.0 (30.9)	<0.001
SMM, cm^2, women	112.4 (20.3)	121.3 (18.6)	99.1 (14.7)	<0.001	113.1 (19.9)	110.9 (20.9)	0.04
Mean MA, HU, men	40.4 (9.6)	42.7 (8.8)	37.6 (9.7)	<0.001	45.0 (6.4)	28.9 (5.4)	<0.001

Mean MA, HU, women	37.2 (10.0)	39.1 (9.3)	34.4 (10.3)	<0.001	42.4 (6.8)	25.9 (5.3)	<0.001
TAT, cm^2, men	403.1 (195.4)	438.2 (198.2)	361.9 (183.7)	<0.001	355.3 (167.4)	521.4 (209.1)	<0.001
TAT, cm^2, women	361.6 (193.8)	369.6 (191.9)	349.7 (196.1)	0.05	313.6 (171.5)	465.7 (198.5)	<0.001
Tumor factors							
Stage							
Stage I	29.8	31.7	27.3	0.001	30.4	28.5	0.23
Stage II	31.7	29.2	35.1		30.8	33.9	
Stage III	38.5	39.2	37.6		38.8	37.7	
Type							
Colon	71.9	69.4	75.1	0.001	68.4	80.0	<0.001
Rectal	28.1	30.6	24.9		31.6	20.0	
Health characteristics							
Smoking history, %							
Never smoker	46.1	48.5	43.0	0.008	50.9	35.2	<0.001
Former smoker	41.9	39.8	44.7		37.7	51.8	
Current smoker	11.9	11.7	12.3		11.5	13.0	
Charlson index							
0	58.3	59.2	57.1	0.49	65.6	41.5	<0.001
1 or 2	31.1	30.5	31.9		27.9	38.6	
>=3	10.6	10.3	11.0		6.5	20.0	

*For BMI and weight change variables, low SMI was defined by optimal stratification with sex-specific cutpoints: men 52.3 cm^2/m^2, women 38.6 cm^2/m^2.Sample sizes were n=1,931 and n=1,120 for normal SMI and low SMI groups. BMI=body mass index, SMI=skeletal muscle index, SMD =Skeletal muscle radiodensity, SMM=skeletal muscle mass, MA=muscle attenuation, TAT=total adipose tissue, PI=Pacific Islander. Percentage data were presented by columns.

Table 4.2 Univariate and Multivariate Logistic Regression Analyses[1] of Pre-existing Comorbidities Predicting low SMI[2] at Diagnosis among non-metastatic Colorectal Cancer Patients at Kaiser Permanente Northern California

Pre-existing comorbidities (n=11)	Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio (95% CI)	p-value
Myocardial infarction (n=91)	1.36 (0.90,2.07)	0.147	1.03 (0.66,1.61)	0.899
Congestive heart failure (n=97)	1.30 (0.87,1.95)	0.198	1.02 (0.66,1.59)	0.929
Peripheral vascular disease(n=100)	2.42 (1.60,3.66)	<0.001	1.48 (0.94,2.34)	0.089
Cerebrovascular disease(n=73)	1.62 (1.02,2.58)	0.043	1.02 (0.62,1.69)	0.939
Chronic obstructive pulmonary disease(n=275)	1.04 (0.81,1.34)	0.752	0.82 (0.62,1.08)	0.163
Rheumatic disease(n=40)	1.08 (0.58,2.02)	0.807	0.86 (0.44,1.72)	0.677
Peptic ulcer disease(n=10)	1.98 (0.56,7.05)	0.289	2.27 (0.52,9.87)	0.275
Mild liver disease(n=38)	0.96 (0.50,1.83)	0.901	0.75 (0.36,1.55)	0.435
Diabetes w/o complications(n=439)	0.87 (0.70,1.06)	0.169	0.85 (0.68,1.07)	0.177
Diabetes w/complications(n=207)	0.77 (0.57,1.03)	0.076	0.64 (0.47,0.88)	0.007
Renal disease(n=172)	1.16 (0.85,1.58)	0.353	0.90 (0.64,1.27)	0.549
Charlson index[3]				
1 or 2	1.08 (0.92,1.27)	0.330	0.91 (0.76,1.09)	0.303
3	1.12 (0.88,1.42)	0.371	0.81 (0.61,1.06)	0.124

[1] Multivariable logistic regression model adjusted for age, sex, body mass index at diagnosis, weight change prior to diagnosis, stage, cancer site, race/ethnicity, and smoking history. [2] Low skeletal muscle index (SMI) is defined using optimal stratification method. For BMI<30 kg/m^2, the cutpoints were <52.3 cm^2/m^2 and <38.6 cm^2/m^2 for men and women respectively; for BMI≥30kg/m^2, the cutpoints were<54.3 cm^2/m^2 and <46.6 cm^2/m^2 for men and women respectively. [3]With Charlson index score of 0 as the reference group.

Table 4.3 Univariate and multivariate logistic regression analyses[1] of pre-existing comorbidities predicting low SMD[2] at diagnosis among non-metastatic colorectal cancer patients at Kaiser Permanente Northern California

Pre-existing comorbidities (n=11)	Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio (95% CI)	p-value
Myocardial infarction (n=91)	3.69 (2.41,5.67)	<0.001	1.77 (1.08,2.88)	0.023
Congestive heart failure (n=97)	5.49 (3.54,8.51)	<0.001	3.27 (1.97,5.41)	<0.001
Peripheral vascular disease (n=100)	4.15 (2.75,6.28)	<0.001	2.15 (1.33,3.47)	0.002
Cerebrovascular disease (n=73)	2.17 (1.36,3.47)	0.001	1.32 (0.76,2.30)	0.328
Chronic obstructive pulmonary disease (n=275)	2.14 (1.67,2.75)	<0.001	1.23 (0.91,1.66)	0.187
Rheumatic disease (n=40)	2.59 (1.39,4.85)	0.003	1.74 (0.85,3.57)	0.131
Peptic ulcer disease (n=10)	1.54 (0.43,5.48)	0.502	0.91 (0.22,3.74)	0.898
Mild liver disease (n=38)	0.94 (0.47,1.91)	0.867	1.01 (0.44,2.33)	0.980
Diabetes w/o complications (n=439)	2.24 (1.83,2.76)	<0.001	1.46 (1.13,1.89)	0.003
Diabetes w/complications (n=207)	3.09 (2.33,4.12)	<0.001	1.61 (1.13,2.29)	0.008
Renal disease (n=172)	3.48 (2.54,4.76)	<0.001	2.21 (1.50,3.25)	<0.001
Charlson Index[3]				
1 or 2	2.19 (1.84,2.60)	<0.001	1.37 (1.11,1.68)	0.003
>=3	4.84 (3.78,6.20)	<0.001	2.34 (1.74,3.17)	<0.001

[1] Multivariable logistic regression model adjusted for age, sex, body mass index at diagnosis, weight change prior to diagnosis, stage, cancer site, ethnicity/race, and smoking history. [2]Low skeletal muscle radiodensity (SMD) is defined using optimal stratification method. The cutpoints were <35.5 HU for men and <32.5 for women. [3]With Charlson index score of 0 as the reference group.

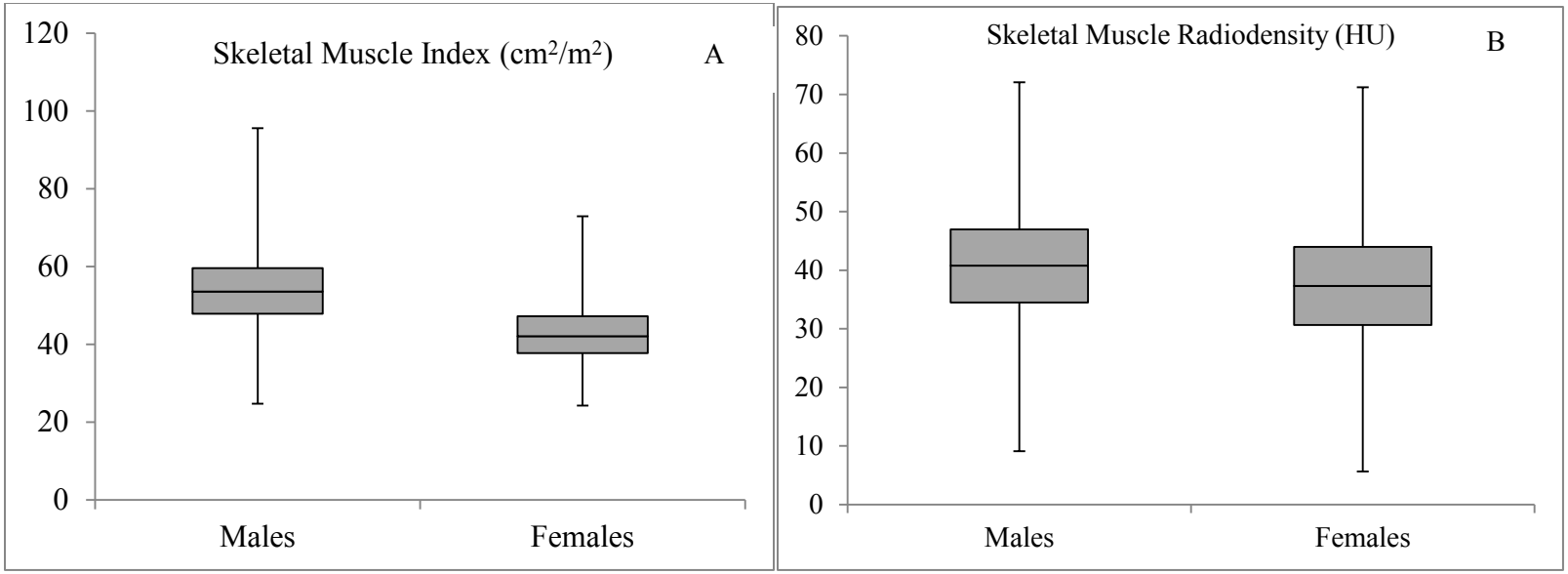

Figure 4.1 Boxplot showing the distribution of Skeletal Muscle Index (SMI) (A) and Skeletal Muscle Radiodensity (SMD) (B) stratified by sex. Cutpoints for low SMI (BMI and sex specific) and low SMD (sex specific) are defined using optimal stratification method.

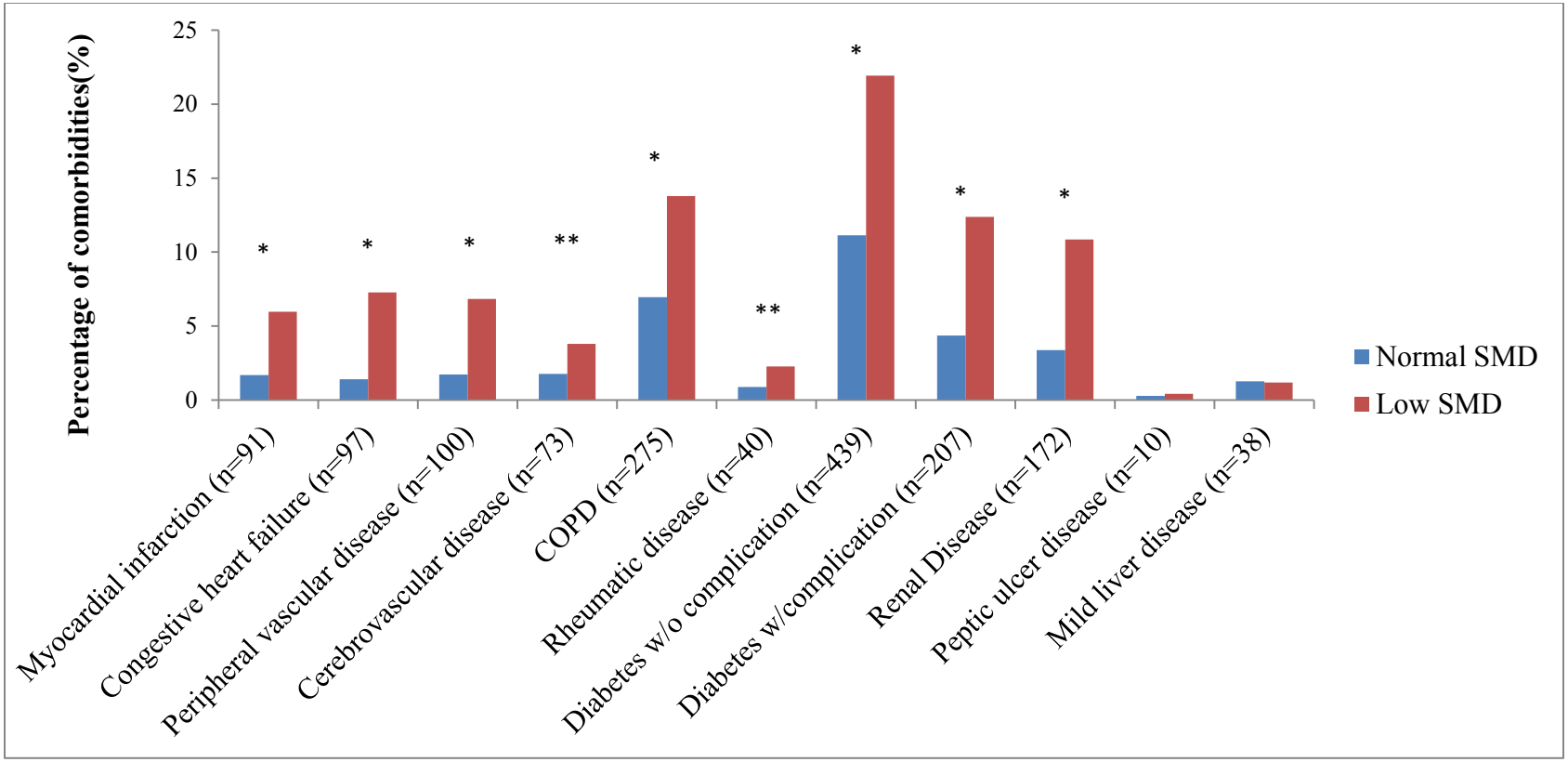

Figure 4.2 Prevalence of pre-existing comorbidities with respect to skeletal muscle radiodensity (SMD). Low SMD is defined using optimal stratification. COPD=chronic obstructive pulmonary disease. *p<0.001, **p<0.05.

Supplementary Table 4.1 Adjusted Multinomial Logistic Regression Analyses[1] of Pre-existing Comorbidities Predicting Muscle Phenotypes at Diagnosis among non-metastatic Colorectal Cancer Patients at Kaiser Permanente Northern California

	Normal SMI / Normal SMD (n=1,360)	**Normal SMI / Low SMD (n=376)**		**Low SMI / Normal SMD (n=770)**		**Low SMI / Low SMD (n=545)**	
Pre-existing comorbidities(n=11)		**RRR** (95% CI)	p-value	**RRR** (95% CI)	p-value	**RRR** (95% CI)	p-value
Myocardial infarction(n=91)	Reference	1.72 (0.89,3.33)	0.109	0.80 (0.38,1.68)	0.555	1.58 (0.87,2.87)	0.131
Congestive heart failure(n=97)	Reference	3.27 (1.70,6.31)	<0.001	0.77 (0.35,1.69)	0.510	2.80 (1.51,5.22)	0.001
Peripheral vascular disease(n=100)	Reference	1.57 (0.76,3.27)	0.225	1.01 (0.50, 2.04)	0.978	2.46 (1.34,4.50)	0.004
Cerebrovascular disease(n=73)	Reference	1.79 (0.83,3.90)	0.140	1.24 (0.62,2.49)	0.543	1.31 (0.64,2.69)	0.457
Chronic obstructive pulmonary disease(n=275)	Reference	1.17 (0.78,1.76)	0.451	0.69 (0.47 1.02)	0.064	1.02 (0.71,1.49)	0.899
Rheumatic disease(n=40)	Reference	1.38 (0.52,3.63)	0.515	0.54 (0.18,1.60)	0.265	1.45 (0.61,3.45)	0.397
Peptic ulcer disease(n=10)	Reference	0.57 (0.05,6.66)	0.654	2.24 (0.39,12.86)	0.366	1.94 (0.30,12.69)	0.489
Mild liver disease(n=38)	Reference	1.32 (0.45,3.93)	0.614	0.83 (0.36,1.95)	0.677	0.72 (0.23,2.20)	0.560
Diabetes w/o complications(n=439)	Reference	1.45 (1.04,2.02)	0.027	0.73 (0.53,1.01)	0.055	1.23 (0.90,1.68)	0.194
Diabetes w/complications(n=207)	Reference	1.90 (1.24,2.92)	0.003	0.57 (0.35,0.94)	0.027	1.04 (0.67,1.60)	0.870
Renal disease(n=172)	Reference	2.73 (1.66,4.49)	<0.001	0.92 (0.54,1.55)	0.743	1.83 (1.13,2.95)	0.013

[1]Adjusted for age, sex, BMI at diagnosis, weight change prior to diagnosis, race/ethnicity, stage, cancer site, and smoking history. BMI=body mass index, SMI=skeletal muscle index, SMD =skeletal muscle radiodensity, RRR=relative risk ratio

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Chapter 5 Computerized Tomography Measured Muscle Abnormalities are Associated with Worse Prognosis in Patients Undergoing Colon Resection Surgery

5.1 Preface

The following chapter included a group of patients who were diagnosed with non-metastatic colon cancer and underwent resection surgery (n=1,715) at Kaiser Permanente Northern California from 2006 to 2011. The sample size of this study was smaller compared to the main cohort in Chapter 3 (n=3,262) due to the exclusion of patients with rectal cancer. Additionally, the analysis is restricted to scans taken within 60 days prior to surgery, as explained in the Methods section. This study aimed to investigate the prognostic effect of muscle abnormalities on adverse surgical outcomes in these patients. Ms. Jingjie Xiao assessed all patients' body composition using computerized tomography (CT) images. Ms. Erin Weltzien and Ms. Valerie Lee contributed to data collection. Ms. Jingjie Xiao contributed to concept formation, study design, data analysis, and write the first manuscript draft. Drs Bette Caan, Elizabeth Cespedes Feliciano, Peter Peng, Candyce Kroenke, Jeffrey Meyerhardt, Vickie Baracos, and Marilyn Kwan, as well as Ms. Erin Weltzien and Ms. Valerie Lee contributed to study design, data interpretation, and critical review of the manuscript. Ms. Adrienne Castillo contributed to study organizational aspects and editing. Dr. Carla Prado supervised and contributed to all aspects of this study. This manuscript is being submitted to Annals of Surgery.

5.2 Introduction

Colon cancer is one of the most commonly diagnosed cancers in the United States; approximately 97,220 new cases are estimated to occur in 2018 (Siegel, Miller, & Jemal, 2018). Resection is the primary treatment for patients with this cancer. With advancement in peri-operative care and operative techniques over the last several decades, the mortality rate after tumor resection of colon cancer has decreased (Siegel, Miller, & Jemal, 2018). Despite the decreased mortality rate, many patients still suffer from post-operative morbidity, leading to delayed subsequent therapy, prolonged hospital stay, and reduced quality of life. Specifically, up to 20-42% of patients will experience some type of complications following tumor resection of colon or rectal cancers (Simmonds et al., 2006; Virani et al., 2007), and 14.8% of patients undergoing colorectal resection experienced unplanned readmission after discharge (Weiss, Elixhauser, & Steiner, 2006). As such, surgeons have established patient-related risk factors of morbidity and other adverse surgical outcomes, such as body mass index (BMI) (Hotouras et al., 2016), Charlson comorbidity index (Hines et al., 2009; Krarup, Nordholm-Carstensen, Jorgensen, & Harling, 2015) and the American Society of Anesthesiologists classification system (Krarup et al., 2015; Sutton et al., 2017) to predict surgical complications or mortality. However, these conventional methods have shown mixed success in their capabilities to identify patients at greater risk of post-operative morbidity or mortality.

More recently, frailty, defined as decreased physiologic reserve, has been proposed as a more general parameter for pre-surgical risk stratification (Makary et al., 2010). Low muscle mass, also known as sarcopenia, is a key component of the frailty syndrome, and is regarded as an objective and robust marker of this condition (Bernabei et al., 2014). Emerging evidence has linked sarcopenia, quantified as low skeletal muscle index (SMI) assessed using computerized

tomography (CT) images, and prognosis in several cancer types. A recent systematic review and meta-analysis of cancer patients undergoing abdominal surgery reported that sarcopenic patients had a 1.6-fold increased risk of having post-operative complications, 2-fold higher risk of death within 30 days after surgery, as well as shortened long-term survival compared to non-sarcopenic patients (K. Jones et al., 2017). An additional CT-assessed prognostic marker is skeletal muscle radiodensity (SMD), which relates to intramuscular lipid deposition and therefore reflects fat infiltration into muscle (Aubrey et al., 2014). Low SMD has been associated with surgical complications and mortality in colon cancer and other cancer types (Boer et al., 2016; Hamaguchi et al., 2016; Malietzis, Currie, et al., 2016; Okumura et al., 2015). Low SMI and low SMD can occur independently, concurrently, and along with different adiposity levels. Previous research has shown that the concurrent appearance of low SMI and low SMD may result in even worse clinical outcomes than either in isolation (Shachar et al., 2017). However, the majority of previous studies reported only the isolated impact of SMI or SMD or have not controlled for the influence of adiposity, an important predictor of treatment outcomes (Xiao, Mazurak, Olobatuyi, Caan, & Prado, 2016). Here, we investigated the independent effects of low SMI and low SMD with post-operative complications, length of hospital stay (LOS), readmission rate and short-term mortality in patients with resectable colon cancer.

5.3 Methods

5.3.1 Study Population and Setting

We performed a retrospective review of the Kaiser Permanente Northern California (KPNC) Cancer Registry from 2006 to 2011. Patients with stage I-III invasive colorectal cancer (CRC) and who had primary tumor resection were identified. Cancer stage was defined according to the American Joint Committee on Cancer. Abdominal CT scans collected for

diagnostic purposes with sufficient image quality for body composition assessment were available for 3,262 patients, as described elsewhere (Caan et al., 2017). Given the effects of neoadjuvant chemotherapy and radiation in rectal cancer, and its potential negative impact on SMI and SMD (Levolger et al., 2017; Yip et al., 2014), we excluded rectal cancer from the analysis. Furthermore, procedure-related factors such as resection margins and surgery types might potentially influence surgical prognosis comparing colon and rectal cancer patients (Rodriguez-Bigas MA, 2003). Therefore, we excluded patients with incomplete electronical medical record (EMR) surgical information. Additionally, only patients whose CT scans were taken within 60 days prior to surgery (mean -18.4 days), before any chemotherapy or radiation treatment, were included. A total of 1,715 patients were included in the final analysis. Registry records were linked with hospital utilization data for information on diagnoses, procedures and outcomes using International Statistical Classification of Diseases and Related Health Problems (ICD) -9 codes. This study was approved by the KPNC Institutional Review Board and University of Alberta Health Research Ethics Board.

5.3.2 Computerized Tomography Image Analysis for Body Composition

A single CT image at the third lumbar vertebra (L3) was selected for muscle mass quantification because skeletal muscle cross-sectional areas at L3 strongly correlate with whole-body muscle volume (Mourtzakis et al., 2008; Shen et al., 2004). According to the standard HU range (Heymsfield et al., 1990), cross-sectional areas of skeletal muscle, intermuscular adipose tissue (IMAT), visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) were quantified by a trained researcher using SliceOmatic Software version 5.0 (TomoVision, Montreal, Quebec, Canada). The intra-observer coefficient variations of muscle mass and radiodensity measurements were 0.7% and 1.2% respectively. Muscle mass was calculated as

SMI, from total muscle cross-sectional area divided by height square (cm^2/m^2) (Mourtzakis et al., 2008; Prado et al., 2008). SMD was generated by the software as the mean radiation attenuation value of the whole muscle area at L3. Total adipose tissue (TAT) was calculated as the sum of IMAT, VAT and SAT.

5.3.3 Definitions of Muscle Abnormalities

We defined dichotomous variables to represent low SMI versus normal SMI and low SMD versus normal SMD. We applied the optimal stratification method to determine the cohort-specific threshold values of SMI and SMD that best separated patients' time to death as described previously (Caan et al., 2017). This method selects a cut point for a continuous variable from a fixed set of possible values, and has been increasingly accepted as a clinically relevant approach for patient risk stratification (Martin et al., 2013; Prado et al., 2008). For normal/overweight patients (BMI <30 kg/m^2), the threshold values of SMI were 52.3 cm^2/m^2 for men and 38.6 cm^2/m^2 for women, while for obese patients (BMI≥30 kg/m^2) these were 54.3 cm^2/m^2 for men and 46.6 cm^2/m^2 for women Caan et al., 2017. Similarly, threshold values of SMD were 35.5 HU for men and 32.5 HU for women (Kroenke et al., 2017). Patients presenting below these threshold values were classified as having either low SMI or low SMD while their respective counterparts having either normal SMI or normal SMD.

5.3.4 Outcome Measures

Post-operative clinical outcomes included the development of complications, LOS, 30-day readmission and 30-day mortality, as identified by ICD-9 diagnostic codes and encounter dates from the patients' EMR. Specifically, a post-operative complication was defined as the presence of one or more of the following conditions with 30 days post-surgery: surgical site infection, wound dehiscence, sepsis, pulmonary embolism, deep vein thrombosis, stroke, cardiac

complications, pneumonia, renal failure, urinary tract infection, clostridium difficile, bleeding, bowel obstruction, or delirium. Anastomotic leakage was also assessed because leak rates are frequently used as an indicator of the quality of surgical care provided and has been associated with high risk of morbidity and mortality (Bruce, Krukowski, Al-Khairy, Russell, & Park, 2001). LOS was calculated by subtracting the date of surgical operation from the date of first discharge after surgery. LOS was analyzed as a continuous variable and as a binary variable by dichotomizing LOS at the 75% percentile (7 days). Any inpatient admission or emergency visit to a KPNC hospital within 30 days beginning with the surgical discharge date was considered a readmission; this variable was dichotomized as a binary variable (no/yes). Death events within 30 days after surgery were identified.

5.3.5 Covariates

Patients' EMR and the Cancer Registry were reviewed for information on cancer stage, tumor characteristics and demographics at cancer diagnosis, including age, height, weight, Charlson comorbidities score, sex, race/ethnicity, smoking history and alcohol use.

5.3.6 Statistical Analysis

Differences in descriptive statistics were analyzed using one-way analysis of variance tests for continuous variables, and Pearson's Chi-square tests for categorical variables. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using logistic regression models, to determine the prognostic effect of muscle abnormalities on post-operative complications, readmissions, LOS, and 30-day mortality. The multivariable models were internally validated using bootstrapping (200 replications) (Steyerberg et al., 2001). Likelihood ratio tests were used to examine possible interactions between low SMI and low SMD, as well as their interactions with TAT, comparing models with and without the interaction term. Receiver

operating characteristics (ROC) curves were used to assess the predictive value of the multivariable logistic regression models by calculating the area under the curve (AUC) (Hanley & McNeil, 1982). We tested for differences between AUCs of two different models using bootstrap standard errors (replications 200) (Pepe, Longton, & Janes, 2009). We also examined additive effects of each muscle abnormality and TAT by categorizing patients into mutually exclusive groups. All statistical analyses were performed using STATA (version 14.2; StataCorp LP). Statistical significance was established with 2-sided tests with p=0.05.

5.4 Results

5.4.1 Baseline Characteristics and Muscle Abnormalities

Characteristics of 1,715 patients by the presence and absence of low SMI or low SMD at diagnosis are given in Table 1. The prevalence of low SMI was 45.8% in men and 41.1% in women, whereas the prevalence of low SMD was 31.0% in men and 32.1% in women. Patients with either low SMI or low SMD were older than those with normal SMI or SMD. Patients with low SMI had lower BMI, and were more likely to be Caucasians or Asians, and to have stage II (versus I) cancer. Patients with low SMD had higher BMI, and were more likely to be Caucasians, former smokers, and to have comorbidities.

5.4.2 Associations of Muscle Abnormalities with Postoperative Outcomes

As shown in Table 1, mean LOS was longer in patients with either muscle abnormality. 42.1% of patients experienced complications and nineteen patients died after surgery; these patients were more likely to have either low SMI or low SMD. 16.6% patients were readmitted within 30 days after their first discharge, and these patients were more likely to have low SMD. We further compared body composition features by presence and absence of post-operative outcomes, stratified by sex. For men, SMI was lower in those who had complications (p=0.049),

LOS ≥ 7 days (p<0.001), and those who died after surgery (p<0.001, Figure 1A); whereas for women, SMI was lower in deceased patients (p=0.022, Figure 1B). Mean SMD was lower for both men and women who presented with complications (both p<0.001), LOS ≥ 7 days (p=0.006 and p<0.001 respectively), or readmission (p=0.007 and p=0.010 respectively), compared to those who did not have the corresponding outcome (Figure 1C and 1D). Additionally, men who died presented with lower SMD compared to those who were alive (p=0.001, Figure 1C).

5.4.3 Independent Effect of Muscle Abnormalities on Surgical Outcomes

We first assessed the association of each muscle abnormality with each surgical outcome in multivariable logistic regression models adjusting for adiposity, Charlson comorbidity score, lifestyle risk factors, demographic and clinical variables (Table 2). As the interaction between low SMI and low SMD was non-significant, we reported the independent (mutually adjusted) associations of each risk factor with surgical outcomes as odds ratios (ORs). Patients with low SMI or low SMD were more likely to have LOS ≥7 days (OR=1.30, 95% CI 1.03-1.63 and OR=1.42, 95% CI 1.08-1.86, respectively, Table 2). Low SMD was not associated with having complications, while patients with low SMI were more likely to have complications (OR=1.26, 95% CI 1.02-1.55, Table 2). Bootstrap validation of these main models demonstrated minimal evidence of model overfit. As for each individual complication, patients with low SMI showed a marginally higher risk of having cardiac complications (OR=1.63, 95% CI 1.00-2.64), and a higher risk of having bowel obstruction (OR=1.33, 95% CI 1.03-1.72, Supplementary Figure 1A). Low SMD was not associated with any individual complications (Supplementary Figure 1B).

In addition, patients who had low SMI had an almost 4-fold higher risk of death (OR=3.85, 95% CI 1.14-13.04) within 30 days post-surgery (Table 2). In contrast, patients with

low SMD did not show higher risk of 30-day mortality compared to those with normal SMD (Table 2). Under the independent effects model, patients with both low SMI and low SMD had an 84% higher risk of having LOS≥7 days (OR=1.84, 95% CI 1.34-2.54), and an almost 10 times higher risk of post-surgical death (OR=9.68, 95% CI 2.05-45.72) compared to patients with neither risk factor. ROC curve analysis further demonstrated an improvement in discriminative capability for mortality risk stratification by including SMI and SMD in the model. The area under the ROC curve for the multivariable model with SMI and SMD was 0.82 (95% CI 0.73-0.92), whereas the area under the ROC curve for the model with age, sex and stage without SMI and SMD was 0.73 (95% CI 0.60-0.86) (Figure 2). These curves were statistically different (p=0.024).

5.4.4 Phenotypes of Muscle Abnormalities and Total Adipose Tissue

The association of low SMI or low SMD with each outcome did not vary by TAT levels; all interaction p-values were >0.05 (data not shown). We speculated a possible additive effect of high TAT and muscle abnormalities, and therefore, stratified patients into mutually exclusive groups based on muscle abnormality and levels of TAT (Table 3). Patients with both low SMI and lowest TAT tertile showed a marginally significant increased risk for LOS≥7 days. Patients in the highest tertile of TAT and low SMI group had a higher risk of complications compared to the reference group (i.e. normal SMI and lowest TAT tertile).

As for the SMD-TAT phenotype, patients with both low SMD and lowest TAT tertile had a higher risk of LOS ≥ 7 days; those with low SMD and in the highest TAT tertile had a higher risk of complications compared to patients who had normal SMD and the lowest TAT tertile. A marginally higher risk of complications was also found in patients with normal SMD in the highest TAT tertile.

5.5 Discussion

This retrospective study in patients with non-metastatic colon cancer shows that low SMI and low SMD at diagnosis assessed from clinically-acquired CT images are independent risk factors for longer LOS. These associations were independent of race/ethnicity, age, disease stage, comorbidities, TAT, smoking history and alcohol use. Low SMI was additionally associated with a higher risk of surgical complications and short-term mortality. The concurrence of low SMI and low SMD was associated with a substantially higher 30-day mortality risk. Patients in the two extremes of TAT (highest or lowest tertiles) with any concurrent muscle abnormality were at higher risk of either complications within 30 days post-surgery or longer LOS. This study expands the existing evidence on body composition and surgical outcomes by highlighting the effect of muscle abnormalities, independent of and in addition to adiposity, with adjustment for a comprehensive set of covariates.

Low SMI, also known as sarcopenia, and low SMD have recently emerged as prognostic markers for these outcomes in surgical oncology. Our finding in patients with non-metastatic colon cancer is in accordance with these previous reports (Boer et al., 2016; Huang et al., 2015; Lieffers et al., 2012; Lodewick et al., 2015; Malietzis, Currie, et al., 2016; Miyamoto et al., 2015; P. D. Peng et al., 2011; J. L. van Vugt et al., 2015), showing low SMI consistently associated with a higher risk of complications. Direct hospital costs for healthcare-associated infections is estimated to range from $35.7 billion to $45 billion per year for inpatient services in the United States alone (ScottII), which inevitably extends recovery time, and potentially leads to delayed subsequent cancer therapy. In contrast to the abundant sarcopenia literature, little is known in regards to the consequences or etiology of low SMD in cancer. Only three studies investigated the prognostic significance of low SMD in patients with colon and/or rectal cancer, with

conflicting findings (Boer et al., 2016; Malietzis, Currie, et al., 2016; Margadant et al., 2016). Our previous report including both colon and rectal cancer patients found that low SMD but not low SMI was related to multiple pre-existing comorbidities prior to CRC diagnosis (Xiao et al. under review). Therefore, SMD is likely an indicator of the degree of disease burden, and possibly an early manifestation of the overall health of patients scheduled for surgery.

Findings on the association between low SMI and LOS are less consistent, with three studies (Lieffers et al., 2012; Miyamoto et al., 2015; P. D. Peng et al., 2011) reporting longer LOS for patients with low SMI, and two studies (Malietzis, Currie, et al., 2016; Miyamoto et al., 2015) finding no association. We found that both low SMI and low SMD were independently associated with LOS≥7 days, and for the first time demonstrated their additive effects in the association with LOS. Prolonged hospital stay observed in patients with low SMI has been related to increased healthcare costs, potentially resulting in further muscle loss (Gani et al., 2016). Interestingly, none of the muscle abnormalities or their combination predicted readmission. However, low SMI predicted short-term mortality, and the combination of low SMI and low SMD was related to an even higher mortality risk. It is likely that surgical complications may have led to premature mortality in these patients. These findings are consistent with previous reports of higher risk of short-term mortality among CRC patients with low SMI (Malietzis, Currie, et al., 2016; Reisinger et al., 2015). ROC curves further confirmed a stronger predictive power for post-surgical mortality risk with the inclusion of both SMI and SMD in the model. The model improvement was not significant when including only SMI or SMD, suggesting the importance of both the quantity (SMI) and "quality" (SMD) of muscle for mortality prediction after surgery. In fact, we previously showed that both low SMI and low

SMD were associated with decreased long-term survival in patients with CRC from the same region independent of cancer site (Caan et al., 2017; Kroenke et al. 2018).

Other than CRC, low SMI and low SMD have been associated with poorer surgical outcomes in patients undergoing other types of surgery such as pancreatoduodenectomy, gastrectomy (Antoun et al., 2013; Hayashi et al., 2016; Van Rijssen et al., 2017). However, a unique feature of our analysis was the adjustment for adiposity, which was either not measured/reported, or not taken into consideration in previous investigations (K. Jones et al., 2017; Lieffers et al., 2012; Miyamoto et al., 2015; J. L. van Vugt et al., 2015). Acting as a metabolic organ, adipose tissue secretes a variety of cytokines, contributing to inflammation status (Xiao et al., 2016). These changes potentially inhibit the healing process and promote infection following surgery (Chang & Bistrian, 1998). From a technical perspective, greater abdominal adiposity has been associated with longer operation time and higher blood loss, increasing patients' risk of having complications (Xiao et al., 2016), all of which could results in readmission or prolonged LOS. Further phenotype analysis has shown that the effect of low SMI or low SMD on LOS was more prominent in patients at the lowest tertile of TAT. Patients at the highest tertile of TAT, with either concurrent low SMI or low SMD, had higher risk for complications. Recent evidence has shown that muscle loss concurrent with increased adiposity results in an imbalance of pro-inflammatory and anti-inflammatory factors favouring the secretion of interleukin-6, tumor necrosis factor-α over the secretion of interleukin-15 and adiponectin (Lutz & Quinn, 2012; Tilg & Moschen, 2006). This milieu likely influence immune function and is compounded by surgery stress. Therefore, it is possible that patients with extreme TAT levels concurrent with either muscle abnormality are at the highest risk of adverse short-term outcomes, requiring close pre- and post-surgical surveillance. As such, it is reasonable to

assume that patients with these abnormal body composition phenotypes are likely to benefit the most from pre-operative interventions. Interestingly, patients with moderate level of TAT had no increased risk for any worse outcomes, regardless of the presence or absence of muscle abnormalities. We could not fully explain why moderate adiposity did not increase risk of adverse outcomes. Further research can elucidate the protective or deleterious effect of specific adipose tissue components.

Future prospective studies are also required to evaluate the efficacy of pre-operative rehabilitation that specifically target increasing SMI and SMD for reducing risks of adverse outcomes. So far, only six physical and nutritional intervention studies have been conducted prior to CRC surgery without a particular target for SMI or SMD modification (Looijaard, Slee-Valentijn, Otten, & Maier, 2017), and the systematic review of these studies has not shown a significant reduction in post-operative complications or LOS (Looijaard et al., 2017). In contrast, a recent systematic review evaluating the effectiveness of structured pre-surgical rehabilitation intervention in adult surgical populations concluded that pre-operative exercise intervention (i.e. cardiovascular and/or resistance training of the upper and/or lower extremities) improved post-operative pain, LOS and physical function (Santa Mina et al., 2014).

Certain limitations of this study merit consideration. Like all cross-sectional designs, we could not determine whether muscle abnormalities are simply markers for poorer surgical outcomes or whether they have a direct effect on outcomes. Prospective studies are needed to determine when these abnormalities occur and the mechanisms through which they impact outcomes. We were unable to explore severity of complications (e.g. Clavien-Dindo classification) as this information is not readily available for our dataset. We instead focused on the association of overall and individual complications with muscle abnormalities. Other

limitations include the lack of information on physical activity, dietary intake, socioeconomic status and perioperative care support (i.e. enhanced recovery after surgery protocols), which could plausibly impact SMI, SMD and outcomes. Despite these limitations, our study is the largest to date to examine the relation between CT-assessed muscle abnormalities and surgical outcomes among non-metastatic colon cancer patients using a robust model adjustment approach for data analysis.

5.6 Conclusions

In conclusion, our work identified low SMI and low SMD as important pre-operative predictors of post-operative outcomes in colon cancer patients; which is in line with the CRC literature associating muscle abnormalities with poorer surgical outcomes (K. Jones et al., 2017). We have additionally reported that the concurrence of low SMI and low SMD were associated with even higher risk after accounting for adiposity levels. Muscle abnormalities are often occult, particularly in the presence of obesity (31.5% in the current cohort). Newly diagnosed patients with non-metastatic cancer have pre-operative CT scans readily available for staging purpose. As such, body composition could be opportunistically assessed using commercially available programs. Semi- or fully- automated programs are also available (Chung H, 2009; Kemnitz et al., 2017), allowing more efficient and cost-effective body composition assessment in large healthcare centers. These techniques can help guide surgeon and patient discussion for treatment strategies, as well as guide the design of personalized intervention programs to modify body composition pre-operatively, potentially optimizing surgical outcomes in clinical care.

Table 5.1 Demographic and Clinical Characteristics by Muscle Abnormalities

	Overall (n=1,715)	**Normal SMI (n=974)**	**Low SMI (n=741)**	**p-value**	**Normal SMD (n=1,173)**	**Low SMD (n=542)**	**p-value**
	Mean (SD) or N (%)						
Age (years)	64.0±11.2	61.5±11.3	67.3±10.2	<0.001	61.4±11.5	69.6±8.1	<0.001
Sex							
Males	764(44.5)	414(42.5)	350(47.2)	0.051	527(44.9)	237(43.7)	0.642
Females	951(55.5)	560(57.5)	391(52.8)		646(55.1)	305(56.3)	
Race/ethnicity							
Caucasian	1,117(65.3)	596(61.3)	521(70.4)	<0.001	694(59.3)	423(78.2)	<0.001
African American	139(8.1)	97(10.0)	42(5.7)		118(10.1)	21(3.9)	
Hispanic	182(10.6)	127(13.1)	55(7.4)		124(10.6)	58(10.7)	
Asian	264(15.4)	146(15.0)	118(16.0)		229(19.6)	35(6.5)	
Others	10(0.6)	6(0.6)	4(0.5)		6(0.5)	4(0.7)	
BMI(kg/m^2)	28.0±6.1	29.9±6.1	24.8±4.4	<0.001	26.9±5.5	30.4±6.6	<0.001
Stage							
I	426(24.8)	269(27.6)	157(21.2)	0.006	294(25.1)	132(24.4)	0.858
II	620(36.2)	331(34.0)	289(39.0)		419(35.7)	201(37.1)	
III	669(39.0)	374(38.4)	295(39.8)		460(39.2)	209(38.6)	
Smoking status							
Never	828(48.3)	482(49.6)	346(46.7)	0.325	616(52.6)	212(39.1)	<0.001
Former	691(40.3)	377(38.8)	341(42.4)		426(36.4)	265(48.9)	
Current	194(11.3)	113(11.6)	81(10.9)		129(11.0)	65(12.0)	
Alcohol use							
Never	470(27.4)	269(27.6)	201(27.1)	0.660	314(26.8)	156(28.8)	0.569
Former	25(1.5)	16(1.6)	9(1.2)		15(1.3)	10(1.9)	
Current	488(28.5)	284(29.2)	204(27.5)		342(29.2)	146(26.9)	
Comorbidities							

0	909(53.0)	506(52.0)	403(54.4)	0.778	705(60.1)	204(37.6)	<0.001
1-2	527(30.7)	304(31.2)	223(30.1)		315(26.9)	212(39.1)	
>=3	179(10.4)	105(10.8)	74(10.0)		74(6.3)	105(19.4)	
Operation							
Endoscopic polypectomy	855(59.8)	474(57.1)	381(63.5)	0.015	567(57.6)	288(64.7)	0.011
Laparascopy	575(40.2)	356(42.9)	219(36.5)		418(42.4)	157(35.3)	
LOS (days), mean (SD)	6.4±6.3	6.0±4.8	6.9±7.9	0.003	5.8±4.1	7.6±9.4	<0.001
30-day complications							
No	993(57.9)	590(60.6)	403(54.4)	0.01	716(61.0)	277(51.1)	<0.001
Yes	722(42.1)	384(39.4)	338(45.6)		457(39.0)	265(48.9)	
30-day readmission							
No	1,430(83.4)	823(84.5)	607(83.4)	0.155	993(84.7)	437(80.6)	0.037
Yes	285(16.6)	151(15.5)	134(18.08)		180(15.4)	105(19.4)	
30-day mortality							
No	1,696(98.9)	970(99.6)	726(98.0)	0.002	1,167(99.5)	529(97.6)	0.001
Yes	19(1.1)	4(0.4)	15(2.0)		6(0.5)	13(2.4)	

BMI=body mass index, SMI=skeletal muscle index, SMD=skeletal muscle radiodensity, LOS= length of hospital stay

Table 5.2 Muscle Abnormalities and Surgical Outcomes in Patients with Non-metastatic Colon Cancer

Independent, Mutually Adjusted Associations	Odds Radios (95%CI)			
	LOS ≥7days	30-day Complications	30-day Readmission	30-day Mortality
Low SMI				
Yes (n=741)	1.30 (1.03-1.63)	1.26 (1.02-1.55)	1.26 (0.96-1.67)	3.85 (1.14-13.04)
No (n=974)	Reference	Reference	Reference	Reference
Low SMD				
Yes (n=542)	1.42 (1.08-1.86)	1.00 (0.78-1.29)	1.04 (0.75-1.45)	2.51 (0.74-8.49)
No (n=1,173)	Reference	Reference	Reference	Reference
Low SMI and low SMD				
Both (n=313)	1.84 (1.34-2.54)	1.26 (0.94-1.70)	1.32 (0.89-1.94)	9.68 (2.05-45.72)
Neither (n=745)	Reference	Reference	Reference	Reference

Models adjusted for age at diagnosis, cancer stage, race/ethnicity, smoking history, alcohol intake history, Charlson comorbidity score, total adipose tissue. SMI=skeletal muscle index, SMD=skeletal muscle radiodensity, LOS=length of hospital stay

Table 5.3 Multivariate Models for Muscle Abnormalities and Total Adipose Tissue Phenotypes

		LOS ≥7days		30-day Readmission		30-day Complications	
	At risk	**#Events**	**OR (95% CI)**	**#Events**	**OR (95% CI)**	**#Events**	**OR (95% CI)**
SMI and TAT							
Normal SMI, low TAT	269	64	Reference	34	Reference	98	Reference
Normal SMI, mid TAT	353	93	1.04 (0.71-1.51)	63	1.41 (0.89-2.25)	136	1.07 (0.76-1.50)
Normal SMI, high TAT	352	94	0.95 (0.64-1.42)	54	1.06 (0.65-1.75)	150	1.23 (0.86-1.74)
Low SMI, low TAT	303	100	1.45 (0.99-2.12)	47	1.31 (0.80-2.14)	120	1.11 (0.78-1.58)
Low SMI, mid TAT	219	77	1.36 (0.89-2.07)	39	1.41 (0.83-2.39)	104	1.39 (0.94-2.04)
Low SMI, high TAT	219	75	1.17 (0.75-1.81)	48	1.59 (0.94-2.72)	114	1.71 (1.14-2.55)
SMD and TAT							
Normal SMD, low TAT	500	130	Reference	69	Reference	181	Reference
Normal SMD, mid TAT	399	105	1.07 (0.78-1.46)	69	1.31 (0.90-1.91)	160	1.24 (0.93-1.64)
Normal SMD, high TAT	274	66	0.96 (0.67-1.38)	42	1.05 (0.68-1.63)	116	1.40 (1.01-1.92)
Low SMD, low TAT	72	34	1.85 (1.10-3.14)	12	1.00 (0.50-2.02)	37	1.28 (0.75-2.13)
Low SMD, mid TAT	173	65	1.32 (0.90-1.96)	33	1.17 (0.72-1.91)	80	1.11 (0.76-1.62)
Low SMD, high TAT	297	103	1.23 (0.87-1.72)	60	1.20 (0.79-1.81)	148	1.43 (1.04-1.97)

Models simultaneously adjusted for SMI and SMD, with additional adjustment for age at diagnosis, cancer stage, race/ethnicity, smoking history, alcohol intake history, Charlson comorbidity score. Mortality was not included due to insufficient number of events in each group for statistical analysis. SMI=skeletal muscle index, SMD=skeletal muscle radiodensity, TAT=total adipose tissue, LOS=length of hospital stay

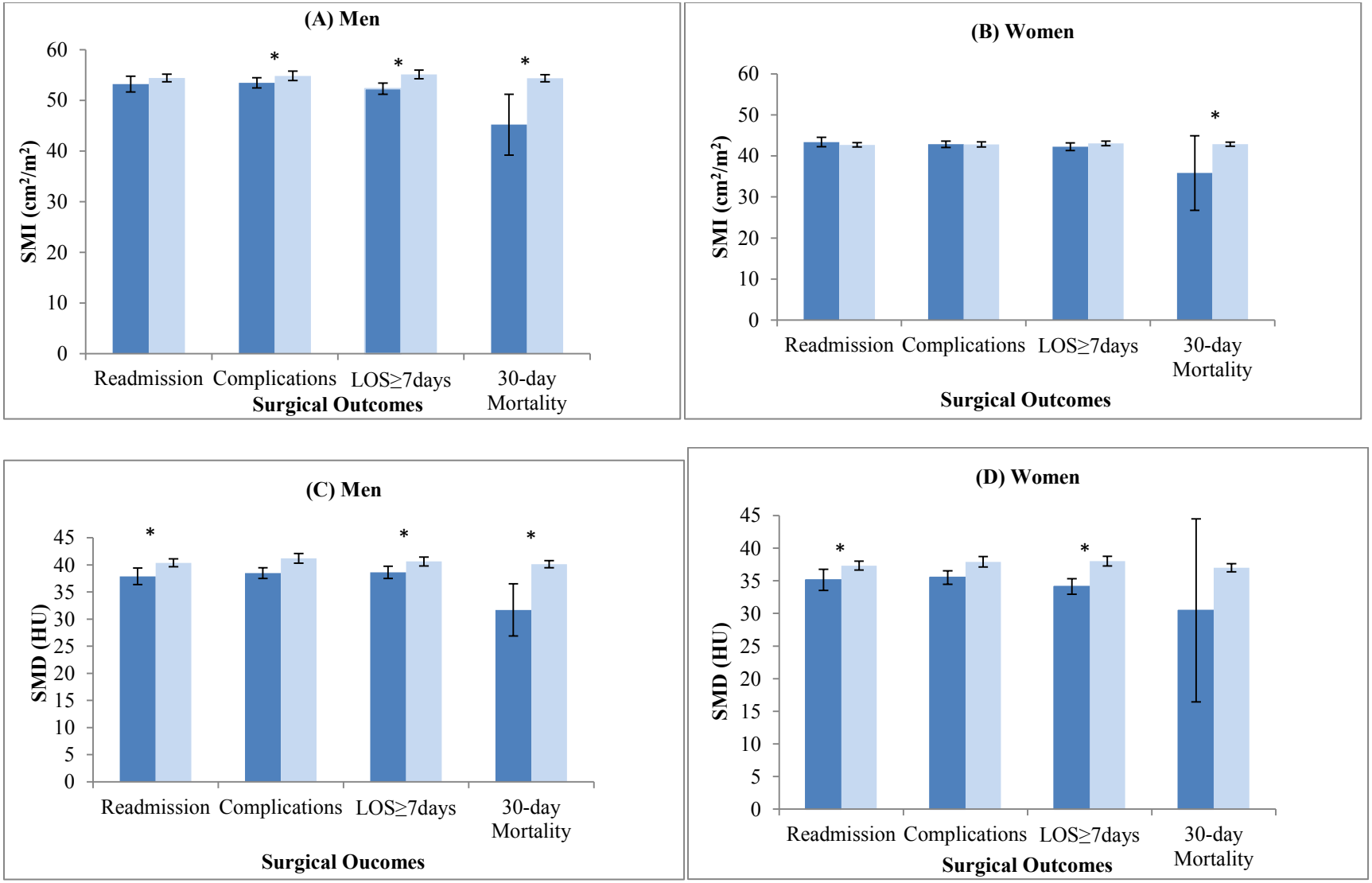


Figure 5.1 Mean Skeletal Muscle Index and Radiodensity by the Presence or Absence of Each Surgical Outcome

(A) SMI - Men; (B) SMI - Women; (C) SMD - Men; (D) SMD - Women. Dark blue: with the event; Light blue: without the event. *P values <0.05. SMI=skeletal muscle index, SMD=skeletal muscle radio-density, LOS= length of hospital stay, HU=Hounsfield unit

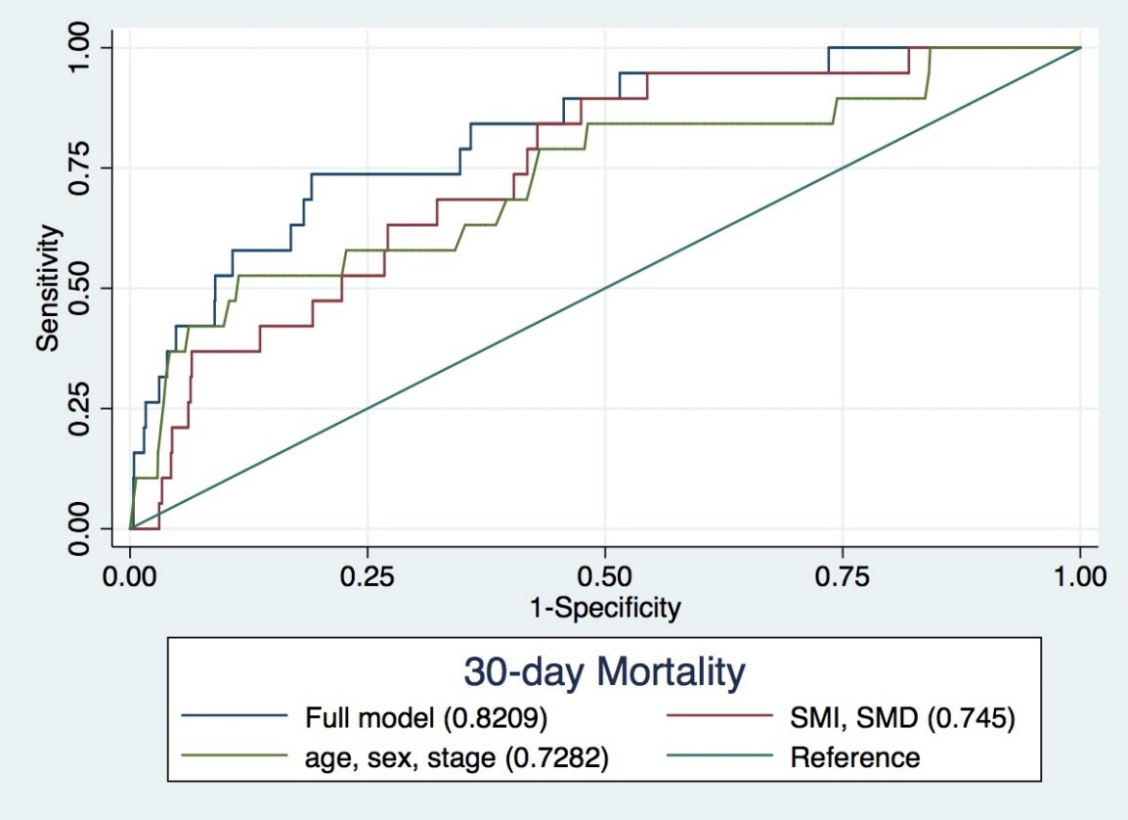
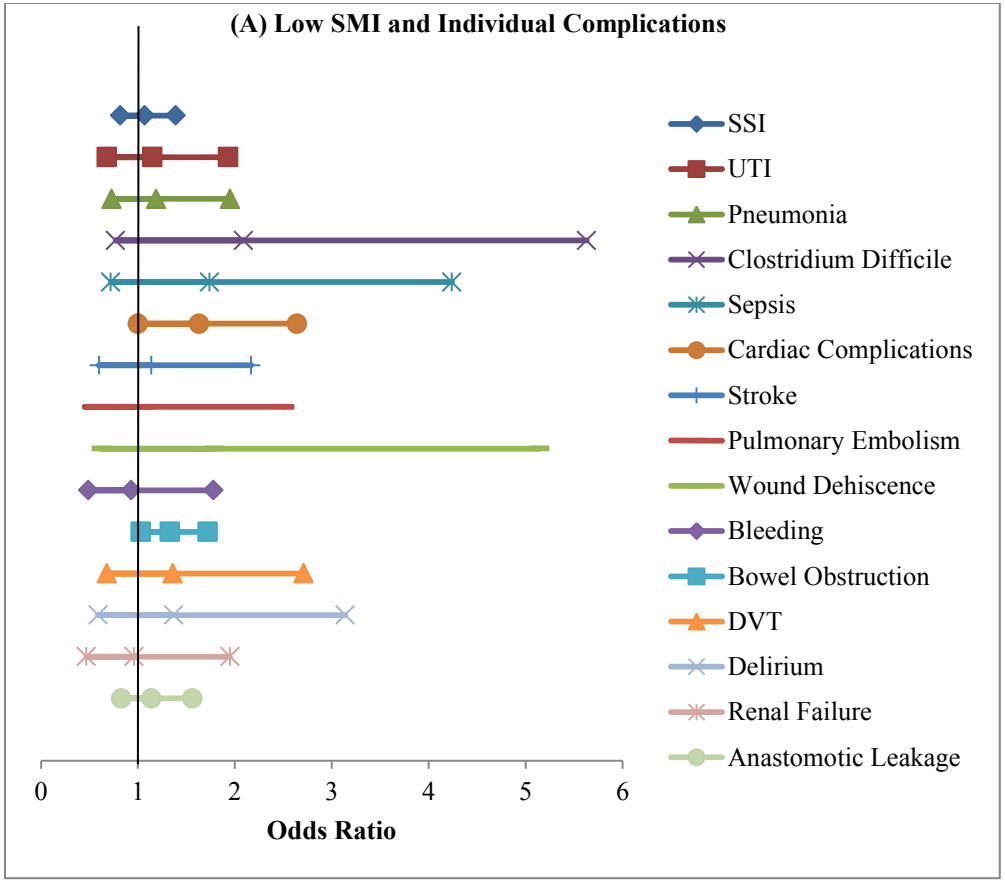
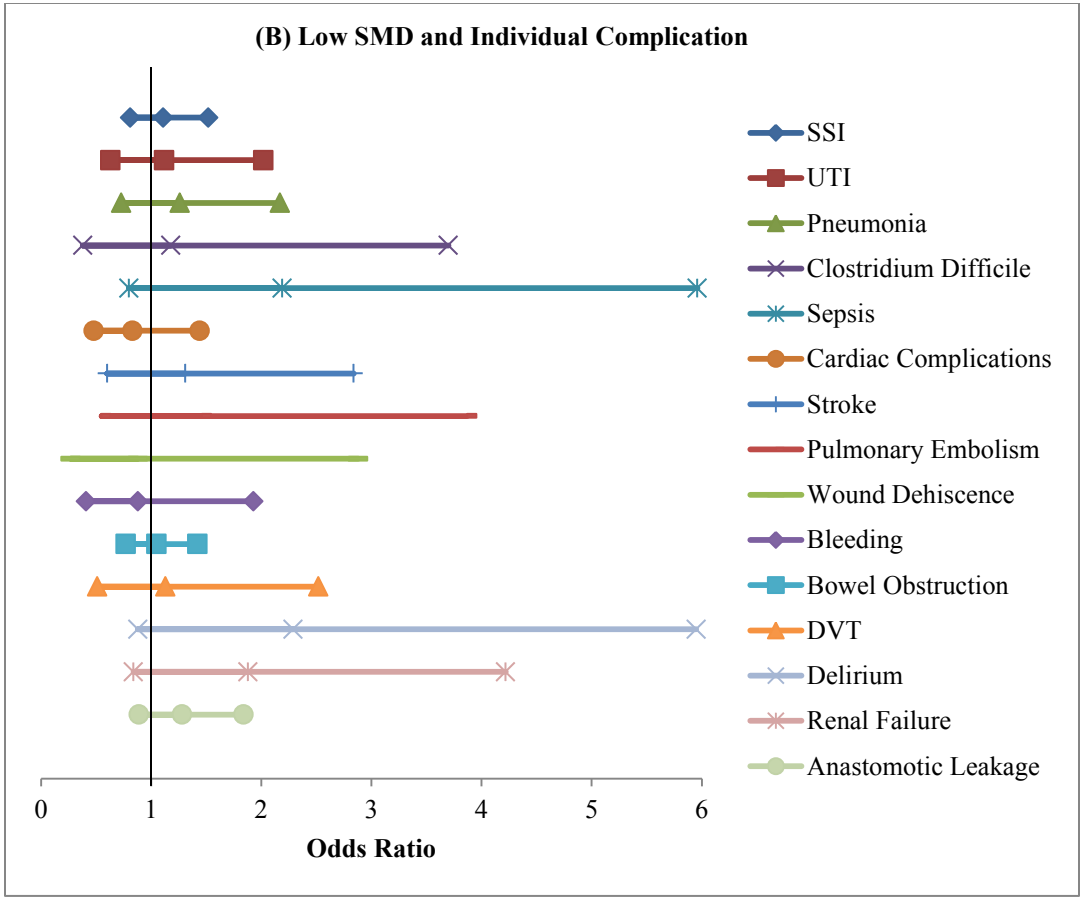


Figure 5.2 Areas under the Receiver Operating Characteristics Curves for 30-Day Mortality.
Full model adjusted for age, sex, stage, SMI and SMD. Chi square test for difference between models shows p<0.001. SMI=skeletal muscle index, SMD=skeletal muscle radiodensity


(A) Low SMI and Individual Complications
SSI
UTI
Pneumonia
Clostridium Difficile
Sepsis
Cardiac Complications
Stroke
Pulmonary Embolism
Wound Dehiscence
Bleeding
Bowel Obstruction
DVT
Delirium
Renal Failure
Anastomotic Leakage
0
1
2
3
4
5
6
Odds Ratio



Supplementary Figure 5.1 The Association between Muscle Abnormalities and Each Individual Complication

(A) Low SMI and Individual Complication; (B) Low SMD and Individual Complication. SMI=skeletal muscle index, SMD=skeletal muscle radiodensity, SSI=surgical site infection, UTI=urinary tract infection, DVT= deep vein thrombosis

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Chapter 6 Final discussion

6.1 Introduction

Skeletal muscle, as one of the key anabolic organs, plays an important role in mediating metabolism and is associated with multiple clinical outcomes during cancer disease trajectory. This research quantified skeletal muscle mass and the amount of fat infiltrated into muscle by using computerized tomography (CT) imaging assessment method to: 1. identify the prevalence and predictors of muscle abnormalities (i.e. low SMI=skeletal muscle index and/or low SMD=skeletal muscle radiodensity) among patients with non-metastatic colorectal cancer (CRC); 2. examine the associations between Charlson comorbidities with each muscle abnormality in non-metastatic CRC patients; 3. investigate the effect of muscle abnormalities on short-term clinical outcomes after resection surgery among colon cancer patients. This discussion summarizes key findings of three individual studies presented in previous chapters and considerations for future research.

6.2 Characteristics and Predictors of Muscle Abnormalities among Non-metastatic Colorectal Cancer Patients (Chapter 3)

In Chapter 3, we aimed to determine whether low SMI (i.e. sarcopenia) and low SMD were prevalent among non-metastatic CRC patients and to describe the variation of SMI and SMD across sex, age, body mass index (BMI) and race/ethnicity groups. We also determined the demographic [i.e. age, total adipose tissue (TAT), race/ethnicities, smoking history, alcohol use, Charlson comorbidity score] and clinical (i.e. cancer stage, cancer site) determinants of sarcoepnia and/or low SMD. It was hypothesized that both sarcopenia and low SMD were highly prevalent in males and females. It was also hypothesized that age, TAT level, and race/ethnicities were independent predictors of sarcopenia and low SMD.

In this study, we reported that 45.3% males and 39.5% females with early stage CRC were sarcopenic. Therefore, we demonstrated our hypothesis of a sarcopenia prevalence exceeding 30% (reported in the elderly) (Cruz-Jentoft et al., 2014) with a higher incidence in males. The sex difference in muscle mass is consistent with previous investigations with a higher muscle mass or SMI generally observed in male cancer patients (Martin et al., 2013; P. D. Peng et al., 2011; Voron et al., 2015). The prevalence of low SMD were also close to 30% in both sexes with a non-significant difference by sex (30.9% females versus 28.4% males). The prevalence of low SMD hereby reported was relatively lower than that of a previous large-scale study (N=1,473) of lung and gastrointestinal cancer patients (49%), which might be attributed to our inclusion of only non-metastatic patients (Martin et al., 2013). Patients with advanced stage of disease had received chemotherapy or radiation treatment. Several recent studies reported significant muscle mass and/or SMD decline during treatment in lung cancer (Stene et al., 2015) and CRC patients (Blauwhoff-Buskermolen et al., 2016), which might explain the relatively higher prevalence of low SMD among cohorts of patients with advanced stage cancers (Blauwhoff-Buskermolen et al., 2016; Martin et al., 2013).

Chapter 3 analysis demonstrated age, TAT and race/ethnicities were significant predictors of sarcopenia and low SMD. Most previous studies have reported a negative relationship between advanced age and SMI in either cancer or non-cancer populations (Kyle et al., 2001; Lieffers et al., 2012), and a limited number of studies found a negative relationship between age and SMD in patients with or without cancer (Esfandiari et al., 2014; Miljkovic et al., 2016; Weinberg et al., 2017). Nevertheless, the current study is the first to simultaneously investigate the risks of sarcopenia and low SMD stratified by age groups, highlighting dose-response associations of age with each muscle abnormality in CRC patients. Of note, the effect

of age was more pronounced for low SMD than that for sarcopenia within each age group. No studies directly compared rates of age-related change in muscle mass and radiodensity among cancer patients. Nevertheless, up to 18% increase in intermuscular adipose tissue over one year has been reported among older adults (Goodpaster et al., 2008). In another five-year longitudinal study in elderly adults, an increase in intermuscular adipose tissue independent of weight change (i.e. gain, loss or stable) has been reported, whereas muscle mass either increased or decreased depending on weight change (Delmonico et al., 2009). Therefore, fat infiltration was a more consistent age-associated characteristic than muscle loss, and was not confounded by weight change.

Most previous investigations in cancer patients have demonstrated that different BMI levels are associated with variable SMI and SMD (Fujiwara et al., 2015; Martin et al., 2013). We described the diverse distribution of muscle abnormalities across TAT levels rather than BMI and determined the effect of TAT on muscle abnormalities using fully-adjusted multivariable models. As we hypothesized, patients with higher TAT levels had lower risk of having sarcopenia, but greater risk of having low SMD. A recently published study in non-metastatic breast cancer patients also reported similar associations (Weinberg et al., 2017). Additionally, a positive relationship between BMI/TAT and SMI and a negative relationship between BMI/TAT and SMD has been reported in other cancer cohorts (Esfandiari et al., 2014; Martin et al., 2013). The majority of patients in our cohort were overweight or obese (67.3%), and previously published data from our study cohort demonstrates that patients in the overweight/obese categories were less likely to have sarcopenia (Caan et al., 2017). A physiological increase in lean mass with increasing adipose tissue has been previously reported across age groups (Bosy-Westphal & Muller, 2015), which partially explains the lower risk of sarcopenia in patients with

high TAT in our study. The higher risk of low SMD associated with higher TAT is likely explained by a defect in the capability of adipose tissue to store lipids with a consequent overflow of lipids into muscle. Likewise, morphological alterations in muscle fiber may allow for more lipid storage within muscle (Gallagher et al., 2005; Marcus et al., 2010).

Several earlier studies using small or large nationally representative samples have investigated differences in muscle mass and adipose tissue distribution by race/ethnicities (Aloia, Vaswani, Mikhail, & Flaster, 1999; Chumlea et al., 2002; Ortiz et al., 1992). Although none of these studies were in cancer patients and most of them used other body composition tools, African Americans presented with higher muscle mass compared to Caucasians. Based on this evidence, we hypothesized African Americans would present with higher SMI than Caucasians. This difference was assessed by comparing mean SMI values between these two race/ethnicity groups in models adjusted by age, sex and BMI. Further fully-adjusted regression analysis showed a lower risk of sarcopenia among African Americans compared with Caucasians. Differences in SMD by race/ethnicities have been less investigated with no comparability among studies. One study compared intermuscular adipose tissue between men with African Ancestry and Caucasian men, and reported a greater intermuscular adipose tissue in the former group (Miljkovic et al., 2009). In contrast, another large-scale multi-ethnic study reported higher intermuscular adipose tissue in Caucasians than African Americans (Shah et al., 2016). Data from the National Health and Nutrition Examination Survey demonstrated that African American females had the highest total and percentage body fat, followed by Mexican Americans and Caucasians, while no ethnic difference in fat was observed among males (Chumlea et al., 2002). In contrast, we found African Americans had the lowest TAT compared with other race/ethnicities for both sexes. This difference might be partially explained by adipose tissue

distribution. In our study, African Americans presented the lowest visceral adipose tissue and the highest subcutaneous adipose tissue. Nevertheless, the difference in visceral adipose tissue was more pronounced than that of subcutaneous adipose tissue among race/ethnicities, which might collectively result in the lowest TAT observed in African Americans. Additional research is needed to investigate fat distribution and/or skeletal muscle composition differences across race/ethnicity groups and to determine the mechanisms contributing such differences.

Findings from Chapter 3 also demonstrate the need for future studies to develop age, sex, BMI and race/ethnicities specific definitions for each muscle abnormality. In this Chapter, we used a binary approach to define muscle abnormalities for each sex and stratified the cutoffs of sarcopenia by BMI. This convenient stratification approach was established based on the associations of SMI/SMD with long-term survival outcome (Caan et al., 2017). Although these cutpoints were stratified by sex and BMI, patients might still be misclassified due to race/ethnicities differences. For example, sarcopenia prevalence might be underestimated for African Americans as they have the highest SMI among all race/ethnicities. Given extensive differences in SMI and SMD associated with age, sex, BMI and race/ethnicity in the current study and previous literature (Esfandiari et al., 2014; Martin et al., 2013; Weinberg et al., 2017), attempts should be made to develop subgroup cutoff values for muscle abnormalities that account for these differences. This can be pursued in future large-scale population studies with sufficient statistical power.

In summary, this is the first study to report determinants of muscle abnormalities in non-metastatic CRC patients and describe the variability of body composition components in this patient cohort. These findings could be used to identify patients who are at risk of sarcopenia and

low SMD at the time of diagnosis, and to guide interventions for body composition modification earlier in the disease trajectory.

6.3 Associations of Pre-existing Comorbidities with Skeletal Muscle Mass and Radiodensity in Early Stage Colorectal Cancer (Chapter 4)

In Chapter 4, we investigated whether the Charlson comorbidity score is associated with muscle abnormalities and identified the individual comorbid conditions predicting muscle abnormalities. Given the high prevalence of sarcopenia and shared mechanisms of muscle loss and fat infiltration into muscle across different chronic diseases (Anker et al., 2014), it was hypothesized that a higher Charlson comorbidity score would be associated with a higher risk of both sarcopenia and low SMD. Opposed to our hypothesis, this association was only evident for low SMD, not sarcopenia. We also demonstrated that myocardial infarction, congestive heart failure, peripheral vascular disease, diabetes with or without complications and renal disease each independently predicted the presence of low SMD at CRC diagnosis. However, most of these diseases were not associated with sarcopenia and only patients with complicated diabetes had a higher risk of having sarcopenia.

The importance of SMD has also been highlighted in a couple recent studies where low SMD, but not sarcopenia had a prognostic relationship with survival in cancer patients (Antoun et al., 2013; Rollins et al., 2015). Therefore, it is reasonable to assume that low SMD might be an earlier indicator of disease progression than muscle loss. Newly diagnosed CRC patients who have any of the above six co-existing chronic conditions might be at even greater risk of adverse clinical outcomes compared to patients without these comorbidities, due to the higher likelihood of having low SMD. However, further research is needed to examine whether fat infiltration is the common mechanism linking these comorbidities to worse clinical outcomes.

The finding from this study is innovative, as no previous study has presented the associations of comorbidities with both sarcopenia and low SMD within a singular cohort of cancer patients with robust model adjustment. The limited number of studies investigating comorbidities and muscle abnormalities in CRC previously reported associations of comorbidities with only one muscle abnormality and did not adjust for any confounding factors, such as age, sex, BMI and stage (Lieffers et al., 2012; Sabel et al., 2013). Lieffers et al. only reported the unadjusted relationship between sarcopenia and a few comorbidities among CRC patients, and reported a higher prevalence of sarcopenia in patients with cardiac arrhythmias, hypertension, chronic pulmonary disease, diabetes, hypothyroidism, anemia, or fluid and electrolyte disorders (Lieffers et al., 2012). In a cohort of colon cancer patients, Sabel et al. reported lower mean SMD values in patients with cardiac disease, pulmonary disease, diabetes, or prior non-CRC cancer, compared to those of patients without the corresponding disease (Sabel et al., 2013).

Although there are commonalities in the etiology of muscle loss and intramuscular infiltration across chronic diseases [e.g. aging, mitochondrial dysfunction, inflammation, and insulin resistance (Marcus et al., 2010; Schrauwen-Hinderling et al., 2006)], the different associations between sarcopenia and low SMD with comorbidities suggest different mechanistic pathways impacting comorbidities and SMI and SMD. For example, reduced capability of subcutaneous adipose tissue to store fat and impairment in lipid metabolism may have a more profound effect on inducing intramuscular fat than muscle breakdown (Vettor et al., 2009). Future experimental studies are warranted to clarify the mechanisms of fat infiltration into muscle in CRC patients who have these comorbidities. Despite the unknown mechanisms,

findings from Chapter 4 provide promising future directions to explore the mechanism and clinical implications of fat infiltration into muscle.

6.4 CT-measured Muscle Abnormalities are Associated with Worse Prognosis in Patients Undergoing Colon Resection Surgery (Chapter 5)

Chapter 5 focused on the prognostic significance of muscle abnormalities on adverse surgical outcomes in a subgroup of colon cancer patients whose CT scans were collected 60 days prior to cancer resection. This study primarily aimed to assess the independent effect of sarcopenia and low SMD in mutually adjusted multivariable models including a comprehensive set of covariates (i.e. age, cancer stage, race/ethnicities, comorbidities, TAT, smoking history and alcohol use). It was hypothesized that both sarcopenia and low SMD would independently place patients at a higher risk of having any complications, longer LOS, readmission after discharge and death after surgery compared to patients without muscle abnormalities.

As hypothesized, both muscle abnormalities were independently associated with a higher likelihood of prolonged LOS after surgery. Patients with sarcopenia were additionally more likely to have any complications and have higher short-term mortality risk. These findings were independent of TAT level and other demographic and clinical covariates. Most previous studies only measured and reported sarcopenia without considering SMD and/or adipose tissue (K. I. Jones et al., 2015; Lieffers et al., 2012; Miyamoto et al., 2015; P. D. Peng et al., 2011; Reisinger et al., 2016; J. L. van Vugt et al., 2015). The impact of adipose tissue, particularly visceral adipose tissue, on adverse clinical outcomes in cancer patients has been previously illustrated (Xiao et al., 2016). In Chapter 3, we demonstrated that SMI and SMD had positive and negative associations with TAT respectively. Taken together, adipose tissue is considered a significant

confounding factor and should be included in multivariable models examining the association between muscle abnormalities and adverse surgical outcomes.

Two additional novel findings emerged from this investigation. This was the first study to report the combined effect of sarcopenia and low SMD in colon cancer patients. Additionally, patients who had both muscle abnormalities were at even higher risk of unfavorable outcomes (i.e. prolonged LOS and 30-day mortality) after surgery than those who had neither muscle abnormalities. In supplementary analysis, we compared the prediction power for mortality outcome by including either SMI or SMD individually or both in multivariable models adjusted by age, sex and stage. Including both SMI and SMD significantly improved the power to predict mortality compared to including either SMI or SMD individually. This further demonstrated the importance of measuring the quantity of both muscle mass and the fat infiltrated into muscle.

The phenotype analysis was used to classify patients based on muscle abnormalities and TAT levels in this study. The results revealed that patients at extreme TAT levels (i.e. highest or lowest tertile) with any concurrent muscle abnormality were at higher risk of poorer outcomes (i.e. any complications or prolonged LOS). In contrast, moderate levels of TAT did not increase risk regardless of the presence of muscle abnormalities, which might be related to the fat distribution (i.e. proportion of visceral and subcutaneous adipose tissues) and the interactions between muscle and adipose tissues. It has been hypothesized that the increased secretion of pro-inflammaroty cytokines from adipose tissue and decreased secretion of anti-inflamamtory cytokines from muscle can lead to an immune deficiency status among patients undergoing surgery (Hamaguchi et al., 2016; Lutz & Quinn, 2012). Surgical stress and its related blood loss, and patient specific factors such as older age and the presence of comorbidities might add additional burden to patients' immune function. The collective burden of the above factors is

likely to increased the risk of complications and prolonged LOS in patients with concurrent muscle abnormalities and extreme TAT levels.

In summary, risk stratification from this study identified particularly high-risk patients who may need close surveillance and individualized intervention strategies to modify body composition before and during treatment. In addition, the integration of CT-assessed body composition into surgical care and its impact on improving healthcare quality need to be explored.

6.5 Limitations and Considerations for Future Research

Common limitations among the three studies presented in this thesis should be considered when interpreting the findings. The cause-effect relationships between exposure and outcome measurements could not be determined due to our cross-sectional study design. Patients' electronic medical record (EMR) lacks comprehensive data on factors such as dietary intake and physical activity, which may confound the findings. Additionally, in Chapter 5, several pre- and post-surgical factors that could potentially influence short-term outcomes were not accounted for such as operative time, intraoperative blood transfusion and temporary diverting stoma, as these were not available (Qu, Liu, & Bi, 2015). Another limitation is the lack of muscle function measurement (e.g. muscle strength and physical performance) in patients' EMR. Muscle function is one component of sarcopenia definition in the aging literature (Cruz-Jentoft et al., 2014), and it is increasingly recognized to be more important than absolute mass in terms of disability risk and mortality (Clark & Manini, 2012; Mitchell et al., 2012). In terms of outcomes, several clinical trials investigating therapeutic agents for cancer cachexia or sarcopenia have reported that muscle strength did not improve in parallel with the increase in muscle mass or body weight (J. M. Garcia et al., 2015; Schroeder et al., 2012; Srinath & Dobs, 2014; Temel et al., 2016).

Considering the importance of muscle function for disease risk and as an endpoint for the efficacy of pharmacological or lifestyle interventions in clinical trials, future studies assessing both muscle mass and function are needed to better understand their independent prognostic impact. A recent study in older adults with cancer evaluating both SMI and SMD found SMD was more associated with physical function than muscle mass, suggesting SMD might be an indicator of muscle strength (G. R. Williams et al., 2017). However, more research is needed to investigate to what extend SMD is correlated to muscle function.

Several considerations should be discussed to move the field of body composition in oncology forward. Total muscle cross-sectional area at lumbar region has the best correlation with whole body muscle mass in both cancer and non-cancer patients (Mourtzakis et al., 2008; Shen et al., 2004), therefore our study adopted quantification of total lumbar muscle cross-sectional area, which includes psoas, erector spinae, quadratus, lumborum, transverse abdominis, external and internal obliques, and rectus abdominus. The majority of previous literature focused on the consequences of systemic muscle loss versus that of individual muscles (Bahat et al., 2016; Batsis et al., 2013). However, we noticed widespread use of a single-muscle approach, especially the use of the psoas muscle alone (as reviewed in Chapter 2). Searching for a more rapid and simple quantification method for sarcopenia diagnosis is understandable, but several concerns have been recently raised regarding this approach (V. E. Baracos, 2017). First, the psoas muscle makes up less than 10% of total trunk muscles and its correlation with total lumbar muscle area is low; therefore, it may not reflect systemic muscle loss (Rutten et al., 2017). As psoas muscle is an asymmetrical muscle, imputation of its area from measures of length and width can lead to high measurement inconsistency and inter-observer variation (V. E. Baracos, 2017). The use of total muscle area versus single muscle groups precludes comparison among

different study findings. Semi- or fully- automated programs are available allowing more efficient and cost-effective body composition assessment in large healthcare centers, and should be explored in future, large-scale studies. (Chung H, 2009).

In addition to differences in muscle quantification methods, heterogeneity of muscle abnormality definitions has been noticed across studies. The current project adopted previously defined cohort-specific cutoffs stratified by sex and BMI (Caan et al., 2017). The approach for developing these cutoffs was based on maximally selected rank statistics as described by Lausen et al. (Berthold Lausen, 1992). Specifically, long-term mortality risks were first estimated on the continuous distribution of SMI or SMD, and for each candidate cut point, log-rank statistic was computed to test between group differences in mortality risk (Berthold Lausen, 1992). The optimal cutoff was determined based on the maximum absolute value of the log-rank statistic test. This approach has been used in many surgical studies to define muscle abnormalities (Achim et al., 2017; Lou et al., 2017; Nakanishi et al., 2017; P. D. Peng et al., 2011; Reisinger et al., 2015; Van Rijssen et al., 2017; Voron et al., 2015). However, instead of developing cohort-specific cutoffs, many studies adopted previously published cutoffs. The two most commonly used references were Prado et al. (Prado et al., 2008) and Martin et al.(Martin et al., 2013). As one of the earliest studies to investigate muscle abnormalities in cancer patients, Prado et al. (Prado et al., 2008) focused on the subgroup of obese patients, therefore their cutoffs may not be appropriate for non-obese patients. Our study and Martin et al. (Martin et al., 2013) both have shown a relatively higher SMI threshold value in patients who were overweight/obese compared to patients who were not, further suggesting the need for BMI stratification when developing muscle abnormality cutoffs. Race/ethnicity difference is another factor to consider. The cohorts in Prado et al. (Prado et al., 2008) and Martin et al. (Martin et al., 2013) were primarily

Caucasians, whose muscle mass and radiodensity are lower than African Americans and Hispanic/Latinos (as discussed in Chapter 3). Therefore, the application of these cutpoints to race/ethnicities other than Caucasians warrants caution. Currently, no consensus values for defining CT-based muscle abnormalities have been established in African American and Hispanic/Latino populations. Asian studies in cancer have developed cohort-specific cutoff values using optimal stratification in relation to survival (Fujiwara et al., 2015; Huang et al., 2017; Zhuang et al., 2016). Among these, the largest scale investigation (n=1,257) was in a cohort of Japanese patients with hepatocellular carcinoma, in which cutpoints were developed for sarcopenia (36.2 cm^2/m^2 and 29.6 cm^2/m^2, males and females respectively) and low SMD (males 44.4 HU, females 39.3 HU) (Fujiwara et al., 2015). While these low SMD cutpoints were comparable to ours, their sarcopenia cutpoints were much lower, suggesting the need for race/ethnicity specific muscle abnormality cutoff values. Future validation studies are needed to test whether these cutoffs are applicable for Japanese and other Asian cohorts.

Although dichotomization is a convenient approach to classify patients into high versus low risk groups, great variations in SMI and/or SMD still exist within high or low risk groups. For example, in the current study, median SMI values were 53.8 cm^2/m^2 (range 38.6 to 95.6 cm^2/m^2) for the non-sarcopenic group and 42.6 cm^2/m^2 (range 24.3 to 54.3 cm^2/m^2) for the sarcopenic group. In a recent non-small cell lung cancer study, chemotherapy dose adjusted by lean soft tissue was associated with grade three or four hematologic toxicity outcome (Sjoblom et al., 2017). Using the group mean dose per kilogram of lean soft tissue as reference, the risk of toxicity became greater or lower with increasing or decreasing percentage deviation from the group mean, respectively. This finding indicates a possible linear association between muscle

mass and clinical outcomes; therefore, patient risk stratification using muscle as a continuous variable should be further explored.

Compared to the majority of previous surgical literature where only one type of muscle abnormality was measured or those not controlling for confounding effect of adipose tissue, we were able to address the independent and additive effect of muscle abnormalities with the adjustment of TAT levels. Nevertheless, the contribution of each specific adipose tissue for surgical outcomes needs further investigation. Adipose tissue is regarded an active endocrine organ, and each component has a unique genetic profile and specific associations with metabolic health (Xiao et al., 2016). Few studies have used optimal stratification to define both muscle and adipose tissue abnormalities, and explored the association between these abnormalities and long-term survival outcomes (Fujiwara et al., 2015; Okumura et al., 2017). Nevertheless, these studies used a ratio between visceral adipose tissue and subcutaneous adipose tissue to represent adipose tissue abnormality without clarifying the independent effect of each specific component. CT imaging allows the understanding of the highly complex nature of body composition, which can potentially relate to clinical outcomes independently or synergistically (Fujiwara et al., 2015; Huang et al., 2015; Prado et al., 2008). The complex and dynamic interactions between muscle mass, fatty infiltration to the muscle, and each adipose tissue component need further investigation in both experimental studies and epidemiological studies using robust statistical analyses, beyond exploring the number of abnormalities to better understand the optimal approach for patient risk stratification.

Regardless of these methodological concerns, most investigations so far have consistently identified sarcopenia as a prognostic factor for adverse surgical outcomes. Preoperative rehabilitation care to modify body composition, either increasing muscle mass or muscle

radiodensity should be conducted, and its respective impact on adverse surgical outcomes explored. Previous investigations have shown that fat infiltration was responsive to exercise in non-cancer individuals (Marcus et al., 2010), and that cancer patients had anabolic potential (Prado et al., 2013). Current evidence in evaluating the efficacy of prehabilitation on postoperative outcomes among cancer patients is still limited (Bruns et al., 2017; Santa Mina et al., 2014). Future clinical trials are warranted to test whether the window of time between cancer diagnosis and surgery is an opportunity to initiate interventions to increase muscle mass and radiodensity.

6.6 Conclusion

Muscle abnormalities, both sarcopenia and low SMD, are prevalent in non-metastatic CRC patients at cancer diagnosis and also before surgery. A great variability in SMI and SMD exist across age, sex, BMI and race/ethnicity groups. Patients who had pre-existing comorbidities are at particularly increased risk of low SMD, which might be an early indicator of disease progression and further muscle loss. Understanding the independent and combined prognostic impact of these two muscle abnormalities may improve risk prediction pre-operatively and guide treatment plan. Taken together, this work suggests patients who have sarcopenia and/or low SMD are at increased risk for adverse treatment outcomes. CT-assessed body composition provides a plethora of prognostic information, and its use in the context of surgical care as a standard oncology biomarker should be explored. Future interventional studies attempting to maintain or increase SMI and SMD may prevent the occurrence of complications, mortality and prolonged hospital stays after surgery.

6.7 References

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