MUSCLE ASSESSMENT THROUGH THE NUTRITION FOCUSED PHYSICAL EXAM COMPARED TO SKELETAL MUSCLE INDEX MEASURED BY CT IMAGING

By

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Table Of Contents

List of Tables

List of Figures

List of Abbreviations

ADL: activities of daily living

AND: Academy of Nutrition and Dietetics

ASPEN: American Society for Parenteral and Enteral Nutrition

BIA: bio-electrical impedance analysis

BMI: body mass index

CKD: chronic kidney disease

CT: computed tomography

DEXA: dual-energy x-ray absorptiometry

EMR: electronic medical record

EWGSOP: European Working Group on Sarcopenia in Older People

HU: Hounsfield unit

L3: 3rd lumbar

MRI: magnetic resonance imaging

NCP: Nutrition Care Process

NFPE: Nutrition Focused Physical Exam

PEMS: protein-energy malnutrition scale

PG-SGA: Patient-generated Subjective Global Assessment

RDN: registered dietitian nutritionist

SGA: Subjective Global Assessment

SM: skeletal muscle

SMA: skeletal muscle area

SMI: skeletal muscle index

US: ultrasound

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Abstract

Research Outcome: The Nutrition Focused Physical Examine (NFPE) is a tool, primarily used by Registered Dietitian Nutritionists (RDNs), to assess subcutaneous fat and muscle stores to aid in the diagnosis of malnutrition. The overall goal of this study was to compare and contrast muscle assessment from the NFPE to skeletal muscle index (SMI) measured by CT imaging.

Methods: SMI was calculated from single cross-sectional CT scans of the 3rd lumbar in 14 oncology and 12 organ transplant patients. Mid upper-arm circumference (MUAC) was also measured in all participants. We described the relationship between SMI, MUAC and muscle status using unpaired t-test. Cohen kappa was used to evaluate inter-rater reliability of muscle assessment from the NFPE.

Results: Participants with moderate and severe muscle loss had significantly lower SMI compared to individuals with normal or mild muscle loss (unpaired t-test; p-value: 0.0126). MUAC was also significantly lower in those with moderate and severe muscle loss (unpaired t-test; p-value: 0.0180). There was substantial agreement between observers for the NFPE (Cohen kappa: 0.649; SE: 0.111).

Conclusion: Muscle status evaluated by NFPE strongly correlates with SMI and MUAC and its accuracy appears to be diminished with increases in BMI. Results from this study suggest that NFPE is an effective tool in capturing broad muscle status in transplant and oncology patients. Furthermore, our results demonstrate that those competent in NFPE assessment procedures demonstrate good inter-rater reliability. Future studies are needed to determine if SMI and NFPE can delineate more specifically between normal, mild, moderate and severe muscle loss.

Chapter 1 Introduction and Specific Aims

Malnutrition is characterized by an imbalance in nutritional status, including both excessive and limited levels of intake. In the clinical setting, patients often present with conditions that both increase their nutritional needs, as well as impact their ability or desire to eat. Therefore, undernutrition is the most common form of malnutrition seen in the healthcare setting. Malnutrition can play a significant role in the loss of both lean and adipose tissue as well as reduced functional status, a syndrome called sarcopenia. This condition can manifest in a wide range of clinical settings including oncology, organ failure, geriatrics, and obesity.[1] Malnutrition and the subsequent development of sarcopenia are directly associated with decreased quality of life, increased hospital length of stay, healthcare costs, and morbidity and mortality.[2]

While it is well known that malnutrition is associated with poor health outcomes, and increased morbidity and mortality, screening and assessment tools to diagnose malnutrition have long been a topic of controversy. For example, serum albumin has been considered an indicator of nutritional status in hospitalized patients. However, evidence has shown that serum albumin levels are often reduced during inflammation, a common condition in hospitalized patients.[3] Yet, many clinicians still use this lab value to inaccurately identify malnutrition.

Identifying malnutrition often requires evaluating multiple assessment parameters, including body composition, anthropometrics, client history, nutrition intake and biochemical values. Multivariate screening tools to assess nutritional status date back to the 1970's with the development of "The nutritional metabolic profile",[4] and have proceeded to evolve into tools such as the "Subjective Global Assessment". The "Nutritional Risk Screening-2002" is another assessment tool specific to the inpatient setting and is used to detect the presence of

undernutrition or the risk thereof in a variety of patient populations.[5] Most recently, the Academy of Nutrition and Dietetics (AND or the Academy) and the American Society of Parenteral and Enteral Nutrition (ASPEN) have developed a consensus statement on the identification of malnutrition using six diagnostic criteria including weight loss, nutrition intake, hand grip strength, fluid status, and subcutaneous fat and muscle loss.[2] The Nutrition Focused Physical Examine (NFPE) is a tool, primarily used by Registered Dietitians/Registered Dietitian Nutritionists (RDs/RDNs), to assess subcutaneous fat and muscle stores to aid in the diagnosis of malnutrition. The Academy and APSEN's position is that the NFPE can provide a more accurate assessment of nutrition status, especially when subjective information is unable to be obtained, or time is limited.[6] This technique can also distinguish between moderate to severe malnutrition, providing further information that can help determine the level of intervention required for the patient. While physical palpation assessments can be a very effective tool, they are still subjective in nature. Other tools exist that can provide more objective measurements, including dual energy x-ray absorptiometry (DEXA), magnetic resonance imaging (MRI), ultrasound (US) and computerized tomography (CT) imaging.

CT is a method often used in clinical settings to help diagnose and surveille certain conditions. This technique provides cross-sectional images of body regions and can distinguish between bones, adipose tissue, muscle, organs and air. A vast body if evidence has focused on CT scans at the 3rd lumbar vertebrae using specific muscle index cutoffs to identify sarcopenia and subsequent morbidity and mortality rates.[7] Although CT imaging can provide some of the most accurate information in regards to body composition, and subsequently nutritional status, they are not indicated or available for all patients in a clinical setting. Additionally, using CT scans to analyze body tissues requires additional training and software. Due to the limitation

associated with methods such as CT imaging, this further exemplifies the importance of having other methods for bedside muscle assessment, such as the NFPE.

Although the NFPE is becoming more widely used, in conjunction with the Academy and APSEN malnutrition consensus statement, in the clinical setting to identify malnutrition, little is known about how results from this subjective assessment of muscle mass compared to objective assessment measures like CT imaging. The overall goal of this study is to compare and contrast muscle assessment from the NFPE to SMI measured by CT imaging.

Specific Aims and Hypothesis

Primary Aim 1: To describe how muscle assessment, measured through the NFPE, compares to SMI, measured through CT imaging

> **Hypothesis 1:** Subjects with moderate and severe muscle depletion, determined by the NFPE, will have lower mean SMI and are more likely to be sarcopenic.

Primary Aim 2: To determine how BMI impacts the accuracy of muscle assessment through the NFPE

> **Hypothesis 2:** Moderate and severe muscle depletion in overweight and obese subjects will be more accurately identified by CT imaging compared to muscle assessment using the NFPE.

Primary Aim 3: To evaluate the interobserver reliability of muscle assessment using the NFPE and how reliability is impacted by BMI.

Hypothesis 3: Muscle assessment using the NFPE will demonstrate positive interobserver reliability among assessors, and interobserver reliability will decrease with an increase in BMI.

Secondary Aim 1: To describe how quality of life is related to muscle mass, described by the NFPE and CT imaging.

Secondary Hypothesis 1: Participants with lower muscle mass, as indicated by NFPE and CT imaging, will have lower quality of life scores.

Exploratory Aim 1: To describe how MUAC measurements are related to muscle mass, described by the NFPE and CT imaging.

Exploratory Hypothesis 1: Participants with lower muscle mass, as indicated by NFPE and CT imaging will have lower MUAC measurements.

Exploratory Aim 2: To describe how frailty scores in organ transplant subjects are related to muscle mass, described by the NFPE and CT imaging.

Exploratory Hypothesis 2: Subjects with lower muscle mass, as indicated by NFPE and CT imaging will have higher frailty scores.

Chapter 2 Background

In adults, lean muscle mass accounts for up to 60% of total body mass, and begins to decline in a linear fashion after age 40 in most adults.[8] Loss of lean muscle mass is associated with decreased functional status, frailty, and the development of many acute and chronic diseases.[9] Skeletal muscle (SM) plays a crucial role in maintaining functional capacity and retaining the ability to carry out activities of daily living (ADL). ADLs are considered the essential physical abilities required to manage basic needs including hygiene, grooming, dressing, eating, and ambulating. Decline in ADLs are directly related to decreased quality of life, increased hospitalization and increased mortality and morbidity.[10] Furthermore, ADL decline is directly related to physical disabilities, increased nursing home admission, depression, and an overall loss in independence.[11] Selva et al.[12] explored the role of muscle quality, defined using ultrasound measurements of the vastus lateralis, vastus intermedius, rectus femoris, and gastrocnemius in older adults. Researchers found that reduced muscle quality was an independent risk factor for reduced functional capacity when measuring dynamometry, knee-extension, 6-m fast walk, timed up and go, stair climb and descent and vertical jump test.

Various health conditions are associated with reduced SM such as obesity, liver disease, kidney disease, [13-15] heart disease,[16] and cancer,[7] and these can often limit physical ability.[17] Additionally, age-related muscle loss is a common manifestation seen in the elderly population, and it is estimate that approximately 8% of SM is lost per decade after age 40.[18] The natural generation of reactive oxygen species (ROS) by skeletal muscle is another factor which can contribute to SM loss. Under normal, healthy, physiological conditions, antioxidant systems work to neutralize ROS, which minimizes their potential damage to lipids, DNA, and proteins. However, under states of inflammation and stress, as seen in many acute and chronic conditions,

or in aged individuals, the production of ROS can outweigh the antioxidant systems or the antioxidant system can be impaired, which leads to an overall negative protein balance, and in turn SM breakdown.[18] SM loss can also contribute to an increased risk of medication toxicity due to its role in drug metabolism.[19,20]

The two most significant strategies to maintain SM involve adequate nutrition,[21] and physical activity.[16,18,21] The human body does not contain a reservoir of amino acids, which is why adequate protein intake is so important. When there is either insufficient protein intake or increased metabolic demands, the body will liberate amino acids from skeletal muscle, resulting in muscle catabolism.[22] Insufficient dietary intake and muscle catabolism are key components that can contribute to conditions like malnutrition.

Malnutrition

Malnutrition is a condition characterized by an imbalance in nutritional status and can play a significant role in the loss of both lean and adipose tissue as well as reduced functional status. Historically, global definitions have been used to further classify subcategories of malnutrition including: undernutrition or stunting, wasting, underweight, overnutrition including overweight and obesity, and micronutrient-related malnutrition.[23] According to the World Health Organization, over 2 billion adults world-wide are affected by some form of malnutrition.[24] While malnutrition poses a significant burden on global health, it also exists within clinical settings. Individuals found in home-care, long-term care, and acute-care facilities often present with malnutrition.[25] It is estimated that approximately 50% of all hospitalized patients are malnourished.[26,27] Certain conditions place individuals at an increased risk for malnutrition, often due to comorbidities and complications associated with these disease states. An increased

prevalence of malnutrition is often seen in patients with various forms of cancer, those anticipating organ transplant, and gastrointestinal (GI) tract, cardiac, and respiratory conditions.[1,7,14] Hospitalized patients who are malnourished experience increased length of stay and medical costs, and higher rates of mortality compared to well-nourished patients.[28] Individuals with overweight or obesity can also experience malnutrition despite having increased body weight. Acute and chronic complications result in altered metabolic demands, and this, in combination with inadequate energy and nutrient intake place many hospitalized patients at an increased risk for malnutrition, including those who are overweight and obese.[17] Low lean mass in the setting of overweight and obesity, referred to as sarcopenic obesity, also leads to poor health outcomes as seen in those who are normal and underweight.[17]

Sarcopenia

The term "sarcopenia" was first introduced in 1989 by Irwin Rosenburg to describe the process of age-related muscle loss. Historically, the term has been used in the context of the elderly population, where the simple act of aging results in a natural loss in lean muscle mass. However, other etiologies can result in the development of sarcopenia at any life-stage. In 2009 the European Working Group on Sarcopenia in Older People (EWGSOP) convened to develop a working definition, and determined that diagnosis requires both muscle loss, and reduced muscle function.[1] Other definitions for sarcopenia exist, all with varying diagnosis cutoffs, however, all focus on both muscle loss and reduced muscle function.[11] Due to the losses in lean muscle, and subsequent decline in functional capacity, sarcopenia places a significant burden on public health. Sarcopenia is often associated with an increased risk of falls, and numerous comorbidities including osteoporosis and bone fractures, endocrine dysfunction, and organ failure. Furthermore, sarcopenia is prevalent among hospitalized patients with varying conditions.[11]

Sarcopenia can also be present in the setting of obesity. This condition is characterized by a loss in muscle mass with a subsequent increase in adipose tissue.[17] This makes the identification of sarcopenic obesity difficult as individuals may present with high body weights or body mass index scores (BMI), yet a significant loss of lean tissue may be present. Similar to other populations, sarcopenic obesity is often attributed to reduced physical capacity, also referred to as "disuse syndrome" and inflammation. In disuse syndrome, a lack of mobility and physical activity results in muscle atrophy. Inflammation associated sarcopenia is associated with an increase in pro-inflammatory cytokines, resulting in increased metabolic demands and overall catabolism.[17] Hospitalized sarcopenic obese individuals experience significantly reduced functional status and survival rates compared to sarcopenic free obese individuals with cancer.[7] Additionally, sarcopenic liver transplant patients experience poor survival and increased mortality rates.[14,15]

It is important to realize that sarcopenia and malnutrition play a significant role in the loss of muscle mass and subsequent decline in functional capacity. Clinicians need to identify signs of muscle loss, so that appropriate interventions can be applied to improve health outcomes.

Assessment of Nutrition Status

History of Nutritional Assessment

Tools to assess nutrition status have existed for many years. In 1977, Blackburn and colleagues developed a comprehensive nutritional/metabolic profile. It was proposed that by using anthropometric measurements, clinicians could be alerted to moderate or severe malnutrition, and additional testing of serum albumin, transferrin and creatinine height index

could provide an objective confirmation.[4] Historically, serum proteins as well as other biological markers have been used by clinicians to evaluate nutritional status.[3,4,29,30] Over time, research has shown these to be more unreliable than originally believed. For example, albumin has been long used as an indicator of protein intake, however, albumin is a negative acute-phase protein, and is affected by inflammatory conditions, which are often present in a clinical setting.[3] Other examples include prealbumin and transferrin, but these too can be affected by various medical and health conditions, leading to possible misidentification of malnutrition.[3] Furthermore, Ataly et al.[31] observed no significant difference in serum albumin and prealbumin between hospitalized elderly patients categorized as well-nourished and malnourished.

Since no single measurement exists for accurate diagnosis of malnutrition in all individuals, multifactorial screening tools have historically been used for evaluating nutritional status. In 1984, Bernard and Linn published an article on the use of the Protein Energy Malnutrition Scale (PEMS). This was a screening tool to detect protein-energy malnutrition using a form which evaluated anthropometric measurements, clinical history, physical examination parameters, and lab values, resulting in an overall nutrition score.[32] This is one of the earlier attempts to identify the severity of malnutrition in hospitalized patients. The PEMS was further used to assess the nutritional status in head and neck cancer patients who underwent surgery. A PEMS score above 8 was considered malnourished, and a score below 8 was considered well-nourished. An overall higher PEMS score was associated with increased age, prolonged hospital stays, and postoperative complications.[33]

Other multifactorial tools such as global assessments, evaluate biological markers including serums proteins, and creatinine-height index, as well as anthropometric measurements and subjective patient history. In 1982, Baker et al. evaluated the nutritional status of 59 patients

admitted to a general surgery ward using a global assessment screening tool, later classified the Subjective Global Assessment (SGA). The screener included determination of albumin, transferrin, total lymphocyte count, delayed cutaneous hypersensitivity, total body nitrogen and body cell mass via total body potassium. Additionally, anthropometric measurements were gathered including height, weight, mid-arm circumference, wrist diameter, back skinfold thickness, pectoral skinfold thickness, and triceps skinfold thickness. Percent ideal body weight, percentage ideal lean body weight, percentage of body fat and creatinine-height index were calculated, in addition to client history of weight loss, reduced intake, vomiting, diarrhea, and edema. Two clinical examiners assessed study participants and patients were giving one of three classifications: A denoted normal nutrition status, B mild malnutrition and C severe malnutrition. Results demonstrated that patients classified with mild and severe malnutrition experienced increased rates of inpatient infections, and increased length-of-stay. Furthermore, there was 81% interobserver reliability between the two clinical examiners, which has also been demonstrated in subsequent studies.[29,34]

More recently, the SGA has been refined and includes weight loss over the past six months, dietary intake over the past two weeks, GI symptoms, functional status, disease state, muscle status, fat stores and presence of edema. The results provide an overall score on a scale of 1 to 7. A score of 1 through 2 indicate severe malnutrition, 3 through 5 indicate moderate malnutrition, and 6 through 7 indicate well nourished.[35] Sum et al.[36] evaluated the use of the SGA in identifying protein energy wasting among adult patients with stage 5 chronic kidney disease (CKD) undergoing hemodialysis. While the SGA was determined to be an effective tool in identifying CKD patients at risk of protein energy wasting, study results indicated that the SGA may miss over 20% of those at risk and may falsely identify over 40% of those not actually at

risk. Sacks et al.[37] used the SGA to evaluate the nutritional status in older adults, age 65 and older who had been residing in a long-term care facility for greater than two weeks. Individuals classified as severely undernourished were associated with increased mortality rates. 30% of residents were classified as well-nourished, 53% of residents were classified as moderately malnourished, and 17% were classified as severely malnourished. Furthermore, a significant association was found between nutritional status, as determined by SGA, and nutrition associated complication experienced by participants. Mortality was significantly associated with nutritional status, with those designated as severely malnourished experiencing the highest mortality rates.

The patient-generated subjective global assessment (PG-SGA) was adapted from the SGA specifically for cancer patients. The difference between the two assessments is that the PG-SGA includes additional questions, which can be answered by patients in regard to short-term weight loss and nutrition-related symptoms. There is still a physical examination component, which must be completed by a healthcare professional, but the PG-SGA scoring varies in that a higher score indicates severe malnutrition.[38] Cavalcante et al.[39] utilized the PG-SGA in 97 head, neck or abdominal cancer patients to determine if it could predict cancer cachexia, hospitalization time, and mortality. Results demonstrated that of those identified as well-nourished by PG-SGA, 30% developed pre-cachexia, of those identified as moderately malnourished, 38% developed cachexia, and of those identified as severely malnourished, 60% developed refractor cachexia. Additionally, mortality rate within each group was 25%, 55% and 80%, respectively.

The SGA has been shown to demonstrate the greatest sensitivity and specificity in identifying and classifying malnutrition as compared to other multivariate screening tools or single objective measurements.[30] Additionally, the SGA has been utilized in a broad range of conditions and patient populations including, geriatric, oncology, and surgical patients.[29-31,34,37,40]

One of the fundamental components of the SGA is the physical assessment to evaluate body composition, particularly muscle and fat stores.

Malnutrition and the Assessment of Muscle Mass

Muscle mass wasting, loss of subcutaneous fat and fluid accumulation are direct indicators of malnutrition diagnosis according to the Academy and ASPEN consensus statement for adult malnutrition.[2] The workgroup consensus statement identified six characteristics to assess for the presence of malnutrition which include: weight loss, energy intake, body fat, muscle mass, fluid accumulation and grip strength. If a patient meets any two of the six criteria, malnutrition can be diagnosed.[2] To accurately evaluate body fat, muscle mass and fluid accumulation, a physical assessment is required. Anatomical sites to assess fat stores include the orbital region, upper arm region, and thoracic and lumbar region. Assessment of muscle mass involves palpation of temporalis, clavicle region including the pectoralis, deltoids, and trapezius, muscles of the scapula region, interosseous muscle of the hand, quadriceps and gastrocnemius.[41]

According to the Academy's scope of practice, the Nutrition Care Process (NCP) is an important competency for all registered dietitians. The NCP involves using evidence-based practices to perform a comprehensive nutrition assessment, determine a nutritional diagnosis, plan and implement a nutritional intervention, and monitor and evaluate an individual's progress toward goals.[42] The RD/RDN scope of practice specifically states "Food, nutrition, and dietetic services and activities performed by RD/RDNs illustrate current practice and include but are not limited to the following: complete a nutrition-focused physical assessment through an evaluation of body systems, muscle and subcutaneous fat wasting, oral health, suck/swallow/breathe ability, skin condition, appetite, and affect."[42] For this reason, dietitians play a crucial role in the diagnosis of malnutrition, as the NFPE is required competency and fall within their scope of

practice. Additionally, the NFPE is a vital component of the assessment, monitoring, and evaluation domains of the NCP. With that said, criticism of the NFPE exists due to its subjective nature. While the NFPE has become a competency for all supervised practice programs and intensive and standardized training programs exist, concerns over interobserver and intraobserver variability still remain.[41,43] Currently, the NFPE is the primary method RD/RDNs use to assess body composition at the bed side.

Assessing Body Composition

Various methods exist to evaluate body tissue. As discussed previously, the NFPE utilizes physical palpation to assess lean mass and adipose tissue. However, this is considered a subjective method and is aimed at assessing anatomical regions specific to the identification of malnutrition. Other assessment methods are more objective in nature but vary in their precision and indication. Bioelectrical impedance analysis (BIA) is often used to estimate total body water, fat-free mass and fat mass by measuring the resistance of small alternating currents as they pass through the body. BIA is typically only considered useful in describing mean body composition for cohorts of people. Large predictive errors make it unreliable for precise individual assessment, and it is insensitive to small improvements associated with clinical treatment.[44] Additionally, estimations are based on population-specific regression equations that are not always made available by manufacturers, and BIA can overestimate fat-free mass and underestimate fat mass in those with a BMI>40.[45]

DEXA is another popular method used to assess body composition. DEXA is often considered the gold-standard for the assessment of fat mass, lean mass and bone mineral content at the molecular level.[46] DEXA uses two low-energy levels of radiation to differentiate total body adipose and soft tissues, in addition to bone mineral density and content. The two x-ray of

varying photon energy pass through the body and are detected by photon receptors. The amount of energy absorbed, or attenuated, by varying tissues is what allows for the differentiation between body tissues.[45] Another advantage of DEXA scans is that they reduce an individual's exposure to potentially harmful radiation. Radiation from a single DEXA scan is equivalent to one day of background radiation exposure, as compared to a single CT scan which is equivalent to one year of background exposure.[46] Limitations of DEXA as a tool to assess body composition include analysis variations between equipment, manufacturer, and software used.[44,45] This limits the ability for comparison of results between studies and institutions. Additionally, individuals who are taller or overweight may not fully fit on the scanning table.[44] Increased body thickness can affect DEXA results and lead to underestimations of fat mass in individuals with overweight or obesity.[45] Moreover, DEXA is often limited to specialized settings and may not always be indicated or appropriate for hospitalized patients.[45]

MRI is another method that can be used to assess body composition. This technique uses a strong magnetic field to align anatomic protons, which are then activated by a radiofrequency wave, and the protons absorb the energy. When the radiofrequency is turned off, the protons release their energy and return to their original position. The energy released by the protons is detected by a receptor, which generates regional or whole body images. While MRI is considered one of the most accurate methods to assess body composition at the tissue-organ level, it requires specialized personnel, and settings. Additionally, MRI is costly and poses a burden to individuals by requiring them to remain in confined conditions and hold their breath during analysis.[45]

CT imaging utilizes x-ray attenuation, which is measured by a computer program. The program then reconstructs cross-sectional images of a two-dimensional map of pixels. To distinguish between various anatomical features, CT imagining utilizes a measured unit, referred

to as Hounsfield units (HU). These are derived from a linear transformation of the measured attenuation coefficients, and presented as a visual pixel ranging in color from black (air) to white (cortical bone). The reference HU are derived from the radiodensity of air at -1000 HU, and water at 0 HU. Subsequently, the results range from -1000 HU for air, and +2000 units for dense, cortical bone.

Specific HU ranges exist for various body tissues including bone, adipose tissue, muscle, and visceral organs. Due to the ability to observe cross-sections of anatomical regions, and differentiation of body tissues based on HU, CT imaging is considered the gold-standard of body composition analysis at the tissue-organ level.[45] Additionally, CT is unique in that it allows for the identification of intramuscular adipose deposition. Intramuscular adipose deposition is of importance to clinicians as it is often associated with negative clinical and health outcomes.[47] Radiation exposure from CT is relatively high. Therefore, it is often not considered practical in a research setting simply for the purpose of studying body composition as this would expose individuals to repeated doses of radiation.[45] However, CT images can be utilized for research purposes when they are obtained from patient medical records. Identifying appropriate treatment courses and condition monitoring often require the use of CT, therefore, researchers can use retrospective or prospective techniques to evaluate body composition by acquiring existing or planned imaging. Extensive body composition research has been conducted utilizing CT scans in the area of the 3rd lumbar (L3) vertebra. [48] Standard HU ranges have been developed to distinguish between adipose tissue (-190 to -30 HU), skeletal muscle (-29 to +150 HU), and bone (+152 to +1000 HU) in CT scans of the L3 region.[49] It has been determined that CT cross-sectional imagining in this region represent the best correlation with whole body muscle mass.[45]

Single Cross-sectional imaging to Assess Body Composition

Single cross-sectional images from CT scans have been validated as an effective method for determining total body muscle volume. Shen and colleagues,[50] conducted a study in 328 health adults, varying in body size and race, who had whole body MRI scans. Six cross-sectional abdominal images from 10cm below and 15cm above the L_4-L_5 region were included to correlate whole image areas with whole body tissue volumes. The highest correlation found was 5cm above the L4-L5 region, which represents the L3 vertebral region. The L3 cross-sectional slice contains psoas, paraspinal muscles (erector spinae, quadratus lumborum) and abdominal wall muscles (rectus abdominus, internal and external obliques, transversus abdominus).[7] Mourtzakis et al.[51] used similar methods and determined that single cross-sectional CT images in the L3 region of cancer patients also showed significant correlation with whole body muscle. These methods have been further explored in renal cancer,[19] metastatic breast cancer,[20] liver transplant,[14,15] surgical,[52] and obese patient populations.[7]

Analysis of single cross-sectional CT images requires the use of special software programs. These specialty programs allow researchers to analyze multi-slice scanner data, from CT or MRI for example, and easily perform tissue segmentation to differentiate between skeletal muscle, subcutaneous adipose, and visceral adipose tissue.[53] Several multi-slice software programs exist, including SliceOmatic, OsiriX, and FatSeg. Van Vugt and colleagues,[53] conducted a study to investigate the agreement between four commonly used analysis software programs, SliceOmatic, OsiriX, FatSeg and ImageJ. It is important to note that the study population consisted of cancer patients ranging in age from 33 to 81 years, and BMI ranges from 16.5 kg/m^2 to 38.3 kg/m^2. Two medically trained observers were used to analyze scans from the perspective programs, and were blinded to each other's measurements. Results demonstrated

statistically significant inter-software agreements as well as inter-observer and intra-observer agreement. Rollins et al.[54] has further explored the comparison of the two most commonly used software packages, SliceOmatic v5.0, and Osirix v7.5.1. The study participants consisted of 50 patients with varying conditions ranging from trauma, GI bleeding, pancreatic and hepatic pathologies, and renal lesions. While OsiriX demonstrated statistically significant greater SMI, fat free mass (FFM) and mean SMHU values, and significantly lower FFM, there was significantly positive correlations for all measures when the two programs were compared. Rollins and colleagues,[55] have also explored whether the phase of the CT scan, non-contrast, arterial phase, and portovenous phase, affect analysis results using L3 slice analysis software. While statistically significant differences were seen in FM between non-contrast and portovenous phase, no significant differences were seen in SMI or FFM by phase of CT. This indicates that the diagnosis of sarcopenia using L3 CT images should not be affected by phase of CT scan.

Using CT to Identify Sarcopenia

Previously, the most common definition of sarcopenia was an appendicular SMI two standard deviations (SD) below a reference value of healthy adults (5.45 kg/m^2 for women, 7.26 kg/m^2 for men) using DEXA.[56] Abdominal CT slices do not contain appendicular skeletal muscle, thus Prado et al.[7] used L3 SMI to establish their own cutoff values for sarcopenia in obese individuals with cancer. Skeletal muscle was identified using preestablished HU threshold ranges (-29 to +150). The L3 slices were analyzed using SliceOmatic software, and the sum of the L3 cross-sectional muscle areas (cm^2) for each image were recorded. The cross-sectional muscle area of CT L3 slices is linearly related to total body muscle mass, and was normalized for height, resulting in L3 SMI represented as cm^2/m^2. Sex-specific cutoffs of 52.4 cm^2/m^2 for men,

and 38.5 cm^2/m^2 for women were identified and individuals below these values were defined as sarcopenic. Results of their study indicated that obese individuals with sarcopenia experience lower functional status, and sarcopenia was an independent risk factor for survival. Their study provided more evidence that body weight alone is not an efficient indicator of mortality and functional status, and that further assessment of skeletal muscle is warranted.

The use of L3 CT slices and the designated SMI cutoffs for sarcopenia first established by Prado et al.[7] have been widely used in various patient populations. In liver transplant patients, sarcopenia defined by L3 SMI was associated with increased hospital length-of-stay, and increased risk of bacterial infections.[57] Sarcopenia has also been shown to be a predictor of toxicity and time to tumor progression (TTP) in women with metastatic breast cancer undergoing chemotherapy.[20] Antoun et al.[19] also observed increased rates of dose-limiting-toxicity in sarcopenic patients with renal cell carcinoma undergoing chemotherapy compared to non-sarcopenic cancer patients. Martin and colleagues,[58] used L3 SMI to classify cancer patients as sarcopenic, and found that sarcopenia was an independent predictor of reduced survival. A high prevalence of sarcopenia has also been observed in patients with colorectal cancer.[59] Montano-Loza et al.[60] used L3 SMI to identify sarcopenia, sarcopenic obesity, and mysteatosis in patients with cirrhosis. They found that patients identified with sarcopenia, sarcopenic obesity and myosteatosis experienced worse liver function assessed by MELD score, and had an 1.5 to twofold increased risk of mortality, as compared to cirrhotic patients without muscular abnormalities. Meza-Junco et al.[61] also found that sarcopenia, defined using L3 SMI, was independently associated with mortality patients with concurrent cirrhosis and hepatocellular carcinoma.

Much of the existing research utilizing CT scans of the L3 region to assess skeletal muscle are in unhealthy populations. Van der Werf et al.[62] conducted one of the first studies to determine sex-specific percentiles for skeletal muscle area (SMA), SMI and muscle radiation attenuation (MRA). Study participants included 420 healthy living kidney donors with an age range of 20 to 82 years. Additionally, participants varied in BMI from 17.5 to 40.7 kg/m^2. CT scans of the L3 were analyzed using SliceOmatic software, with threshold values of -29 to +150 HU for muscle tissue. In regards to SMI, the study concluded that among healthy individuals, the 5^{th} percentile was identified to be 41.3 cm^2/m^2 for men and 32.7 cm^2/m^2 for women, and SMI below these values indicates sarcopenia. The SMI sarcopenic cutoff values identified by van der Werf et al.[62] of 41.3 cm^2/m^2 and 32.7 cm^2/m^2, are different than those identified by Prado et al.[7] which were 52.4 cm^2/m^2 and 38.5 cm^2/m^2. It is important to note that van der Werf et al. included health participants of varying ages and BMI ranges, whereas Prado et al. only included obese participants.

Malnutrition and sarcopenic-related losses in muscle mass are strongly associated with poor health outcomes and a decline in quality of life. Therefore, it is vital that clinicians assess skeletal muscles to better determine treatment and nutrition interventions aimed at minimizing further losses. While CT images are considered the gold-standard for body composition assessment, they are not always appropriate or available. Criticism on the use of NFPE is that it is subjective in nature, however, it is a simple and low-risk method for muscle assessment at the bedside and research is needed to determine how well it compares to true muscle mass. The overall goal of this study was to compare and contrast muscle assessment from the NFPE to SMI measured by CT imaging.

Chapter 3 Materials and Methods

Study Design

This observational, descriptive study aimed to compare and contrast muscle assessment through the NFPE to SMI measured by CT imaging. This study was conducted at Oregon Health & Science University (OHSU) and included patients seen at the ambulatory transplant and oncology clinics. Subjects were renal or liver transplant patients or oncology patients with various stage of disease and tissue origin of neoplasm. Subjects were included if they had received, or were scheduled to receive, a CT scan including the L3 region within +/- 1 month of NFPE. As part of the standard of care, subjects underwent a nutrition assessment by a RDN, including assessment of their muscle mass with the NFPE. After consenting to the study, trained study personnel conducted another assessment of muscle mass with the NFPE, measured mid-upper arm circumference (MUAC), and provided the subject with a quality of life questionnaire to be completed at home or in the office. Approval was obtained for this research from the OHSU Institutional Review Board (IRB #20385).

Study population

Subjects were recruited from patients being seen at Surgical Oncology, Medical Oncology, Digestive Health Center, Infusion Clinic, Liver Transplant Clinic and Kidney Transplant Clinic at OHSU Hospital between September 2019 and March 2020. All recruited subjects were adults between the ages of 18 and 95 years with a diagnosis of cancer, or individuals being evaluated for either renal or kidney transplant. Oncology subjects with various forms of cancer effecting the GI and associated organs at various stages of disease progression and treatment were included.

Inclusion/Exclusion Criteria

The transplant and oncology RDN schedules were monitored by a member of the study team for potential study subjects based on specific inclusion and exclusion criteria (Table 1). Upon immediate completion of their visit with the RDN, a member of the study team followed-up with potential subjects and consented those who were interested and willing to participate.

Table 1. Inclusion and exclusion criteria

Inclusion	Exclusion
English Speaking	Non-English Speaking
Age ≥ 18 years of age	< 18 years of age
Oncology patient	NFPE not performed by RDN
Renal or Liver Transplant patient	No CT scan available or scheduled
NFPE performed by RDN including assessment of muscle	-
CT scan of L3 region conducted +/- 1 month of NFPE	-

Demographics

Demographic information, including but not limited to medical diagnosis, age, sex, height, and weight, was obtained from the electronic medical record (EMR) or from the subject after consent. NFPE assessments, frailty scores and CT images were also accessed from the EMR.

NFPE

The NFPE was utilized for the assessment of muscle mass in study subjects. The NFPE is an integral tool used by RDNs to help assess nutrition status and coordinate best care practices,

and is directly outlined within the profession's scope of practice.[42,63] While the NFPE can include assessment of fluid status, grip strength, fat stores and signs of micronutrient deficiencies, this study only utilized the NFPE assessment of muscle mass. NFPE muscle assessment included: assessment of the temples requiring light palpation of the temporalis muscle using the index and middle fingers, also requiring the patient to open and close their mouth; assessment of the shoulder and clavicle region including visual inspection and palpation of the deltoid and pectoralis muscles; assessment of the interosseous muscle requiring the patient to touch their index finger and thumb forming a circle; assessment of the scapula region requiring palpation of the latissimus dorsi, trapezius and deltoids while having the subject extend their arm against some resistance; assessment of the thigh region requiring palpation of the quadriceps while having the subject slightly elevate their leg; and assessment of the calf requiring palpation of the gastrocnemius muscle while having the subject flex and extend their foot.[2]

The RDN conducted the first NFPE during their scheduled office visit. Immediately following the office visit, consented study participants underwent another NFPE performed by trained study personnel. During the follow-up NFPE assessment, only anatomical regions indicative of muscle mass were evaluated. Participant's mid-upper arm circumference (MUAC) was also measured and recorded in centimeters (cm).

Overall muscle assessment, determined by the NFPE and categorized as normal, mild, moderate, or severe depletion, from the RDN was recorded within the patient's medical record per standard practice of patient care and documented by the study personnel. A study assessment form was used to document the follow-up NFPE of muscle mass conducted by study personnel (Table 2). Muscle status at each region as well as an overall assessment was documented.

Table 2. NFPE muscle assessment form	
Region	Severity of Wasting: Normal, Mild, Moderate, Severe
Temporalis	
Shoulder	
Clavicle	
Interosseous	
Scapula	
Quadricep	
Calf	
Overall	
MUAC	

Quality of Life

Quality of life was measured using the Medical Outcomes Study Questionnaire Short Form 36 Health Survey (SF-36). Subjects were given the survey at the end of their visit as well as a self-addressed, stamped envelope. Subjects could complete the survey during their visit or return it via mail to the study team. Subjects who did not complete the survey were sent a reminder message through the EMR and were provided with a link to access the survey electronically.

Frailty Scores

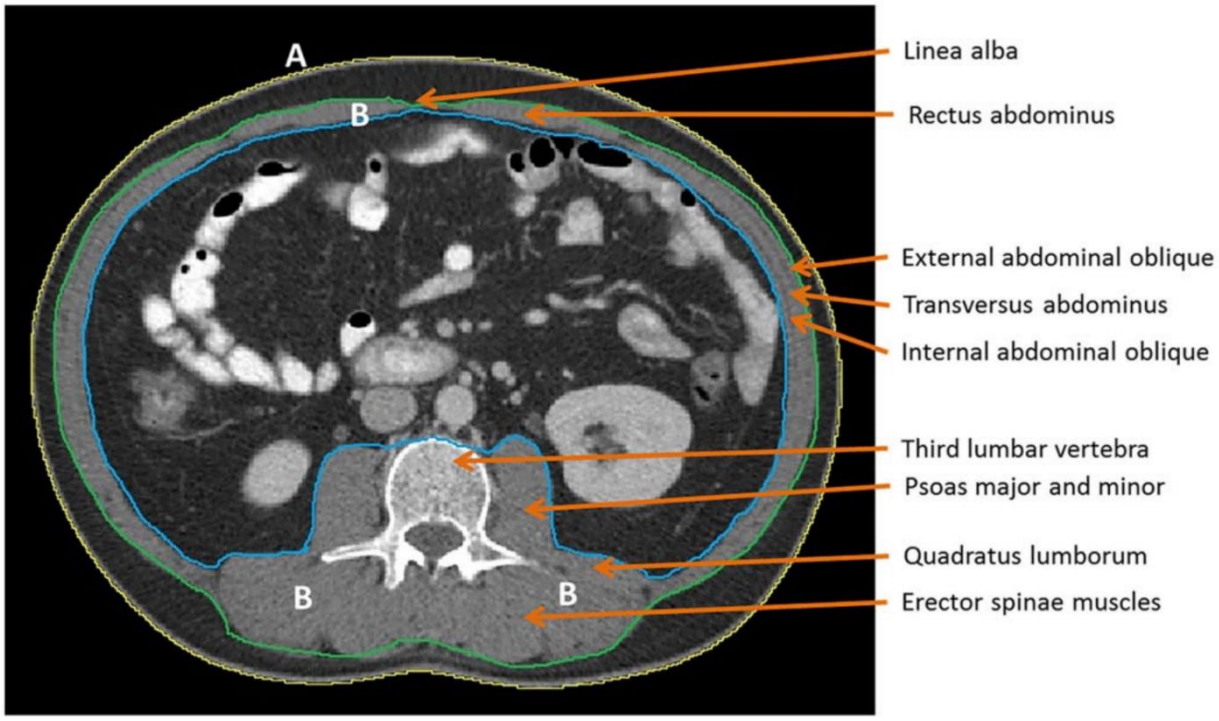
Frailty scoring is used to determine a patient's suitability for transplants surgery, as well as their risk for post-transplant outcomes. The transplant RDN evaluated transplant subject's frailty status using the Fried Scoring Method based on unintentional weight loss, self-reported exhaustion, hand-grip strength, walking speed, and low physical activity. Frailty scores were obtained from subject's EMR after their scheduled visit with the RDN. A score of 0-1 represents no frailty, 2 represents frail risk, and 3-5 represents frail.[64,65]

Skeletal Muscle Area & Skeletal Muscle Index

Skeletal muscle area (SMA) was measured on an axial CT of the L3 region obtained during pelvic and abdominal CT or PET/CT imaging as part of the standard of care. CT scans were obtained retrospectively from subject's medical records and only CT images obtained +/- 30 days from NFPE assessment were included. Using these scans, a single trained examiner measured SMA of the cross-sectional area of the L3 muscle group, which includes the external oblique, internal oblique, transversus abdominis, rectus abdominus, psoas, quadratus lumborum, and erector spinae. CT scans were removed from subjects' EMR by a qualified and trained Radiologist, then uploaded into an OHSU approved cloud storage via Box where they could be accessed by study personnel. CT image files were then uploaded into the open source 64-bit edition of Horos based on OsiriX® analysis software (GNU Lesser Public License, Version 3 (LGPL-3.0)).) for the analyses. The 'Grow Region (2D/3D segmentation tool)' was used to semi-automatically select skeletal muscle regions within HU threshold regions of -29 to 150. The brush option was utilized to manually remove non-skeletal muscle tissue regions adjacent to skeletal muscle. The SMAs were computed automatically, expressed in square centimeters using

a MacBook Air. Furthermore, SMA measures were normalized by the patient's height (in m^2) to determine SMI (cm^2/m^2) using the following equation: SMI = SMA / height $(m)^2$.

Figure 1. Muscles contained in L3 CT image



A: Abdominal Perimeter (yellow line)
B: Abdominal Muscles (between blue and green lines)

Statistical Plan

Subjects who met inclusion criteria with L3 CT images and NFPE findings of muscle status from both RDN and study personnel were included for analysis. Study subjects were excluded if they did not have NFPE findings from both the RDN and study personnel, or if their L3 CT imaging was not readable in analysis software. Subjects were further divided into cohorts based on NFPE status. According to the Academy and ASPEN Consensus statement, moderate and severe muscle depletion are both indicative of severe malnutrition and will present similarly in a clinical setting as compared to mild muscle depletion or normal muscle status. Therefore,

study subjects were divided into two groups based on their NFPE muscle status, combining those with normal muscle status or mild muscle depletion (Normal/Mild NFPE), and those with moderate or severe muscle depletion (Moderate/Severe NFPE). Furthermore, we made the decision to group NFPE classifications to increase the power of our analyses due to population size limitations. All analysis were performed using RDN NFPE assessment of muscle status. Study personnel findings were only utilized for interobserver reliability analysis.

To explore associations based on BMI, study subjects were further grouped according to their BMI classification. Due to sample size limitations, study subjects with Low (<18.5) or Normal BMI (18.5-24.9) classifications and Overweight (25.0-29.9) or Obese (>30.0) BMI classifications were combined to create dichotomous groups. For analysis exploring sarcopenia, sex-specific SMI cut-off values of 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women were used. Subjects who fell below these values were classified as having sarcopenia.

Analyses were preformed using Graphpad Prism version 8.4.1 for Windows, GraphPad Software, San Diego, California USA, graphpad.com, Contingency table calculations were performed using Graphpad Quickcalcs online resource (graphpad.com), and Vassarstats online calculator (vassarstats.net).

A histogram was created to determine the normality of SMI data. Mean differences in age, sex, race, height, weight, BMI, SMA, and MUAC between Normal/Mild NFPE and Moderate/Severe NFPE groups were evaluated using unpaired t-tests. Utilizing previously published sex-specific L3 SMI cut-offs of 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women, we evaluated the association between sarcopenia and NFPE muscle status. Associations between NFPE and sarcopenia were evaluated using Fisher's Exact tests. Pearson's tests were used to evaluate correlations between SMA and BMI as well as SMI and MUAC. To account for

changes based on BMI, 2-way ANOVA was utilized and multiple comparisons were calculated using Sidak's adjustment. To evaluate the agreement of NFPE classification from two independent study personnel, Cohen's Kappa coefficient was calculated. To explore the relationship between frailty and NFPE, subjects were categorized according to their frailty scores using the Fried Frailty Index, and further grouped based on their NFPE classification. To evaluate associations between frailty, NFPE and SMI, we utilized Fisher's Exact Freeman-Halton extension and multiple comparisons were calculated using Tukey's adjustment. All relevant tests will be considered statistically significant with a p-value<0.05.

Table 3. Statistical analysis summary

Specific Aim	Hypothesis	Statistical Test
Primary Aim 1: To describe how muscle assessment, measured through the NFPE, compares to skeletal muscle index, measured through CT imaging.	Subjects with moderate and severe muscle depletion, determined by the NFPE, will have lower mean SMI and are more likely to be sarcopenic.	Unpaired t-test were performed to compare mean SMI between subjects grouped according to NFPE. Fisher's Exact test was performed to evaluate associations between NFPE classification and sex-specific SMI sarcopenia cut-off values.
Primary Aim 2: To determine how BMI impacts the accuracy of muscle assessment through the NFPE.	Moderate and severe muscle depletion in overweight and obese subjects will be more accurately identified by CT imaging compared to muscle assessment using the NFPE.	Pearson's coefficient test was performed to evaluate correlation between SMA and BMI. Two-way ANOVA was performed to evaluate associations between NFPE and SMI while accounting for BMI. Multiple comparisons were calculated using Sadik's adjustment.

Table 3. Statistical analysis summary (con't)		
Primary Aim 3: To evaluate the interobserver reliability of muscle assessment using the NFPE and how reliability is impacted by BMI.	Muscle assessment using the NFPE will demonstrate positive interobserver reliability among assessors, and interobserver reliability will decrease with an increase in BMI.	Cohen's kappa coefficient was used to measure interrater reliability of 2 raters and their agreement on muscle assessment using NFPE.
Secondary Aim 1: To describe how quality of life is related to muscle mass, described by the NFPE and CT imaging.	Subjects with lower muscle mass, as indicated by NFPE and CT imaging, will have lower quality of life scores.	Unpaired t-test were performed to compare mean QOL scores between NFPE groups and between subjects classified as sarcopenic using SMI -cut-off values.
Exploratory Aim 1: To describe how MUAC measurements are related to muscle mass, described by the NFPE and CT imaging.	Subjects with lower muscle mass, as indicated by NFPE and CT imaging will have lower MUAC measurements.	Pearson's correlation coefficient was performed to evaluate the correlation between MUAC and SMI. Unpaired t-test were performed to compare mean MUAC between NFPE groups.
Exploratory Aim 2: To describe how frailty scores in organ transplant subjects are related to muscle mass, described by the NFPE and CT imaging.	Subjects with lower muscle mass, as indicated by NFPE and CT imaging will have higher frailty scores.	One-way ANOVA was performed to evaluate associations between SMI among frailty scores. Frailty scores were grouped as follows: 0 = no risk, 1-3 = frail risk, 4-5 = frail. Fisher's Exact Freeman-Halton extension test was performed to evaluate associations between frailty scores and NFPE groups.

Chapter 4 Results

Demographics

One hundred and forty-five (145) subjects were screened for enrolment. Of those, 58 subjects met inclusion criteria and were enrolled into the study. Six (6) subjects failed to receive CT scans including imagining of the L3 region, or scans were unreadable in analysis software and were excluded. One (1) subject was excluded due to missing RDN note including NFPE findings. In total, 23 oncology and 28 transplant subjects were included in the analysis for a total of 51 subjects. For transplant subjects, 27 were being evaluated for liver transplant, and one subject was being evaluated for kidney transplant. For oncology subjects, 11 had pancreatic cancer, and the remaining 11 subjects had various forms of cancer including bladder, cholangiocarinoma, and colorectal. The cancer stage and status of treatment varied across the oncology subjects. After grouping subjects according to their muscle status based on the NFPE, we had 24 subjects with normal muscle status or mild muscle depletion, and 27 subjects with moderate or severe muscle depletion. The median age for subjects in the Normal/Mild NFPE group (n=24) was 57 years and 64 years for subjects in the Moderate/Severe NFPE group (n=27) (Table4). There was no significant difference in age or race (categorized as white or other) between subjects in the Normal/Mild NFPE and Moderate/Severe NFPE groups (p=0.0893, p=0.376 respectively).

Table 4. Selected demographic distributions

Characteristic	Total (n=51)	NFPE Categories	
		Normal/Mild (n=24)	Moderate/Severe (n=27)
		Median (range)	
Age (yrs)	62 (22-77)	57 (22-75)	64 (36-77)
		n (%)	
Sex			
Male	25 (49.1)	13 (54.2)	13 (48.1)
Female	26 (50.9)	11 (45.8)	14 (51.9)
Race			
White	47 (92.2)	23 (95.8)	24 (88.9)
Other[a]	4 (7.8)	1 (4.2)	3 (11.1)
Clinic[b]			
Oncology	23 (45.0)	11 (45.8)	12 (44.4)
Transplant	28 (55.0)	13 (54.2)	15 (55.6)

[a]Includes black, hispanic, asian or undeclaired.

[b]Clinic of recruitment

Abbreviations: NFPE (nutrition focused physical exam), BMI (body mass index)

Anthropometrics

There were no significant differences in BMI (p =0.66), between males and females (Table 5). Mean BMI in males was significantly lower in subjects in the Moderate/Severe NFPE compared to Normal/Mild NFPE group (BMI=23.91 ± 3.77 kg/m^2 and 29.63 ± 3.87 kg/m^2, respectively, p=0.001). Mean weight in males was significantly lower in subjects in the Moderate/Severe group compared to Normal/Mild NFPE group (75.43 ± 11.62 kg and 93.83 ± 16.27 kg, respectively, p =0.0008). In females, there was no significant difference in mean BMI, or weight, between subjects in the Normal/Mild NFPE and Moderate/Severe NFPE groups (Table 6).

Table 5. Anthropometric comparison between gender

Variable	Gender		p-value
	Males (n=25)	Females (n=26)	
BMI (kg/m^2)	26.4 ± 4.7	21.2 ± 6.9	0.66
Weight (kg)	84.4 ± 17.4	73.4 ± 18.1	0.0258
Height (m)	1.8 ± 0.1	1.6 ± 0.1	<0.0001

Abbreviations: BMI (body mass index)

Table 6. Anthropometric characteristics by NFPE group

Variable		NFPE Categories		p-value
		Normal/Mild (n=24)	Moderate/Severe (n=27)	
BMI (kg/m^2)				
	Male	29.63 ± 3.87	23.91 ± 3.77	0.0011
	Female	28.95 ± 6.01	25.40 ± 7.54	0.196
Weight (kg)				
	Male	93.83 ± 16.27	75.43 ± 11.62	0.0008
	Female	77.00 ± 14.57	69.83 ± 21.07	0.323
Height (m)				
	Male	1.81 ± 0.07	1.78 ± 0.06	0.299
	Female	1.63 ± 0.05	1.66 ± 0.05	0.299

Abbreviations: NFPE (Nutrition Focused Physical Exam), BMI (body mass index).

Skeletal Muscle area (SMA) and Skeletal Muscle Index (SMI)

Mean SMA was significantly lower in females compared to males (146.7 ± 30.3 cm^2 and 113.7 ± 22.8 cm^2 respectively, p<0.0001) (Table 7). Mean SMA was significantly lower in subjects in the Moderate/Severe NFPE group compared to subjects in the Normal/Mild NFPE group for both males (132.9 ± 22.82 cm^2 and 164.3 ± 30.37 cm^2, respectively, p=0.007) and females (102.5 ± 19.74 cm^2 and 124.8 ± 20.52 cm^2, respectively, p=0.009) (,Table 8).

Table 7. Lean mass momparison between gender

Variable	Gender		p-value
	Males (n=25)	Females (n=26)	
SMA (cm^2)	146.7 ± 30.3	113.7 ± 22.8	<0.0001
SMI (cm^2/m^2)	45.9 ± 9.7	42.1 ± 8.8	0.15

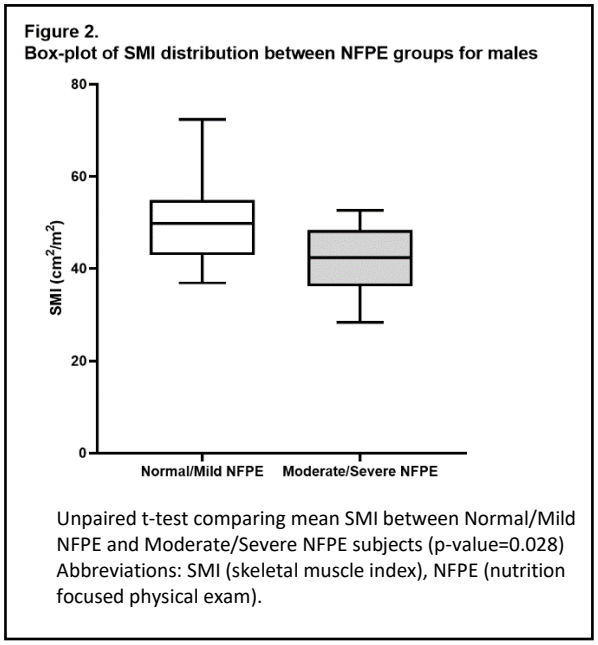
Abbreviations: SMA (skeletal muscle area), SMI (skeletal muscle index).

Table 8. Lean mass comparison between NFPE groups

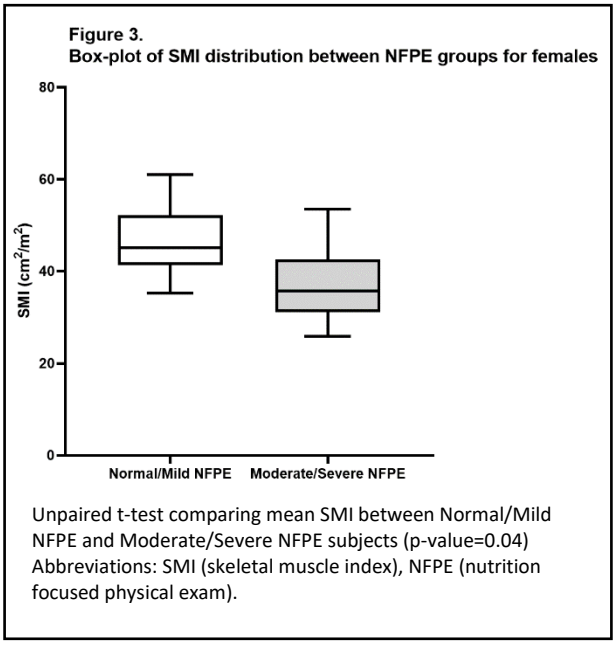
Variable		NFPE Categories		p-value
		Normal/Mild (n=24)	Moderate/Severe (n=27)	
SMA (cm^2)				
	Male	164.3 ± 30.4	132.9 ± 22.8	0.007
	Female	124.8 ± 20.5	102.5 ± 19.7	0.009
SMI (cm^2/m^2)				
	Male	50.6 ± 10.2	42.2 ± 7.8	0.028
	Female	46.8 ± 7.4	37.4 ± 7.6	0.004

Abbreviations: NFPE (Nutrition Focused Physical Exam), SMI (skeletal muscle index), SMA (skeletal muscle area).

Mean SMI was significantly lower in the Moderate/Severe NFPE group compared to the Normal/Mild NFPE group for both males (42.2 ± 7.8 cm^2/m^2 and 50.6 ± 10.2 cm^2/m^2 respectively, p=0.028) and females (37.4 ± 7.6 cm^2/m^2 and 46.8 ± 7.4 cm^2/m^2 respectively, p=0.004) (Table 8, Figures 2 and 3).



Unpaired t-test comparing mean SMI between Normal/Mild NFPE and Moderate/Severe NFPE subjects (p-value=0.028)
Abbreviations: SMI (skeletal muscle index), NFPE (nutrition focused physical exam).



Unpaired t-test comparing mean SMI between Normal/Mild NFPE and Moderate/Severe NFPE subjects (p-value=0.04)
Abbreviations: SMI (skeletal muscle index), NFPE (nutrition focused physical exam).

Sarcopenia

Subjects were determined to be sarcopenic if their SMI was below 52.4 cm^2/m^2 for males and 38.5 cm^2/m^2 for females. For subjects in the Normal/Mild NFPE group, 15 (62.5%) were non-sarcopenic based on the sex-specific SMI cut-off values and nine (37.5%) were classified as sarcopenic (Table 9). In contrast, for subjects in the Moderate/Severe NFPE group, 20 (74%) were classified as sarcopenic and only seven (26.9%) were classified as non-sarcopenic. The incidence of sarcopenia was significantly associated with the NFPE's classification of moderate to severe muscle depletion (p=0.012).

Table 9. Association between sarcopenia and NFPE

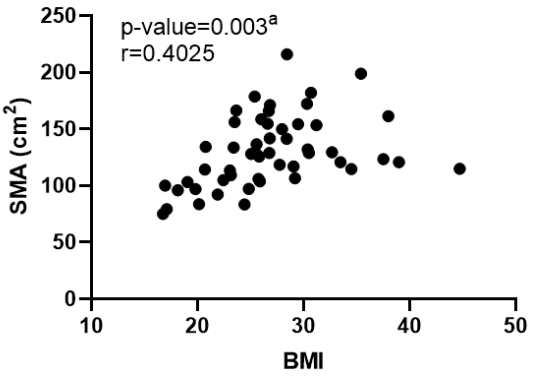
	NFPE Category	
	Normal/Mild	Moderate/Severe
Sarcopenic	9 (37.5)	20 (74.1)
Non-sarcopenic	15 (62.5)	7 (25.9)

Values are expressed as n (%) based on colum.
Abbreviations: NFPE (nutrition focused physical exam).

Muscle Assessment and BMI

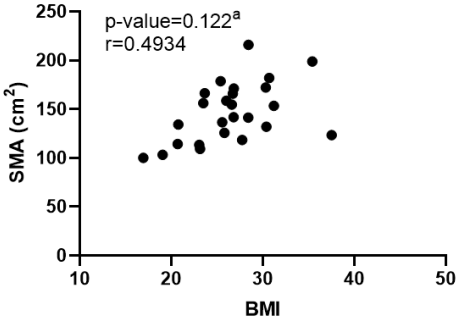
When looking at the relationship between SMA and BMI, there was a significant positive correlation (r=0.4025, *p*=0.003) in the study population when men and women were combined (Figure 4). In this cohort, BMI accounted for 16% of the variance of SMA (r^2=0.162). When males and females were examined independently, a significant positive correlation was still observed (r=0.4934, *p*=0.0122 and r=0.5916, *p*=0.0016, respectively) with a strong correlation observed in the females (Figures 5 and 6). In males, BMI accounted for 24% of the variance of SMA (r^2=0.244), and in females, BMI accounted for 35% of the variance of SMA (r^2=0.35). For this analysis, SMA was used in place of SMI due to the confounding influence of height in both BMI and SMI.

Figure 4.
Correlation between BMI and SMA



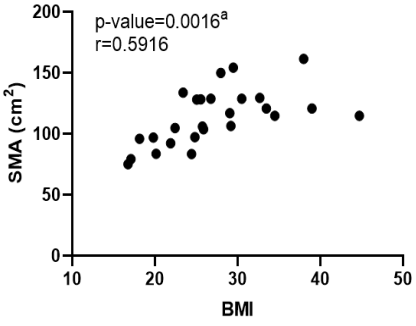
[a]Pearson's Correlation.
Abbreviations: BMI (body mass index), SMA (skeletal muscle area).

Figure 5.
Correlation between BMI and SMA in males



[a]Pearson's Correlation.
Abbreviations: BMI (body mass index), SMA (skeletal muscle area).

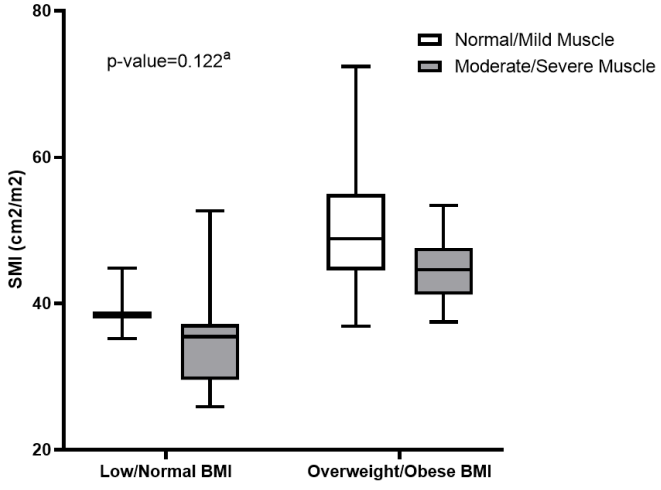
Figure 6.
Correlation between BMI and SMA in females



[a]Pearson's Correlation.
Abbreviations: BMI (body mass index), SMA (skeletal muscle area).

When BMI was taken into account, the association between NFPE and SMI is diminished (*p*=0.122) (Figure 7). Post-hoc multiple comparisons analysis suggests that subjects with both Low/Normal BMI and Moderate/Severe NFPE had significantly lower SMI than subjects with both Overweight/Obese BMI and Normal/Mild NFPE (*p*=<0.001; predicted mean diff.=-14.05) and subjects with both Overweight/Obese BMI and Moderate/Severe NFPE (*p*=0.013; predicted mean diff.=-9.286) (Table 10).

Figure 7.
Box-plot comparing SMI And NFPE Between BMI Groups



[a]Two-way ANOVA.
Abbreviations: SMI (skeletal muscle index), BMI (body mass index)

Table 10. Comparisons of SMI accounting for BMI and NFPE

Group	p-value	Predicted mean diff.
Low/Normal BMI: Normal/Mild NFPE vs. Low/Normal BMI: Moderate/Severe NFPE	0.966	3.73
Low/Normal BMI: Normal/Mild NFPE vs. Overweight/Obese BMI: Normal/Mild NFPE	0.159	-10.32
Low/Normal BMI: Normal/Mild NFPE vs. Overweight/Obese BMI: Moderate/Severe NFPE	0.823	-5.56
Low/Normal BMI: Moderate/Severe NFPE vs. Overweight/Obese BMI: Normal/Mild NFPE	<0.0001	-14.05
Low/Normal BMI: Moderate/Severe NFPE vs. Overweight/Obese BMI: Moderate/Severe NFPE	0.013	-9.29
Overweight/Obese BMI: Normal/Mild NFPE vs. Overweight/Obese BMI: Moderate/Severe NFPE	0.401	4.76

Sadik's multiple comparison. Abbreviations: NFPE (Nutrition Focused Physical Exam), BMI (body mass index).

Subjects were stratified by BMI (low/normal and overweight/obese) and sarcopenia status, determined by CT imaging, was compared to NFPE classification. There were 18 (35%) subjects with low and normal BMI classifications. Fifteen (15) of these subjects (83%) were in the Moderate/Severe NFPE group, indicating moderate to severe muscle depletion based on the NFPE. Of these 15 subjects, 93% fell below the sex specific SMI cut-off values indicating the presence of sarcopenia. For those classified as overweight or obese based on BMI (n=33, 65%), 12 (36%) were in the Moderate/Severe NFPE group. Of those 12 subjects, six (50%) fell below sex specific SMI cut-off values for sarcopenia (Table 11).

Table 11. Distribution of subjets based on sarcopenia and NFPE classification grouped according to BMI

	Low/Normal BMI (n=18) NFPE Category		Overweight/Obese BMI (n=33) NFPE Category	
	Normal/Mild	Moderate/Severe	Normal/Mild	Moderate/Severe
Sarcopenic[a]	2 (66.7)	14 (93.3)	7 (33.3)	6 (50.5)
Non-Sarcopenia[a]	1 (33.3)	1 (6.7)	14 (66.7)	6 (50.5)

Values are expressed as n (%) by column.
aSarcopenia defined as an SMI below 52.4 cm2/m2 for men and 38.5 cm2/m2 for women.
Abbreviations: NFPE (nutrition focused physical exam), BMI (body mass index)

Looking further into the classification of sarcopenia, stratified by BMI, 16 (88%) out of 18 subjects were classified as sarcopenic in those with a low/normal BMI. Of these 16 sarcopenic subjects, the majority of subjects (n=14, 87.5%) were also classified as having moderate to severe muscle depletion using the NFPE with only two (12.5%) falling into the Normal/Mild NFPE group. For those with an overweight or obese BMI, 13 (39%) out of 33

subjects were classified as sarcopenic. Of these 13 sarcopenic subjects, six (46%) were classified as having moderate to severe muscle depletion using the NFPE and seven (53.8%) were classified as having normal muscle stores or mild depletion according to the NFPE. A greater proportion of subjects with low/normal BMI were classified as both sarcopenic and having moderate to severe muscle wasting based on the NFPE when compared to subjects with obese/overweight BMI (87.5% and 46%, respectively).

Interobserver Reliability

Results demonstrated that there was moderate agreement (kappa=0.521) between observers (Table 6). The total number of observed agreements was 39 (76.5%). The number of agreements expected by chance was 26 (50.9%). Sample size limitations did not allow for the analysis of interobserver reliability based on BMI classification.

Table 12. Interobserver reliability of NFPE

	Observer #1			
Observer #2	Normal/Mild	Moderate/Sever	Total	Kappa
Normal/Mild	15	3	18	
Moderate/Severe	9	24	33	0.52
Total	24	27	51	

Abbreviations: NFPE (Nutrition Focused Physical Exam).

Quality of Life

To assess quality of life measures, the RAND 36-item Health Survey was provided to study participants and included questions pertaining to the following measures: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain and general health. In total, 45% (23) of study participants returned QOL questionnaires. Each category is scored on a scale from 0-100, 100 representing a more favorable health state. There was no significant difference in

QOL scores pertaining to physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain or general health between subjects in the Normal/Mild NFPE group compared to subjects in the Moderate/Severe NFPE group (Table 13). While not statistically significant, it is important to note that subjects in the Moderate/Severe NFPE group did have lower QOL scores pertaining to physical functioning (53.3 ± 22.4 and 65.0 ± 25.7), role limitations due to physical health (27.1 ± 44.5 and 40.9 ± 45.1), role limitations due to emotional problems (61.1 ± 44.6 and 66.7 ± 42.2), social functioning (51.0 ± 27.9 and 65.9 ± 19.4) and general health (46.7 ± 16.0 and 49.1 ± 21.0).

Table 13. Comparison of quality of life measures between NFPE groups

Variable	NFPE Categories		p-value
	Normal/Mild (n=11)	Moderate/Severe (n=12)	
	Mean ± SD		
Physical functioning	65.0 ± 25.7	53.3 ± 22.4	0.258
Role limitation due to physical health	40.9 ± 45.1	27.1 ± 44.5	0.468
Role limitations due to emotional problems	66.7 ± 42.2	61.1 ± 44.6	0.762
Energy/fatigue	43.2 ± 18.3	44.2 ± 17.2	0.895
Emotional well-being	55.5 ± 9.4	60.3 ± 11.4	0.285
Social functioning	65.9 ± 19.4	51.0 ± 27.9	0.157
Pain	62.1 ± 23.3	64.0 ± 31.4	0.871
General health	49.1 ± 21.0	46.7 ± 16.0	0.757

Variables derived from RAND 36-item Health Survey.
Abbreviations: NFPE (Nutrition Focused Physical Exam).

To evaluate the relationship between SMI and QOL, we compared QOL scores between subjects grouped according to the previously discussed SMI sex-specific sarcopenia cut-off

values of 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women. There was no significant difference in QOL scores pertaining to physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain or general health between subjects classified as sarcopenic compared to subjects classified as non-sarcopenic based on SMI cut-off values (Table 14).

Table 14. Comparison of quality of life measures by sarcopenia

Variable	Sex-specific SMI cut-off values		p-value
	Non-sarcopenic[a] (n=8)	Sarcopenic[a] (n=15)	
	Mean ± SD		
Physical functioning	52.5 ± 26.1	62.3 ± 23.4	0.366
Role limitation due to physical health	15.6 ± 35.2	43.3 ± 46.7	0.158
Role limitations due to emotional	58.3 ± 49.6	66.7 ± 39.9	0.665
Energy/fatigue	40.0 ± 13.1	45.7 ± 19.4	0.468
Emotional well-being	59.6 ± 8.0	57.2 ± 11.9	0.62
Social functioning	57.8 ± 23.1	58.3 ± 26.6	0.963
Pain	64.7 ± 21.7	62.2 ± 30.4	0.838
General health	39.4 ± 12.1	52.3 ± 19.5	0.104

Variables derived from RAND 36-item Health Survey.

[a]Sex-specific SMI cut-off values of 52.4 cm2/m2 for men and 38.5 cm2/m2 for women

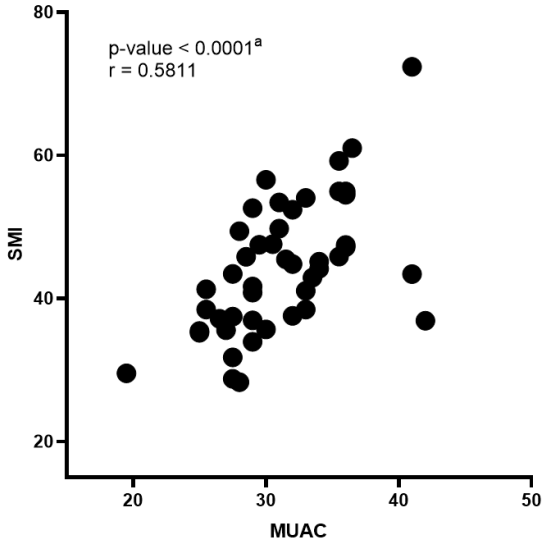
Abbreviations: NFPE (Nutrition Focused Physical Exam).

Mid-upper Arm Circumference

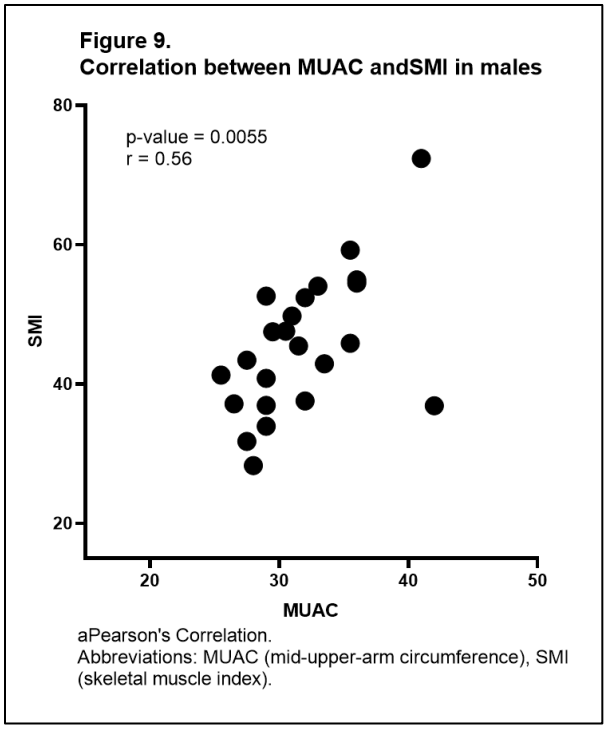
There was a positive linear association between SMI and MUAC in our study population when we combine males and females (Figure 6). SMI and MUAC share approximately 33% of their variability (R^2=0.33, *p*=<0.001). When we look at males and females independently, we

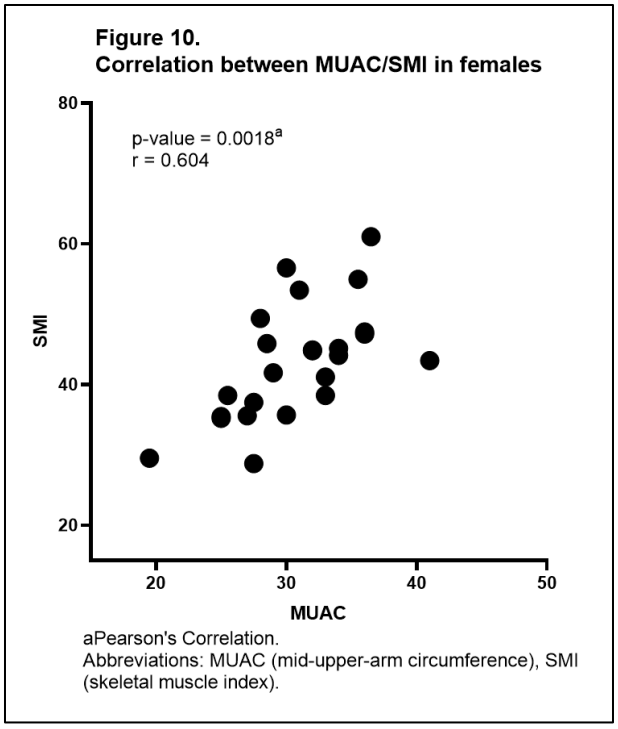
still observed a positive linear association. In males, SMI and MUAC share approximately 31% of their variability (R^2=0.313, *p*=0.006). In females, SMI and MUAC share approximately 37% of their variability (R^2=0.365, *p*=0.002) (Figures 7, 8 and 9).

Figure 8.
Correlation between MUAC and SMI



aPearson's Correlation.
Abbreviations: MUAC (mid-upper-arm circumference), SMI (skeletal muscle index).





There was no significant difference in MUAC between males and females (p=0.43) (Table15). Mean MUAC in males was significantly lower in the Moderate/Severe NFPE group compared to the Normal/Mild NFPE group (29.12 ± 2.54 cm and 35.15 ± 3.81 cm respectively, p=0.0002) (Table 16). In females there was no significant difference in mean MUAC between the Normal/Mild NFPE group and the Moderate/Severe NFPE group (32.1 ± 3.9 cm and 29.0 ± 5.3 cm respectively, p=0.112) (Table 16). Mean MUAC was significantly lower in subjects with Low and Normal BMI classification compared to subjects with Overweight and Obese BMI classification (27.1 ± 2.9 and 33.1 ± 3.8 respectively, p=<0.0001) (Table 17). Mean MUAC is significantly lower in subjects with sarcopenia compared to subjects who are non-sarcopenic. These results are true for both males (34.3 ± 3.6 and 30.4 ± 4.1 respectively, p=0.0343) and females (33.1 ± 3.6 and 26.7 ± 3.7 respectively, p=0.0004). (Table 18).

Table 15. Arm circumference comparison between gender

Variable	Gender		p-value
	Males (n=25)	Females (n=26)	
MUAC (cm)	31.7 ± 4.3	30.7 ± 4.8	0.43

Abbreviations: MUAC (mid-upper arm circumference)

Table 16. Arm circumference comparison by NFPE Group

Variable	NFPE Categories		p-value
	Normal/Mild (n=24)	Moderate/Severe (n=27)	
MUAC (cm)			
Male	35.15 ± 3.81	29.12 ± 2.54	0.0002
Female	32.12 ± 3.92	29.00 ± 5.29	0.112

Abbreviations: MUAC (mid-upper-arm circumference).

Table 17. Arm circumference comparison between BMI classification

Variable	BMI Classification		p-value
	Low/Normal (n=15)	Overweight/Obese (n=32)	
MUAC (cm)	27.1 ± 2.9	33.1 ± 3.8	<0.0001

Abbreviations: BMI (body mass index), MUAC (mid-upper arm circumference)

Table 18. Arm circumference comparison by sarcopenia

Variable	Sex-specific SMI sarcopenia cut-offs		p-value
	Non-sarcopenic[a] (n=15)	Sarcopenic[a] (n=9)	
MUAC (cm)			
Male	34.3 ± 3.6	30.4 ± 4.1	0.0343
Female	33.1 ± 3.6	26.7 ± 3.7	0.0004

[a]Sex-specific SMI cut-off values of 52.4 cm2/m2 for men and 38.5 cm2/m2 for women.
Abbreviations: SMI (skeletal muscle index), MUAC (mid-upper-arm circumference).

Frailty Scores and SMI

Twenty-eight (28) subjects in total had frailty score data and were included in this exploratory analysis. Ten subjects (35.7%) had frailty scores of 0-1 indicating no risk, six subjects (21.4%) had frailty scores of 2 indicating frailty risk, and 12 subjects (42.9%) had frailty

scores of 3-5 indicating frailty. Mean SMI was 52.4 ±10.8 cm^2/m^2 for subjects with no frailty risk, 43.8 ± 3.1 cm^2/m^2 for subjects with frailty risk and 42.2 ± 7.4 cm^2/m^2 for frail subjects. Multiple comparison test (Table 19) shows that SMI is significantly greater in individuals with a score of 0-1, indicating no risk of frailty, compared to those with a score of 3-5 indicating the presence of frailty (p=0.021). While not statistically significant, results are suggestive that there is a trend in lower SMI between individuals with scores of 2 indicating frailty risk and those with scores of 0-1 indicating no risk (p=0.13). There is evidence to support an association between muscle depletion as identified by NFPE and higher frailty scores (p=0.0133) (Table 20).

Table 19. Comparisons of frailty and SMI

Group	p-value	Predicted mean diff.
No risk[a] vs. Frail risk[b]	0.1321	8.5
No risk[a] vs. Frail[c]	0.021	10.2
Frail risk[b] vs. Frail[c]	0.913	1.7

Tukey's multiple comparison test.

[a]Fried frailty score 0-1

[b]Fried frailty score 2

[c]Fried frailty score 3-5

Abbreviations: SMI (skeletal muscle index).

Table 20. Association between frailty scores and NFPE

	Frailty Category[a]		
NFPE	No risk[a]	Frail risk[b]	Frail[c]
Moderate/Severe	2 (20.0)	3 (50.0)	10 (83.3)
Normal/Mild	8 (80.0)	3 (50.0)	2 (16.7)

Fishers Exact test Freeman-Holton extension (p-value=0.0133.

Values are expressed as n (%) based on colum.

[a]Fried frailty scoring method: No risk=0-1, Frail risk=2, Frail-3-5.

Abbreviations: NFPE (nutrition focused physical exam).

Chapter 5 Discussion

One of the most significant findings of this study was that SMI, as measured by CT imaging, was significantly different between NFPE classification and this was true for both male and female subjects. Results indicate that SMI appears to be lower in individuals who are classified as having moderate and severe muscle depletion through the NFPE, and that the NFPE does agree with SMI. Furthermore, results show that NFPE classifications of moderate and severe muscle loss are associated with the presence of sarcopenia, utilizing previously established sex-specific SMI sarcopenia cut-off values.[7] It is important to note that there are a variety of proposed methods to determine SMI-based sarcopenia classification including percentiles based on age and BMI,[62] and optimum stratification based on mortality.[7,59] Due to the cross-sectional nature of this study, there was a lack of prospective data to establish cut-off values based on optimum stratification. For this study, it was determined that the previously established sex-specific values from Prado et al.[7] were most appropriate as these have been explored in studies with similar patient populations including subjects with obesity,[7] oncology subjects,[20] as well as liver and kidney disease subjects.[19,57,60]

The relationship between SMI, SMA and BMI and how BMI impacted NFPE assessment of muscle mass was examined in this study. SMA and BMI were positively correlated indicating that as bodyweight increases muscle status also increases. However, SMA does show variability among individuals with similar BMIs (Figures 4, 5 and 6). For example, subjects with a BMI>30.0 had SMA that ranged from 114.8 cm^2 to 198.9 cm^2. Van der werf et al. also observed a positive correlation between BMI and SMA and reported a stronger association among men compared to women.[62] Those results differ from this study however, as women showed a stronger correlation compared to men. (r^2=0.35, p=0.0016 and r^2=0.24, p=0.0122, respectively).

Other studies have also demonstrated that BMI and measures of lean tissue are positively correlated. Zhang et al. demonstrated that baseline BMI was significantly higher in subjects with normal lean tissue index values as compared to subjects with low lean tissue values.[13] As previously mentioned, SMI is significantly different between those with normal muscle status or mild muscle depletion and those with moderate and severe muscle depletion, as designated by the NFPE. When accounting for BMI the association is diminished. Post-hoc analysis demonstrates that individuals with lower BMI and moderate/severe NFPE classification had significantly lower SMI as compared to individuals with greater BMI, whether or not their NFPE classification was normal/mild or moderate/severe. It is important to note that there are limitations with sample size. For example only three individuals with a low (<18.5) or normal BMI (≥18.5 to 24.9) were also identified as having normal muscle status or mild muscle depletion by NFPE. Furthermore, males and females were grouped for this analysis due to sample size limitations. However, while SMA was significantly different between males and females, adjusting for height resulted in no significant difference in SMI between gender. This is in contrast to what other studies have demonstrated. Van der werf et al. reported that SMI was significantly lower in females compared to males.[62] Furthermore, Prado et al. reported mean SMI as 59.1 cm^2/m^2 for men and 48.8 cm^2/m^2 for women for their study consisting of obese subjects with solid tumors of the respiratory and GI tract.[7] However, Montano-Loza et al. reported that SMI was significantly lower in males compared to females among a study population consisting of subjects with cirrhosis.[57,60] The discrepancies seen between SMI based on gender may be attributed to the variety of study populations this variable has been explored in. This study included both kidney and liver transplant subjects as well as oncology subjects. The literature showing females trend toward lower SMI appears to be in study populations consisting of

oncology subjects while studies including liver disease subjects tend to demonstrate that males have lower SMI.

To further evaluate the accuracy of NFPE in those with excess adiposity, subjects were distributed based on NFPE and sarcopenia, grouping those with low or normal BMI and those with overweight or obese BMI. An extremely high proportion (93%) of low/normal BMI subjects classified as having moderate or severe muscle loss by the NFPE, also had an SMI indicating sarcopenia. However, in subjects with overweight/obese BMI, only half of those classified with moderate or severe muscle loss by the NFPE also had an SMI indicating sarcopenia (Table 11). While this is a novel study including the variable of NFPE muscle assessment, other studies have reported findings on the associations between sarcopenia, BMI and SMI. Montano-Loza et al. found that subjects with sarcopenia (as defined using sex-specific SMI cut-off values similar to those used in this study) were less likely to be overweight or obese, and had lower SMI values compared to those above the defined SMI cut-off values.[60] Those results mirror the findings of this study, as an extremely high proportion of subjects with low and normal BMI, also had SMI values indicating sarcopenia. This may indicate that the NFPE more accurately identifies muscle loss in those with lower body mass and this accuracy is diminished as mass increases. It is important to note that this study is making the assumption that BMI is representative of adiposity, however this is not always the case. BMI may falsely classify those with increased bone mass or muscle mass as overweight or obese.[66]

This study utilized two independent NFPE evaluators, both of which had received training on the NFPE, for each study participant enrolled. Results showed that there was moderate agreement between observers with evaluators agreeing on 76.5% of subjects. Agreement rate in this study was similar to that observed in Baker et al. of 81%, which also

explored the interobserver reliability in nutrition assessment.[29] While interobserver agreement was not as strong as anticipated it is important to note some of the factors that may have contributed to the results. First, one of the evaluators was a Registered Dietitian Nutritionist, who has received extensive training on the NFPE over their career in addition to vast experience in its use. The second evaluator was a graduate student with more limited experience and training in the NFPE. Furthermore, observers may have been biased to seek muscle depletion in the NFPE due to the nature and goals of this study.

This study utilized the RAND 36-item Health Survey to evaluate QOL in study subjects. Subjects were provided surveys during their time of enrollment, and electronic versions were sent to subjects via EMR for those who failed to return the initial paper version. Survey response rate was 45% for this study. Rates appear to range from 16-46% in patient-related survey studies indicating that the return rate for this study was above average.[67-70] Mean QOL scores for physical functioning, role limitations due to physical health, role limitation due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain and general health were not significantly different between NFPE groups. Mean scores were also not significantly different between subjects with sarcopenia compared to those who were non-sarcopenic. The lack of significant findings from this study could be attributed to the fact that subjects were not able to be compared to healthy controls or that study subjects were grouped from both oncology and transplant populations. Other studies have explored QOL measures in various populations including more specific disease states and comparing measures to controls. A meta-analysis by Peng et al. evaluated articles exploring QOL measures in end-stage liver disease patients, and concluded that health-related quality of life measures were significantly impaired compared to those of healthy controls.[71] Kelpin et al. explored the effects of intensive chemotherapy on

physical, cognitive and emotional health in older adults with cancer. While this study did not specifically utilize the RAND-36 item Health Survey, it did find that subject's ability to perform ADLs was diminished, but there was no significant change in cognitive function or depressive symptoms after intensive chemotherapy.[72]

It was predicted that MUAC would correlate with SMI, and that subjects with lower muscle status would have lower MUAC. In fact, there was a positive linear correlation between MUAC and SMI, indicating that as muscle status increases arm circumference will also increase. This association is present in both males and females. While there is a statistical correlation, there is still variability of SMI among individuals with similar MUAC (Figures 6, 7 and 8). Although there were associations between SMI and MUAC in both males and females, NFPE classification was only associated with MUAC in males. Male subjects in the Moderate/Severe NFPE group had significantly lower MUAC compared to males in the Normal/Mild NFPE group. Furthermore, when subjects were grouped based on sex-specific SMI cut-off values, mean MUAC was significantly lower in subjects with sarcopenia compared to those who were non-sarcopenic for both males and females (Table 18). Lidoriki et al. also showed that MUAC was significantly lower in study subjects with sarcopenia compared to subjects who were non-sarcopenic and that MUAC showed a positive correlation with SMI.[73] This study utilized the same sex-specific SMI cut-off values of 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women.

An exploratory aim was to examine the relationship between frailty scores in transplant patients with SMI and NFPE. Results indicate that muscle status is significantly greater in individuals with no risk of frailty, compared to those who are frail. Fougere et al. explored the relationship between frailty scores and lean mass. The Fried Frailty Index and appendicular lean mass (ALM) were utilized in this study. Results demonstrated that there was no significant

difference in ALM when subjects were stratified by frailty scores.[74] Williams et al. also explored the relationship between frailty scores and lean mass using SMA measured from L3 CT images and frailty scores calculated using the Carolina 36-item frailty index. This study found significant differences in skeletal muscle density (SMD) and skeletal muscle gauge (the product of SMD and SMI) between subjects with no frail risk and frail subjects. Researchers reported that there was no significant difference between groups for SMI.[75] There was also evidence to suggest that NFPE classification is related to frailty and those with moderate or severe muscle loss may be at an increased risk of frailty.

Strengths of this study include the following: To our knowledge, this is one of the first studies to explore the relationship between SMI and NFPE. This study compared NFPE findings to objective measurements of muscle mass from CT imaging, and utilized only one RD/RDN for each patient population to evaluate muscle status using the NFPE. Additionally, results from our study suggest that NFPE accurately captures muscle status and may be an effective tool as CT scans are not indicated for all patients, nor is CT analysis readily available in the clinical setting.

Limitation of this study include the following: due to sample size limitations, we were required to group both BMI categories as well as NFPE classifications. This limited our ability to further explore specific relationships that may have been present between low and normal as well as overweight and obese subjects. Additionally, we were not able explore relationships between subjects classified as having normal muscle status and mild muscle depletion, or moderate muscle and severe muscle depletion. The poor response rate in QOL surveys limited the strength of findings and may have contributed to the discrepancies observed in scores between subjects based on NFPE muscle status and SMI. It was also assumed that BMI is representative of

adiposity and this study lacked additional measurement variables indicative of adiposity such as analysis of visceral adiposity, skin-fold measurements or NFPE of fat stores.

In conclusion, our findings support the continued use of the NFPE in clinical settings to determine muscle status, as this tool correlates with SMI. It appears that NFPE accuracy is diminished in those with excess adiposity, however, the small sample size of our study limits these findings. Future studies are needed with a larger study population to further investigate the impact of adiposity on the accuracy of muscle assessment using the NFPE. Additionally, future studies would benefit from the inclusion of variables indicative of muscle quality and additional variables more appropriate for assessing adiposity. Lastly, MUAC is currently used as a diagnostic-criteria for malnutrition in the pediatric population, however, it is not currently used in assessing adults for malnutrition. Results from this study demonstrate that there is an association between MUAC and lean mass indicating that this tool needs to be further explored in adults.

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Appendix A: IRB-Approved Study Documents

OREGON HEALTH & SCIENCE UNIVERSITY

MED. REC. NO._____

NAME_____

BIRTHDATE_____

IRB#: __20385_____

CO1450

OHSU Knight Cancer Institute Consent and Authorization Form

TITLE: MUSCLE ASSESSMENT THROUGH PALPATION COMPARED TO CT IMAGES

Study Investigator:

Julie McGuire, MS, RDN, LD
Graduate Programs in Human Nutrition
Oregon Health & Science University
3181 SW Sam Jackson Park Road
Portland, OR 97239
Phone: 503-494-7839
Email: mcguirju@ohsu.edu

OREGON HEALTH & SCIENCE UNIVERSITY

MED. REC. NO._____

NAME_____

BIRTHDATE_____

IRB#: __20385_____

CLINICAL RESEARCH CONSENT AND AUTHORIZATION
-SUMMARY OF KEY INFORMATION ABOUT THIS STUDY-

TITLE: MUSCLE ASSESSMENT THROUGH THE NUTRITION FOCUSED PHYSICAL EXAM COMPARED TO SKELETAL MUSCLE INDEX MEASURED BY CT IMAGING.

PRINCIPAL INVESTIGATOR: Julie McGuire, MS, RDN, LD *(503)-494-7839*

You are being asked to join a research study. This consent form contains important information to help you decide if you want to join the study or not.

PURPOSE:
The purpose of the study is to learn how muscle assessment through light palpation, called the nutrition focused physical exam, compares to muscle mass measured by CT images. We also want to look at how extra fat tissue impacts these measures.

DURATION:
Your participation in the study will consist of one (1) visit. Visits will last up to 30 minutes. We may ask to follow your health through the use of electronic medical records for up to one year.

PROCEDURES:
If you decide to take part in this study, you will undergo a brief physical exam of your muscles called a nutrition focused physical exam (NFPE). During this exam, light palpation will be used to examine the temporalis around your temples, the muscles of the chest, shoulder and back, and the muscles of the lower and upper leg. You may be asked to do clench your jaw, and raise your arm, legs, and toes during the exam. You may also be asked to push lightly on the examiner's hand and open and close your mouth. The exam can be done over light clothing.

You will also be asked to complete a brief, written or electronic survey during your visit or at home.

RISKS: Although we have made every effort to protect your identity, there is a minimal risk of loss of confidentiality.

BENEFITS: You may or may not personally benefit from being in this study. However, by serving as a participant, you may help us learn how to benefit patients in the future.

ALTERNATIVES:
You may choose not to participate in this study, and may receive standard treatment or participate in another study if one is available.

This is a voluntary research study. You do not have to join the study. Even if you decide to join now, you can change your mind later. Please ask the Investigator if you have any questions about the study or about this consent form.

END OF CONSENT SUMMARY

STUDY CONTACT INFORMATION

Purpose	Role	Contact Name	Contact Phone Number	Email
For medical questions about the study	Principal Investigator	Julie McGuire, MS, RDN, LD	503-494-7839	mcguirju@ohsu.edu
	Co-Investigator	Tyler Chase	503-494-7839	chasety@ohsu.edu
For non-medical questions about the study	Study Coordinator	Tyler Chase	503-494-7839	chasety@ohsu.edu
For questions about research in general	Ethics Committee	ORIO	503-494-7887	irb@ohsu.edu
For 24-hour medical emergencies	911	Emergency Dispatch	911	

INTRODUCTION

Medical personnel who carry out research studies are called "investigators." The investigator will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You can discuss your decision with your friends and family. You can also discuss it with your health care team or another doctor. If you have any questions, ask the investigator.

You are being asked to take part in this study because you are being seen by the Registered Dietitian Nutritionist for a nutrition focused physical exam as part of your routine care.

WHAT ARE MY OTHER CHOICES IF I DO NOT TAKE PART IN THIS STUDY?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the standard treatment
- you may choose to take part in a different study, if one is available

PURPOSE

WHY IS THIS STUDY BEING DONE?

The purpose of the study is to learn how muscle assessment through light palpation, called the nutrition focused physical exam, compares to muscle mass measured by CT images. We also want to look at how extra fat tissue impacts these measures.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

As many as 120 people will take part in this study which will be conducted at Oregon Health & Science University.

PROCEDURES

WHAT ARE THE STUDY GROUPS?

If you choose to participate in this study, you will have a brief physical exam after your visit with the Registered Dietitian Nutritionist. During this exam, light palpation will be used to assess the muscles of your upper and lower body.

HOW LONG WILL I BE IN THIS STUDY?

You will be in the study for one visit on the day of your visit with the Registered Dietitian Nutritionist. We make contact after your study visit, by phone or electronically, to follow-up on the completion of a brief survey.

WHAT TESTS AND PROCEDURES WILL I HAVE IF I TAKE PART IN THIS STUDY?

You will have a brief physical exam after your visit with the Registered Dietitian Nutritionist.

Before you begin the study:
You will be scheduled to see a Registered Dietitian Nutritionist as part of you routine care. You will also need to have or be scheduled for a CT scan ± 1 month from your nutrition visit as part of your routine care.

During the study:
If you can take part in the study, and you choose to take part, then you will need the following:

- Brief physical exam of the muscles of your upper and lower body
- Complete a brief, 36 question survey, during your visit or at home, about your health and how it impacts your quality of life. The survey should only take 10-15 minutes to complete.
- CT scan as part of your routine care if one has not been completed already

RISKS

WHAT POSSIBLE RISKS CAN I EXPECT FROM TAKING PART IN THIS STUDY?

Although we have made every effort to protect your identity, there is a minimal risk of loss of confidentiality.

BENEFITS

WHAT POSSIBLE BENEFITS CAN I EXPECT FROM TAKING PART IN THIS STUDY?

You may or may not personally benefit from being in this study. However, by serving as a participant, you may help us learn how to benefit patients in the future.

PRIVACY

WHO WILL SEE MY MEDICAL INFORMATION?

We will take steps to keep your personal information confidential, but we cannot guarantee total privacy.

We will create and collect health information about you as described in the WHY IS THIS STUDY BEING DONE and the WHAT TESTS AND PROCEDURES WILL I HAVE IF I TAKE PART IN THIS STUDY?

sections of this form. Health information is private and is protected under federal law and Oregon law. By agreeing to be in this study, you are giving permission (also called authorization) for us to use and disclose your health information as described in this form.

The investigators, study staff and others at OHSU may use the information we collect and create about you in order to conduct and oversee this research study.

We may release this information to others outside of OHSU who are involved in conducting or overseeing this research, including:

- The Food and Drug Administration (FDA)
- The Office of Human Research Protections (OHRP), a federal agency that oversees research in humans
- The National Cancer Institute (NCI)

Those listed above may also be permitted to review and copy your records, including your medical records.

We will not release information about you to others not listed above, unless required or permitted by law. We will not use your name or your identity for publication or publicity purposes, unless we have your special permission.

A code number will be assigned to your medical information. Only the investigators and people involved in the conduct of this study will be authorized to link the code number to you. Other investigators who may receive your medical information for research will be given only the code number which will not identify you.

When we send information outside of OHSU, they may no longer be protected under federal or Oregon law. In this case, your information could be used and re-released without your permission.

We may continue to use and disclose your information as described above indefinitely. Some of the information collected and created in this study may be placed in your OHSU medical record. While the research is in progress, you may or may not have access to this information. After the study is complete, you will be able to access any study information that was added to your OHSU medical record. Ask the investigator if you have questions about what study information you will be able to access, and when it will be available.

PARTICIPATION

CAN I STOP TAKING PART IN THIS STUDY?

Yes. You can decide to stop at any time. If you stop, you can decide whether or not to let the investigator continue to provide your medical information to the organization running the study.

Once your participation has ended, your cancer doctor will help you choose the next step in your cancer care.

The investigator will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study. The investigator may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

WHAT ARE MY RIGHTS IN THIS STUDY?

Your participation in this study is voluntary. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights. If you have any questions, concerns, or complaints regarding this study now or in the future, contact the principal investigator listed at the beginning of the form.

This research has been approved and is overseen by an Institutional Review Board ("IRB"), a committee that protects the rights and welfare of research participants. You may talk to the IRB at (503) 494-7887 or irb@ohsu.edu if:

- Your questions, concerns, or complaints are not being answered by the research team
- You want to talk to someone besides the research team
- You have questions about your rights as a research participant
- You want to get more information or provide input about this research.

You may also submit a report to the OHSU Integrity Hotline online at https://secure.ethicspoint.com/domain/media/en/gui/18915/index.html or by calling toll-free (877) 733-8313 (anonymous and available 24 hours a day, seven days a week).

You do not have to join this or any research study. You do not have to allow the use and disclosure of your health information in the study, but if you do not, you cannot be in the study.

If you do join the study and later change your mind, you have the right to quit at any time. This includes the right to withdraw your authorization to use and disclose your health information. If you choose not to join any or all parts of this study, or if you withdraw early from any or all parts of the study, there will be no penalty or loss of benefits to which you are otherwise entitled, including being able to receive health care services or insurance coverage for services. Talk to the investigator if you want to withdraw from the study

If you no longer want your health information to be used and disclosed as described in this form, you must send a written request or email stating that you are revoking your authorization to:

Knight Cancer Institute Clinical Trials
Attn: CRQA Assistant Director
Mail Code: KR-CRQA
3181 SW Sam Jackson Park Road
Portland, OR 97239
Email: trials@ohsu.edu

Your request will be effective as of the date we receive it. However, health information collected before your request is received may continue to be used and disclosed to the extent that we have already taken action based on your authorization.

The participation of OHSU students or employees in OHSU research is completely voluntary and you are free to choose not to serve as a research participant in this protocol for any reason. If you do elect to participate in this study, you may withdraw from the study at any time without affecting your relationship with OHSU, the investigator, the investigator's department, or your grade in any course.

You will be told of any new information that might make you want to change your mind about continuing to be in the study.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

There will be no cost to you or your insurance company to participate in this study.

WHAT HAPPENS IF I AM INJURED OR HURT BECAUSE I TOOK PART IN THIS STUDY?

If you believe you have been injured or harmed as a result of participating in this research and require treatment, contact Julie McGuire, MS, RDN, LD at 503-494-7839.

If you are injured or harmed by the brief physical exam, you will be treated. OHSU does not offer any financial compensation or payment for the cost of treatment if you are injured or harmed as a result of participating in this research. Therefore, any medical treatment you need may be billed to you or your insurance. However, you are not prevented from seeking to collect compensation for injury related to negligence on the part of those involved in the research. Oregon law (Oregon Tort Claims Act (ORS 30.260 through 30.300)) may limit the dollar amount that you may recover from OHSU or its caregivers and researchers for a claim relating to care or research at OHSU, and the time you have to bring a claim.

If you have questions on this subject, please call the OHSU Research Integrity Office at (503) 494-7887.

ADDITIONAL INFORMATION

WHERE CAN I GET MORE INFORMATION?

If you want more information about this study, ask the investigator.

WHO CAN ANSWER MY QUESTIONS ABOUT THIS STUDY?

You can talk to the investigator about any questions or concerns you have about this study or to report side effects or injuries.

SIGNATURE

MY SIGNATURE AGREEING TO TAKE PART IN THE STUDY

Your signature below indicates that you have read this entire form and that you agree to be in this study. We will give you a copy of this signed form.

Participant Printed Name	**Participant Signature**	**Date**
Person(s) Obtaining Consent Printed Name	**Person(s) Obtaining Consent Signature**	**Date**

Study Title:	**Muscle assessment through the nutrition focused physical exam compared to skeletal muscle index measured by CT imaging.**
Protocol Number:	STUDY00020385
Version Number:	1
Version Date:	4/16/20
Replaces:	N/A
Principal Investigator:	**Julie McGuire, MS, RDN, LD**
	Graduate Programs in Human Nutrition OHSU 3181 SW Sam Jackson Park Road Portland, OR 97239 Phone: 503-494-7839 Email: mcguirju@ohsu.edu
Participating Investigator(s):	Robert Martindale, M.D., Ph.D. OHSU Gastrointestinal and General Surgery 503-494-6900 Savitha Chandra, M.S., R.D., C.S.R., C.D.E., L.D OHSU Clinical Nutrition UHS SJH7 3181 S.W. Sam Jackson Park Rd. Portland, OR 97239 503-494-3779 Email: chandra@ohsu.edu Amanda Bryant, RD, CSO, LD OHSU Clinical Nutrition OC9C 3485 SW Bond Avenue Portland, OR 97239 503-494-5052 Email: bryanam@ohsu.edu Tyler Chase MS in Human Nutrition Graduate Student Graduate Programs in Human Nutrition OHSU 3181 SW Sam Jackson Park Road Portland, OR 97239 Phone: 503-494-7839 Email: Chasety@ohsu.edu **Alexander Guimaraes, MD, PhD** **OHSU Diagnostic Radiology**

	503418-0990

SUMMARY OF CHANGES

#	Section	Description of Change	Justification for Revision
1.	5.1.2	Follow-up for completion of QOL survey; addition of a survey link to complete survey electronically	Improve collection of QOL data; avoid the use of mail during COVID-19 pandemic
2.			
3.			
4.			
5.			

KNIGHT CANCER Institute

OHSU

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

AE	Adverse event
AND	Academy of Nutrition and Dietetics
ASPEN	American Society of Parenteral and Enteral Nutrition
CFR	United States Code of Federal Regulations
CRQA	Clinical Research Quality & Administration
CRRC	Clinical Research Review Committee (OHSU)
CRF	Case report form
CT	Computerized tomography
DEXA	Duel
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
eCRF	Electronic Case Report Form
eCRIS	Electronic Clinical Research Information System
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HIPPA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
MRI	Magnetic resonance imaging
MUAC	Mid-upper arm circumference
N/A	Not applicable
NCI	National Cancer Institute
NFPE	Nutrition Focused Physical Exam
OHRP	Office for Human Research Protections
OHSU	Oregon Health & Science University
PI	Principle Investigator
QOL	Quality of life
RDN	Registered Dietitian Nutritionist
SAE	Serious adverse event
SMA	Skeletal muscle area
SMI	Skeletal muscle index

1. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 OVERVIEW OF MALNUTRITION AND MUSCLE ASSESSMENT

Malnutrition is characterized by an imbalance in nutritional status, including both excessive and limited levels of intake. In the clinical setting, patients often present with conditions that both increase their nutritional needs, as well as impact their ability or desire to eat. Therefore, undernutrition is the most common form of malnutrition seen in the healthcare setting. Malnutrition can play a significant role in the loss of both lean and adipose tissue as well as reduced functional status, a syndrome called sarcopenia. This condition can manifest in a wide range of clinical settings including oncology, organ failure, geriatrics, and obesity.[1] Malnutrition and the subsequent development of sarcopenia are directly associated with decreased quality of life, and increased hospital length of stay, healthcare costs, and morbidity and mortality.[2]

While it is well known that malnutrition is associated with poor health outcomes, and increased morbidity and mortality, screening and assessment tools to diagnose malnutrition have long been a topic of controversy. For example, serum albumin has long been considered an indicator of nutritional status in hospitalized patients. However, evidence has shown that serum albumin levels are often reduced during inflammation, a common condition in hospitalized patients.[3] Yet, many clinicians still use this lab value to inaccurately identify malnutrition.

Identifying malnutrition often requires evaluating multiple assessment parameters, including body composition, anthropometrics, client history, nutrition intake and biochemical values. Multivariate screening tools to assess nutritional status date back to the 1970's with the development of "The nutritional metabolic profile",[4] and have proceeded to evolve into tools such as the "Subjective Global Assessment". Most recently, the AND and ASPEN have developed a consensus statement on the identification of malnutrition using six diagnostic criteria including weight loss, nutrition intake, hand grip strength, fluid status, and subcutaneous fat and muscle loss.[2] The NFPE is a tool, primarily used by RDNs, to assess subcutaneous fat and muscle stores, through palpation, to aid in the diagnosis of malnutrition. The AND and ASPEN's position is that the NFPE can provide a more accurate assessment of nutrition status, especially when subjective information is unable to be obtained, or time is limited.[5] This technique can also distinguish between moderate to severe malnutrition, providing further information that can help determine the level of intervention required for the patient. While physical palpation assessments can be a very effective tool, they are still subjective in nature. Other tools exist that can provide more objective measurements, including DEXA, MRI, ultrasound and CT imaging.

CT is a method often used in clinical settings to help diagnose and surveille certain conditions. This technique provides cross-sectional images of body regions and can distinguish between bones, adipose tissue, muscle, organs and air. Therefore, muscle loss and sarcopenia can be diagnosed using CT imaging. A vast body if evidence has focused on CT scans at the 3rd lumbar vertebrae using specific muscle index cutoffs to identify sarcopenia and subsequent morbidity and mortality rates.[6] Although CT imaging can provide some of the most accurate information in regards to body composition, and subsequently nutritional status, they are not indicated or available for all patients in a clinical setting. Additionally, using CT scans to analyze body tissues requires additional training and software. Due to the limitation associated with methods such as CT imaging, this further exemplifies the importance of having other methods for bedside muscle assessment, such as the NFPE.

1.2 STUDY RATIONALE

Although the NFPE is becoming more widely used in the clinical setting, in conjunction with the AND and APSEN malnutrition consensus statement, to identify malnutrition, little is known about

how results from this subjective assessment of muscle mass compare to objective assessment measures like CT imaging. The overall goal of this study is to compare and contrast muscle assessment from the NFPE to skeletal muscle index measured by CT imaging.

2. OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE AND ENDPOINT

To describe how muscle assessment, measured through the NFPE, compares to skeletal muscle index, measured through CT imaging using defined skeletal muscle index cutoffs.

2.2 SECONDARY OBJECTIVE(S) AND ENDPOINT(S)

To determine how excess adiposity impacts the accuracy of muscle assessment through the NFPE using abdominal CT skeletal muscle index cutoff values as a comparative standard.

To evaluate the interobserver reliability of muscle assessment using NFPE and how reliability is impacted by excess adiposity.

2.3 EXPLORATORY OBJECTIVES

To describe how quality of life is related to muscle mass, described by the NFPE and CT imaging.

3. INVESTIGATIONAL PLAN

3.1 STUDY DESIGN

This is a descriptive study including patients, who have a NFPE and CT image as part of their standard of care, seen at the Surgical and Medical Oncology, Infusion, and Liver and Kidney Transplant Clinics and Digestive Health Center at OHSU in Portland, OR. Participants will be screened for recruitment prior to their nutrition consult or visit with the clinic RDNs. As part of their routine clinical evaluation, participants will undergo a NFPE performed by a RDN. Following the participant's scheduled appointment/visit, participants will be consented and trained study personnel will perform a NFPE focused only on muscle assessment through palpation. Additional demographic and clinical data, as well as NFPE assessment data from the primary RDN, will be gathered from the electronic medical record. A quality of life questionnaire will be completed by the patient. CT images will be obtained from the participant's medical record and the borders of muscles of interest will be identified by OsiriX® analysis software (version 5.8 PIxemo SARL, Geneva, Switzerland) to generate SMA based on predefined Hounsfield units between -29 to 150. Furthermore, SMA measures will be normalized by the patient's height (m2) to determine skeletal muscle index (SMI) (cm2/m2). The goal will be to asses approximately 20 participants per month for six to seven months.

3.2 STUDY SETTING

The study will be conducted at one site (OHSU). It is expected that approximately 80-120 participants will be enrolled in this study.

3.3 STUDY DURATION

The recruitment and enrollment period will be from September 2019 to May 2020.

3.3.1 DURATION OF STUDY PARTICIPATION

The study duration per participant will be one day, with up to 7-14 days screening. There will be no follow-up period.

4. STUDY POPULATION

This study will include men and women 18 years and older. The participants will be liver/kidney transplant and oncology patients seen at OHSU. Subjects will be screened for eligibility prior to their nutrition consult or visit with the clinic RDN. Approximately 40-60 participants will be screened each month with a goal enrollment of 20 participants per month.

4.1 PARTICIPANT INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. Age ≥ 18 years. Both men and women and members of all races and ethnic groups will be included.
2. English speaking
3. OHSU patient seen by the Surgical and Medical Oncology, Infusion, or Liver and Kidney Transplant Clinics or Digestive Health Center with a CT scan including the 3rd lumbar vertebrae completed or scheduled as part of their routine care ± 1 month from their nutrition consult or visit with the clinic RDN
4. Ability to understand and the willingness to sign a written consent document

4.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. < 18 years old
2. Non-English speaking
3. No CT scan available or scheduled.

4.3 VULNERABLE POPULATIONS

No vulnerable populations will be included in this study.

4.4 STRATEGIES FOR RECRUITMENT AND RETENTION

All patients who meet the inclusion criteria and who are receiving care at OHSU's Surgical and Medical Oncology, Infusion, or Liver and Kidney Transplant Clinics or Digestive Health Center will be invited to participate in this this study. Potential participants will be approached by a member of the research staff and will be asked to review a copy of the informed consent form after their routine nutrition consult or visit with the clinic RDN. The study personnel will review the informed consent form with potential participants and address any questions or concerns prior to obtaining written informed consent for participation in this study. The research staff will also address any future questions or concerns of the participants.

Only the individuals who have provided directly their written informed consent for participation in this study will be placed in the study. The participation of patients who are mentally incapacitated (e.g., comatose, unresponsive) will not be sought (i.e., during the period in which they are mentally incapacitated).

4.4.1 ACCRUAL ESTIMATES

No participant will be excluded from the study on the basis of gender, racial or ethnic origin. Male, female and minority volunteers will be recruited for this study from the general population and approximately 50% men and 50% women will be studied. Gender-nonconforming and gender-fluid individuals as members of the general population will also be recruited. The projected gender, racial, and ethnic composition of the study will represent that of the state of Oregon.

TABLE 1. PROJECTED ACCRUAL FOR PRESENT STUDY BASED ON OREGON POPULATION DEMOGRAPHICS

Ethnic Category	**Sex/Gender**					
	Females		**Males**		**Total**	
	n	*%*	n	*%*	n	*%*
Hispanic or Latino		*6.4*	-	*6.3*	1	*12.7*
Not Hispanic or Latino		*38.7*	-	*37.9*		*87.3*
Ethnic Category: Total of all participants*			-		1	*100**
Racial Category						
American Indian or Alaskan Native		*0.9*		*0.9*		*1.8*
Asian		*2.2*		*2.2*		*4.4*
Black or African American		*1.1*		*1.0*		*2.1*
Native Hawaiian or other Pacific Islander		*0.2*		*0.2*		*0.4*
White		*44.2*		*43.4*		*87.6*
Two or more races		*1.9*		*1.8*		*3.7*
Racial Category: Total of all participants*		*50.5*		*49.5*		*100*

Source: Adapted from U.S. Census Bureau, 2016.
*Totals may not equal 100 due to rounding.

4.5 REGISTRATION PROCEDURES

In order to participate in this study, signed informed consent must be obtained from the participant or the participant's legally acceptable representative. The current Institutional Review Board (IRB) approved informed consent must be signed and dated by each participant prior to undergoing any study procedures that are not part of institutional standard care.

Registration from all consented participants must be entered into the electronic data capture

system. At a minimum, registration of study participants will include signed copies of the local IRB-approved, informed consent form and HIPAA authorization

Each study site is expected to maintain a screening log of all participants who are approached for the study. The log documents an explanation for exclusion due to screen failure.

4.6 PARTICIPANT SCREENING AND ENROLLMENT

The study personnel and/or clinic RDN will identify potential patients through review of the clinic schedule. The screening process will end when 120 participants are enrolled or the end of the study period. Patients that qualify for the study will be asked for their consent after the nutrition consult visit or visit with the clinic RDN.

4.7 PARTICIPANT WITHDRAWAL OR DISCONTINUATION

Participants are free to withdraw consent and discontinue participation in the study at any time and without prejudice to their care. No further participant contact should be made if the participant withdraws consent for participation in the study. Information about the reason(s) for discontinuation should be collected at the time the participant withdraws consent.

5. STUDY PROCEDURES/EVALUATIONS AND SCHEDULE

5.1 STUDY SPECIFIC PROCEDURES

5.1.1 NFPE

While the NFPE can include assessment of fluid status, grip strength, fat stores and micronutrient deficiencies, this study will focus on the utilization of the NFPE for the assessment of muscle mass through palpation. During their scheduled nutrition visit, the clinic RDN will perform a NFPE as part of the participant's standard care. Immediately following the visit, consented participants will undergo another NFPE performed by trained study personnel. This NFPE will be an evaluation of muscle stores only. NFPE muscle assessment will include: assessment of the temporalis muscles using light palpation with the index and middle fingers; assessment of the shoulder and clavicle region including visual inspection and palpation of the deltoid and pectoralis muscles; assessment of the scapula region requiring palpation of the latissimus dorsi, trapezius and deltoids while having the subject extend their arm against some resistance; assessment of the interosseous muscle requiring the patient to touch their index finger and thumb forming a circle; assessment of the thigh region requiring palpation of the quadriceps while having the subject slightly elevate their leg; and assessment of the calf requiring palpation of the gastrocnemius muscle while having the subject flex and extend their foot.[2] Participant's mid-upper arm circumference (MUAC) will also be measured. NFPE results from the clinic RDN will be recorded within the participant's medical record per standard care. Results from follow-up NFPE of muscle mass conducted by study personnel will be recorded on a study assessment form (Table 2).

TABLE 2: NFPE MUSCLE ASSESSMENT FORM

Region	Muscle Mass: Normal or Mild, Moderate, Severe Wasting
Temporalis	
Shoulder Region	

Clavicle Region	
Scapular Region	
Interosseous	
Quadricep	
Calf	
Overall Assessment of Muscle Mass	

5.1.2 QUALITY OF LIFE

Quality of life will be measured using the Medical Outcomes Study Questionnaire Short Form 36 Health Survey (SF-36). Participants will be given the survey at the end of their visit as well as a self-addressed, stamped envelope. Participants can complete the survey during their visit or return it via mail to the study team. The study team will use an electronic message through MyChart or a phone call to follow up with participants who do not return the survey by mail. A link will be provided to complete the survey electronically through OHSU's secured survey tool Qualtrics.

5.1.3 CT ANALYSIS

Skeletal muscle area (SMA) will be measured on an axial CT section of the L3 region obtained during abdominal CT or PET/CT imaging as part of the standard of care. Only CT images obtained +/- 30 days from NFPE assessment will be included. CT images will be obtained from participant's medical records. Using these scans, a single trained examiner will measure skeletal muscle area (SMA) (cm2) of the cross-sectional area of the L3 muscle group which includes the external oblique, internal oblique, transversus abdominis, rectus abdominus, psoas, quadratus lumborum, and erector spinae. The borders of muscles of interest will be identified using OsiriX® analysis software (version 5.8 PIxemo SARL, Geneva, Switzerland) to generate SMA based on predefined Hounsfield units between -29 to 150. Further, SMA measures will be normalized by the patient's height (m2) to determine skeletal muscle index (SMI) (cm2/m2). Relative SMI will be calculated for each sex as follows: relative SMI= (SMI)/ (sex-specific median SMI).

5.2 **SCREENING ASSESSMENTS**

Seven to 14 days prior to their nutrition clinic visit, the following information will be screened in potential participant medical records: medical diagnosis, age, sex, height, weight, and availability of CT image of L3 region. Participants who meet the inclusion criteria will be considered eligible for the study.

5.3 **BASELINE ASSESSMENTS**

During their scheduled nutrition visit, the clinic RDN will perform a NFPE as part of the participant's standard care.

5.4 **ON-STUDY ASSESSMENTS**

Immediately following the visit, consented participants will undergo another NFPE performed by trained study personnel. This NFPE will be an evaluation of muscle stores only. The participant will be given a QOL survey to complete. Age, sex, height, and weight may be obtained during the time of consent if these items are not listed in their medical record.

5.5 SCHEDULE OF EVENTS

TABLE 3. SCHEDULE OF PROCEDURES AND EVALUATIONS

	Screening	
Visit Days (± 3 Days)	**Days -14 to -1**	**Day 1**
Medical chart review	X	
Informed consent		X
Inclusion/exclusion criteria	X	
Medical history (including weight loss history)	X	
Height and weight	X	X
Nutrition Focused Physical Exam		X
Mid-upper Arm Circumference		X
Medical Outcomes Study Questionnaire Short Form 36 Health Survey (SF-36)		X
CT imaging	X	X
Standard nutrition consult or visit		X

6. SAFETY

6.1 SPECIFICATION OF SAFETY PARAMETERS

The Investigator is responsible for monitoring the safety of participants who have enrolled in the study. Any clinically significant adverse events persisting at the end of study visit will be followed by the Investigator until resolution/stabilization or death, whichever comes first.

6.2 DEFINITIONS

6.2.1 ADVERSE EVENT (AE)

An adverse event is defined as any undesirable physical, psychological or behavioral effect experienced by a participant during their participation in an investigational study, in conjunction with the use of the investigational product, whether considered intervention-related (21 CFR 312.32 (a)). In general, this includes signs or symptoms experienced by the participant from the time of signing the informed consent to completion of the study.

AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the participant and/or observed by the Investigator or medical staff.
- Clinically significant laboratory abnormalities.
- A significant worsening of the participant's condition from study entry.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study treatment that resolve but then recur after treatment.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study treatment which increase in frequency, intensity, or a change in quality after treatment.

6.2.2 SERIOUS ADVERSE EVENT (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor-investigator, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
- In-patient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and/or participant may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include:

- Allergic bronchospasm requiring intensive treatment in an emergency room or at home,
- Blood dyscrasias or convulsions that do not result in in-patient hospitalization, or
- The development of drug dependency or drug abuse.

6.2.3 UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers UPs involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

1. Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
2. Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

This study will use the OHRP definition of UP.

6.2.4 SEVERITY OF EVENT

The Investigator will grade the severity of each AE using, when applicable, the current version of the CTCAE v5.0. In the event of an AE for which no grading scale exists, the Investigator will classify the AE as defined below:

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2:	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4:	Life-threatening consequences; urgent intervention indicated.
Grade 5:	Death related to AE.

Note: a semi-colon indicates 'or' within the description of the grade.

6.2.5 ASSESSMENT OF CAUSALITY RELATIONSHIP TO STUDY INTERVENTION

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

Definitely Related:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Potentially Related:	There is some evidence to suggest a causal relationship
Unrelated:	The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology.

6.3 REPORTING PROCEDURES

6.3.1 OHSU IRB REPORTING OF UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

Unanticipated Problems and AEs will be reported to OHSU IRB according to the policies, procedures and guidelines posted on the OHSU IRB web site.

Events that must be reported by the Investigator to the IRB are detailed in the OHSU IRB **Investigator Guidance: Prompt Reporting Requirements (HRP-801)**. At a minimum, events requiring reporting to the IRB include:

- Data Safety Monitoring Board/Committee letters recommending changes or discussing new risks
- Unauthorized disclosure of confidential participant information

6.4 RISK ASSESSMENT

Although we have made every effort to protect your identity, there is a minimal risk of loss of confidentiality.

6.4.1 POTENTIAL BENEFITS OF STUDY PARTICIPATION

You may or may not personally benefit from being in this study. However, by serving as a participant, you may help us learn how to benefit patients in the future.

7. STATISTICAL CONSIDERATIONS

7.1 STUDY OUTCOME MEASURES

Primary outcome measures are muscle assessment as described by the NFPE, as a categorical variable, and muscle mass measured by CT imaging using SMI, as a continuous variable, and then categorized by sarcopenia status.

7.2 ANALYSIS PLAN

Data analysis will include descriptive statistics for all study subjects including age, sex, race, height, weight, BMI, type of cancer or organ transplant. Means, medians, standard deviations and ranges will be calculated for continuous outcome variables including SMI of L3 region CT scans. Analysis of variance (ANOVA) will be used to determine the differences in CT muscle area among the various NFPE muscle assessment groups. Categorical outcome variables include NFPE muscle assessment: normal, mild, moderate and severe. Logistic regression analysis will be performed using muscle assessment described as a categorical variable using NFPE data (normal, mild, moderate, severe) and as a continuous variable based on muscle areas calculated by CT scans. Chi-squared tests will be performed using muscle assessment described as a categorical variable using NFPE data (normal, mild, moderate, severe) and as a categorical variable based on sarcopenic and non-sarcopenic muscle area identified using pre-defined muscle area cut-off values. Logistic regression analysis will be performed using muscle assessment described as a categorical variable using NFPE data (normal, mild, moderate, severe) and as a continuous variable based on muscle areas calculated by CT scans, stratified by weight status (BMI ≥ 25). Chi-squared tests will be performed using muscle assessment described as a categorical variable using NFPE data (normal, mild, moderate, severe) and as a

categorical variable based on sarcopenic and non-sarcopenic muscle area identified using pre-defined muscle area cut-off values, stratified by weight status (BMI < 25.5, BMI > 25.5). P values <0.05 will be considered statistically significant for all analyses. Cohen's kappa coefficient will be used to measure interrater reliability of two raters and their agreement on muscle assessment using NFPE. Estimates of means, standard error and confidence intervals for each of the SF-36 scales will be examined. Differences in means according to muscle mass variables will be tested using linear and logistic regression analysis.

8. DATA HANDLING AND MANAGEMENT RESPONSIBILITIES

8.1 SOURCE DATA/DOCUMENTS

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The Investigator will maintain adequate case histories of study participants, including source documentation.

8.2 PARTICIPANT & DATA CONFIDENTIALITY

The information obtained during the conduct of this study is confidential, and unless otherwise noted, disclosure to third parties is prohibited. Information contained within this study will be maintained in accordance with applicable laws protecting participant privacy, including the provisions of the Health Insurance Portability and Accountability Act (HIPAA).

Participant confidentiality is strictly held in trust by the participating Investigator(s) and study team. This confidentiality is extended to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

Upon enrollment, participants will be assigned a code that will be used instead of their name, medical record number or other personally identifying information. Electronic files for data analysis will contain only the participant code. Codes will not contain any part of the 18 HIPAA identifiers (e.g., initials, DOB, MRN). The key associating the codes and the participants' personally identifying information will be restricted to the Investigator and study staff. The key will be kept secure on a restricted OHSU network drive a in a limited access folder.

The study participant's contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and institutional regulations. Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored within the Knight Cancer Institute per OHSU's Information Security Directives. Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Knight Cancer Institute research staff will be secured and password protected per OHSU's Information Security Directives.

8.3 MAINTENANCE OF RECORDS

Records and documents pertaining to the conduct of this study, source documents, and consent forms, must be retained by the Investigator for a period of [3 years] post discontinuation of the study. No records will be destroyed without the written consent of the investigator.

If the Investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another investigator at OHSU. Records must be maintained according to institutional or FDA requirements.

8.4 HANDLING OF STORED DATA

Participant medical information will be stored electronically within the OHSU-approved Box secure cloud storage. Study folders will only be shared with and accessed by study personnel. Participant medical information will be curated from OHSU's Epic electronic health record (EHR) and the data entered into the spreadsheet. Upon enrollment, a code will be assigned to each participant's chart that will be used in place of name, medical record number or other personally identifying information. Electronic files for data analysis will contain only the participant code. Codes will not contain any part of the 18 HIPAA identifiers (initials, DOB, MRN). The key associating the codes and the participants personally identifying information will be restricted to the Investigator and study staff. The key will be kept secure on a restricted OHSU network drive a in a limited access folder. The data will be stored until completion of study and publication.

8.5 PUBLICATION AND DATA SHARING POLICY

Results from this study may be disseminated through publication.

9. MONITORING

9.1 DATA QUALITY

Quality control procedures for this study include routine (i.e., quarterly) monitoring by the Principal Investigator of:

1. the removal of direct identifiers from information,
2. the documentation of investigator access to the data,
3. the security of the database linking the codes with participant identifiers and the documentation of investigator access to this database;
4. any conditions that may negatively impact the confidentiality of information.

9.2 OHSU KNIGHT CANCER INSTITUTE DATA & SAFETY MONITORING PLAN

This study is under the oversight of the Knight Cancer Institute's Data and Safety Monitoring Committee (DSMC) as described in the Knight institutional Data & Safety Monitoring Plan (DSMP). The Knight DSMP outlines the elements required to ensure the safety of clinical study participants, the accuracy and integrity of the data and the appropriate modification of cancer-related clinical research for which significant benefits or risks have been discovered or when the clinical study cannot be successfully concluded. The Knight DSMP also describes the methods and procedures for ensuring adequate oversight of cancer-related research at OHSU.

As described in the Knight DSMP, regardless of a study's risk level and any specific Knight oversight in place, the Investigator is singularly responsible for overseeing every aspect of the

design, conduct, and final analysis of his/her investigation. The DSMC is responsible for conducting Quality Assurance audits on CI approved protocols. This low risk investigator-initiated study may be randomly audited by the DSMC audit team.

10. ETHICS/PROTECTION OF HUMAN PARTICIPANTS

10.1 ETHICAL STANDARD

The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and the ICH E6.

10.2 INSTITUTIONAL REVIEW BOARD

The protocol and informed consent form will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

10.3 INFORMED CONSENT

Written informed consent will be obtained from all participants, or the legally authorized representative of the participant, participating in this study, as stated in the Informed Consent section of 21 CFR Part 50. If a participant's signature cannot be obtained, and for all participants under the age of 18, the Investigator must ensure that the informed consent is signed by the participant's legally authorized representative. Documentation of the consent process and a copy of the signed consent shall be maintained in the participant's medical record.

Informed consent is a process that is initiated prior to the individual's agreement to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families as appropriate. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The Investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks/benefits of the study, alternatives to participation, and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.4 PROTOCOL REVIEW

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Cancer Institute's Clinical Research Review Committee (CRRC) and the appropriate IRB prior to any participant being consented on this study.

10.5 CHANGES TO PROTOCOL

Any modification of this protocol must be documented in the form of a protocol revision or amendment submitted by the Investigator and approved by the CRRC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the participant. In that event, the Investigator must notify the IRB within 5 business days after the implementation.

11. REFERENCES

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6. Prado CMM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *The Lancet Oncology.* 2008;9(7):629-635.

36-Item Short Form Survey Instrument (SF-36)

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- 1 - Excellent
- 2 - Very good
- 3 - Good
- 4 - Fair
- 5 - Poor

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2. **Compared to one year ago**, how would you rate your health in general **now**?

- 1 - Much better now than one year ago
- 2 - Somewhat better now than one year ago
- 3 - About the same
- 4 - Somewhat worse now than one year ago
- 5 - Much worse now than one year ago

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○ 1	○ 2	○ 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○ 1	○ 2	○ 3
5. Lifting or carrying groceries	○ 1	○ 2	○ 3
6. Climbing **several** flights of stairs	○ 1	○ 2	○ 3
7. Climbing **one** flight of stairs	○ 1	○ 2	○ 3
8. Bending, kneeling, or stooping	○ 1	○ 2	○ 3
9. Walking **more than a mile**	○ 1	○ 2	○ 3
10. Walking **several blocks**	○ 1	○ 2	○ 3
11. Walking **one block**	○ 1	○ 2	○ 3
12. Bathing or dressing yourself	○ 1	○ 2	○ 3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	1	2
14. **Accomplished less** than you would like	1	2
15. Were limited in the **kind** of work or other activities	1	2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	1	2
18. **Accomplished less** than you would like	1	2
19. Didn't do work or other activities as **carefully** as usual	1	2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- 1 - Not at all
- 2 - Slightly
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely

21. How much **bodily** pain have you had during the **past 4 weeks**?

- 1 - None
- 2 - Very mild
- 3 - Mild
- 4 - Moderate
- 5 - Severe
- 6 - Very severe

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22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- 1 - Not at all
- 2 - A little bit
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

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32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- 1 - All of the time
- 2 - Most of the time
- 3 - Some of the time
- 4 - A little of the time
- 5 - None of the time

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

ABOUT

The RAND Corporation is a research organization that develops solutions to public policy challenges to help make communities throughout the world safer and more secure, healthier and more prosperous. RAND is nonprofit, nonpartisan, and committed to the public interest.

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