Exploring the Relationship between CT Determined Skeletal Muscle Mass and Physical Functional Limitation in Lung Cancer Patients: A Gender-Based Analysis

Shiva Raj Timsina

A Thesis Submitted in Partial Fulfillment of the

Requirements for the Degree of Master of Science in Health Sciences

and Clinical Research

Prince of Songkla University

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Major Program	Health Sciences and Clinical Research

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I hereby certify that this work has not been accepted in substance for any degree, and is not being currently submitted in candidature for any degree.

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ABSTRACT

Background: Low skeletal muscle mass is a prevalent issue in lung cancer patients, with potential implications linked to poor prognosis, treatment toxicity, impaired physical functions and reduced survival. Despite previous reports on the associations between low skeletal muscle mass and physical functions, conflicting results have been reported in the literature. The relationship between skeletal muscle mass and physical function in cancer patients is complex depending on various factors such as age, gender, co morbidities and treatment received. The influence of gender differences on muscle mass and its impact on physical function is not clearly understood.

Objective: To explore gender differences in skeletal muscle mass measured using CT-defined 3rd lumbar vertebra skeletal muscle index(L3SMI) and its association to physical functional limitation measured using short physical performance battery test (SPPB) in lung cancer patients.

Material and methods: A cross-sectional study of 172 lung cancer patients. 59.9 % of patients were enrolled before treatment, 27.9 % during treatment and 12.2 % during surveillance after treatment. Skeletal muscle index (SMI) was assessed utilizing CT determined skeletal muscle area (SMA) at the 3rd lumbar vertebra. The SPPB score was

used to assess physical functions and physical functional limitation was defined as a score less than or equal to 9. SMI, age and gender impact on physical limitation was assessed using logistic regression.

Results: The study included 95 females and 77 males with a mean(SD) age of 66 (9.7) years. Females had a lower mean(SD) weight of 53 (10.4) kg and a slightly higher mean(SD) BMI of 23 (4.1) as compared to males. The logistic regression analysis revealed that SMI was significantly associated with the outcome of PFL in lung cancer patients (OR = 0.96, 95% CI: 0.91-1.00, p = 0.034). However, the inclusion of gender as a predictor did not show a significant impact on the outcome (OR = 0.50, 95% CI: 0.21-1.15, p = 0.11). Age, on the other hand, emerged as a significant predictor of the outcome (OR = 1.14, 95% CI: 1.09-1.21, $p < 0.001$), with each year increase in age associated with 14% higher odds of experiencing physical functional limitation. The best-fitting model, based on AIC and BIC values, included SMI, gender, and age as predictors. The AIC and BIC values for this model were 165.43 and 178.02, respectively. In comparison when SMI was included as the only predictor, it showed higher AIC (199.21) and BIC (205.50) values.

Conclusion: Increasing age and decreasing skeletal muscle mass were associated with a higher likelihood of experiencing physical functional limitations. Gender, however, did not significantly affect the relationship between skeletal muscle mass and functional limitations. Instead, the combined effect of sex, age, and skeletal muscle mass was found to be important in determining the likelihood of individuals facing physical functional limitations.

Keywords: Skeletal muscle mass, SPPB, lung cancer, sarcopenia, physical functions

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Shiva Raj Timsina

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List of abbreviations

World Health Organization: WHO

Non-small cell lung cancer: NSCLC

Body mass index: BMI

Computed tomography: CT

Magnetic resonance imaging: MRI

Dual energy X-ray absorptiometry: DEXA

Bioelectrical impedance analysis: BIA

Time up and go test: TUG

Short physical performance battery: SPPB

Skeletal muscle index: SMI

Skeletal muscle area: SMA

Appendicular skeletal muscle mass: ASM

SMI at L3 vertebra: L3SMI

European working Group on Sarcopenia in Older People: EWGSOP

Asian Working Groups in Sarcopenia: AWGS

Physical functional limitation: PFL

Quality of Life: QoL

Hospital Information System: HIS

Chapter 1

Introduction

1.1 Background and Rationale

Lung cancer is second most commonly diagnosed cancer in 2020 with an estimated total cases of 1,435,943 in males and 770,828 in females [1]. Lung cancer accounts for 18% of global cancer deaths, making it a significant contributor to cancer mortality worldwide. [2]. The cumulative risk of developing lung cancer between the ages of 0 and 74 is 3.78 % in males and 1.77 % in females [1]. Non-small cell lung cancer (NSCLC) represents 80-85% of all lung cancers as compared to less common small cell lung cancer [3]. Past few years have seen improved progress in newer therapies for lung cancer treatment, particularly in the areas of genetic identification, targeted therapies, and immunotherapies [4]. The outcome of lung cancer can vary depending on various factors such as the stage of the disease, age of diagnosis, and socioeconomic status [5]. Furthermore, sarcopenia, with prevalence of 43% among lung cancer patients, has been consistently associated with adverse outcomes such as poor prognosis, treatment-related complications, impaired physical function, and reduced survival. [6–11].

Sarcopenia is defined as decline in muscle strength, muscle quantity/quality (skeletal muscle mass), and physical performance [12,13]. Diagnosis of sarcopenia is confirmed by demonstrating reduced skeletal muscle mass while physical performance can be used to assess severity of sarcopenia [12]. The changes in patients' weight and BMI doesn't always mirror the progressive loss of skeletal muscle mass particularly in patients with sarcopenic obesity and other pathologic conditions causing fluid retention [14,15]. Assessment of skeletal muscle mass is performed with tests like computed tomography/magnetic resonance imaging (CT/MRI), dual energy Xray absorptiometry (DXA) or bioelectrical impedance analysis (BIA). Physical performance is evaluated using gait speed, time up and go test (TUG) or short physical performance battery (SPPB) [12]. Measuring physical performance with SPPB allows a reliable performance based assessment of physical functions and can be used to appropriately

measure changes in functional limitation overtime [16,17]. Moreover, SPPB has potential to predict completion of chemotherapy and post-surgical complications in lung cancer patients[18,19].

In 2020 Williams et al reported that there is expedited decline in skeletal muscle mass in cancer patients as compared to normal age-related decline in participants without cancer [20]. Similar findings have been observed in lung cancer patients, particularly when patients are treated with chemotherapy [9,14,21,22]. In addition to decline in skeletal muscle mass, cancer patients also exhibit decline in other parameters of sarcopenia i.e., muscle strength and physical performance which leads to functional limitation [9,20]. However, the association between skeletal muscle mass and functional limitation is not completely understood. Despite several previous reports on the associations between low skeletal muscle mass and physical functions, conflicting results have been reported in the literature [9,23–25]. A recent meta-analysis of studies on various types of cancer, including lung cancer patients, found that lower skeletal muscle mass was associated with low physical function [23]. This is consistent with another study which included 734 lung cancer patients and found a significant non-linear association between skeletal muscle mass and physical functions. Notably, these studies relied on patient-reported questionnaires rather than performance-based tests. A study by Naito et al. involving 30 lung cancer patients undergoing chemotherapy treatment, observed a positive association between decline in skeletal muscle mass and physical functions assessed through performance-based measures [9]. Conversely, a study encompassing patients with various cancer types, which evaluated physical function using both patient-reported and performance-based tests, did not observe a significant association between skeletal muscle mass and physical function [24]. These findings suggest that the relationship between skeletal muscle mass and physical function in cancer patients may be complex and influenced by various factors such as age, gender, co-morbidities and assessment methods.

Previous research in lung cancer patients has demonstrated the presence of gender differences in the development of low skeletal muscle mass [26–28]. For instance, Baracos et al conducted an evaluation of 441 lung cancer patients and observed that

61% of males exhibited a decline in skeletal muscle mass, whereas the corresponding proportion among females was 31% [27]. The exact cause of these differences is not well understood however it is believed that men have a higher susceptibility for weight loss, grip strength loss and loss of muscle mass owing to biological differences in muscle fibers, gene expression and other factors such as sex hormones [29]. More importantly it has been observed it's not just the difference in skeletal muscle mass, but outcome associated with these differences also differs in male and female. A study on advanced gastrointestinal and lung cancer patients found that low skeletal muscle mass is associated with increased cancer fatigue in males but not in females. [28]. Similar gender differences may exist in defining the complex association of skeletal muscle mass and physical functions. A better understanding of this relationship may aid in early identification of patients with increased risk of developing functional impairment which can be helpful to provide targeted intervention. Therefore, we aim to explore the effect of gender differences in CT determined skeletal muscle mass and its association to physical functions in lung cancer patients.

1.2 Primary objective:

To evaluate effects of gender differences in CT determined skeletal muscle mass measured at 3rd lumbar vertebra (L3SMI) and its association to physical functional limitation (SPPB score) in lung cancer patients.

1.3 Literature review

Lung cancer

In 2020, World Cancer Report, WHO reported that lung cancer leads to 18% of all cancer deaths worldwide with 5-year survival rate at 10-20 percent [2]. Overall, lung cancer is second most common diagnosed cancer in 2020 with estimated total cases of 1,435,943 males and 770,828 females. It is commonest diagnosed cancer in males and second most common diagnosed cancer in females with a cumulative risk of developing

lung cancer from 0-74 years of age is 3.78 % in males and 1.77 % in females [1]. Lung cancer is divided into non-small cell lung cancer (NSCLC) and small cell lung cancer. The former accounts for 80-85% of all lung cancers cases [3]. Lung cancer is common throughout the globe, however highest incidence is noted in parts of North America, East Asia, Central and Eastern Europe [2]. Despite improvements in medical therapies for advanced lung cancer patients, there still remains a low overall survival rate.

Sarcopenia: definition, pathogenesis and evaluation

Cancer cachexia is a syndrome that cannot be treated with standard diet therapy, characterized by progressive decline in skeletal muscle mass plus or minus fat mass loss which slowly leads to functional impairment. Deviant metabolism and reduced oral intake led to this multifactorial syndrome where there is negative protein-energy balance. Sarcopenia is an important component of cancer cachexia [30]**.** In 2019, the European working Group on Sarcopenia in Older People (EWGSOP) defined sarcopenia as decline in parameters such as muscle strength, muscle quantity/quality and physical performance. In the same year updated consensus report from Asian Working Groups in Sarcopenia (AWGS) recommended using similar criteria for diagnosis of sarcopenia. According to these consensuses various tests like computed tomography(CT)/magnetic resonance imaging (MRI), bioelectrical impedance analysis(BIA) and dual energy x-ray absorptiometry(DEXA) scan were recommended for measuring skeletal muscle mass. These modalities use different parameters to express skeletal muscle mass such as in BIA/ DEXA skeletal muscle mass is expressed in terms of appendicular skeletal muscle mass (ASM) and in CT scan the skeletal muscle mass is expressed in terms of cross-sectional skeletal muscle area (SMA)[12,31]. Over the years there have been many studies focusing on sarcopenia, while older studies have used the terms sarcopenia and cancer cachexia interchangeably and have primarily relied on skeletal muscle mass to define sarcopenia, recent studies have investigated sarcopenia as a distinct condition defined by muscle strength, skeletal muscle mass and physical performance.

The pathogenesis of sarcopenia involves several mechanisms such as endocrine related abnormalities of insulin resistance, abnormal thyroid function, or neuromuscular

factors such as neurodegenerative diseases , low physical activity and immobility. In addition, especially in cancer patients, it is believed that there is direct effect of cancer therapies on skeletal muscle mass together with poor nutritional intake and chronic fatigue that contributes to development of sarcopenia [32]. Primary sarcopenia is an age-related decline in skeletal muscle mass with associated decline in muscle strength and physical performance. Secondary sarcopenia is associated with chronic diseases such as malignancies and organ failure[12]. Evaluating sarcopenia in cancer patients is important because measuring merely the weight of patients doesn't always give a definitive idea about skeletal muscle mass, as it is now known that changes in patient's weight and BMI are inconsistent with progressive loss of skeletal muscle mass particularly in patients with sarcopenic obesity and other pathologic conditions causing fluid retention [14,15].

Table 1. Tests for measuring different parameters of sarcopenia.

Variables	**Technique**
Skeletal muscle strength	Grip strength Chair stand test
Skeletal muscle mass	DXA CT MRI BIA
Physical performance	Gait speed SPPB(short physical performance battery) Time-up-and-go test

HGS= Hand Grip Strength, DEXA= Dual X-ray Absorptiometry, BIA=Bioelectrical Impedance Analysis, CT= Computed Tomography, MRI=Magnetic Resonance Imaging, SPPB=Short Physical Performance Battery

Measuring skeletal muscle mass with computed tomography

CT scan is considered the gold standard test for non-invasive measurement of skeletal muscle mass in cancer patients. Measuring skeletal muscle area (SMA) at L3 vertebral level is used to estimate total body skeletal muscle mass (SMM) [33,12,34]. SMA can be adjusted for height to calculate the skeletal muscle index (SMI) in cm^2/m^2. There are different methods used in analyzing the CT data and determining skeletal muscle mass.

Some of the older studies have used software such as Slice-O-matic software, version 4.3 and Terarecon 3.4.2.11, SYNAPSE VINCENT version 3 [15,26,35]. A method using deep learning U-Net algorithm described by Ronneberger et al in 2015 provides accurate measurement of skeletal muscle mass. It has been previously employed by many other investigators in measuring skeletal muscle mass [36–38]. The process involves careful selection of a single CT slice at the third lumbar vertebra (L3) which is further processed into form of Digital Imaging and Communications in Medicine (DICOM) data. This DICOM files are analyzed using the deep learning technology to calculate body composition. This technique have been used previously by researchers with high accuracy of 99.17% and validity over union co-efficiency of 89 % [39].

Table 2. Examples of various cut off values for CT based skeletal muscle mass used in past for various disease types from 3 different Asian countries.

Author and year of publication	**Cut off at L3 vertebra(Male)**	**Cut off at L3 vertebra(Female)**
Kim et al. 2014([35], South Korea	49 cm^2/m^2	31cm^2/m^2
Kimura et al, 2015[26] , Japan	41 cm^2/m^2	33 cm^2/m^2
Zhuang et al. 2016[40], China	40.8 cm^2/m^2	34.9 cm^2/m^2
Nishikawa et al. 2016[41], Japan	42 cm^2/m^2	38 cm^2/m^2

There are various cut off values used for defining CT based sarcopenia in patients with chronic diseases. Different CT-based cut off values have been used in Asian countries which are listed in Table 2. From this table, it is clear that the cut off values are inconsistent, and it varies among different countries[26,35,40,41].

Measuring physical performance and physical functions with SPPB

Although there is no standard definition for physical functioning, the World Health Organization's International Classification of Functioning, Disability and Health (ICF) highlights the assessment of physical function as an important aspect of health. On the other hand, physical performance means the ability to perform daily activities which involves various factors such as muscle strength, nervous function, and balance to execute a given task[12]. The assessment of physical performance provides an objective

assessment of physical function. Commonly used tools for assessment of physical performance are listed in Table 1.

SPPB is considered among the most reliable and valid tests for assessment of physical functions enabling it to be used in measuring changes in functional limitation overtime capability[16,17]. In a 2016 systematic review of 11 articles, found that physical performance measured by tests such as TUG, SPPB, or gait speed, was significantly associated with all-cause mortality in 8 out of 11 articles [42]. Specifically in lung cancer patients it has been observed that patients with low SPPB scores had more chemotherapy-related adverse effects and were able to complete fewer cycles of chemotherapy (OR 1.849, p=0.04) [18]. Furthermore, a study conducted on lung cancer patients awaiting lung resection revealed that the SPPB test can be utilized as a valuable tool for patient stratification prior to surgery, in order to predict the likelihood of post-surgical complications [19]. These findings highlight the importance of assessing performance based physical functions in cancer patients to predict outcomes and identify those at risk of increased mortality.

SPPB consists of three tests including balance test, gait test and 5 times chair stand test. Patients are asked to stand side-by-side, semi-tandem and tandem to measure balance and are asked to walk 4 meters to assess gait speed. The chair stand test is performed by asking the patient to fold their arms and stand up from seated position for five times. In all the components of the test, time required to perform the task is measured and points are given accordingly. Points are given from 0 to 12, where 0 is worst performance and 12 is best performance. [43]. The SPPB cut off for defining impaired mobility as recommend by AGWS is score of less than or equal to 9 points. This recommended was based on a systemic review which showed that using this cut off was more predictive of all-cause mortality as compared to cut off of less than or equal to 8 points recommend by EWGOP [42].

Sarcopenia and negative outcomes in lung cancer patients

A matched cohort study in 2020 by Williams et al reported that there is expedited decline in skeletal muscle mass in cancer patients as compared to normal age-related

decline in participants without cancer [20]. In lung cancer patients, similar findings have been consistently observed since last 10-15 years and was highlighted in a meta-analysis of 13 studies in 2019 by Yang et al who reported that prevalence of sarcopenia was 43 % among NSCLC (I^2 C=96%; 11 studies with 1544 participants 95% CI, 32-54%). They also observed that sarcopenic patients had reduced overall survival (HR, 2.57; CI 95%, 1.79-3.68) [6]. In the same year similar meta-analysis by Buentzel et al found that there was significant increase in hazard risk for the risk of death (retrospective studies: 1.77(1.44,2.17), p<0.001; prospective studies: 2.38(1.48, 3.83, p<0.001) and concluded that presence of sarcopenia significantly predicts increased death risk [7].

Previous studies carried out in different types of cancer have reported increased chemotherapy toxicity in patients with low skeletal muscle mass [44,45]. This observation was also seen in lung cancer patients. A recent study evaluating 167 NSCLC patients reported that patients with low skeletal muscle mass had significantly higher incidence of hematological toxicity as compared to those with intermediate or high skeletal muscle mass (48.5 % in low SMM, 28.6% in intermediate SMM and 32.7% in high SMM) [11]. As already mentioned patients with low SPPB scores had more chemotherapy-related adverse effects and were able to complete a fewer cycles of chemotherapy [18]. These studies highlighted the need for understanding the different aspects of sarcopenia, so that we can enhance screening and identify patients achieve better outcomes.

CT defined skeletal muscle mass and physical functions

Older studies on sarcopenia primarily focused on measuring skeletal muscle mass, but other parameters were not given much attention. However, recent studies indicate that assessment of all three parameters of sarcopenia is crucial. A matched cohort study by Williams et al, which followed 3075 well-functioning patients, found that of the 515 patients who developed cancer during the follow-up period, had a faster decline in gait speed and skeletal muscle mass compared to participants who did not develop cancer ($\beta = -0.02$; 95% CI, −0.03 to −0.01; $P < .001$). Interestingly, they observed that decline in gait speed occurs even before the diagnosis of cancer (in patients who later developed

cancer during follow up) and development of low skeletal muscle mass followed only after cancer diagnosis [20]. Despite several previous reports on the associations between low skeletal muscle mass and physical functions, conflicting results have been reported in the literature [9,23–25].

A recent meta-analysis, which included 14 studies focused on the association between quality of life and skeletal muscle mass, found that low skeletal muscle mass showed a negative correlation with physical function domains of quality-of-life scores. Among these studies, 4 had patients with lung cancer. [23]. Similar findings were observed in another study, also aimed at studying associations between skeletal muscle mass measured using CT at 3rd lumbar vertebra and quality of life(QoL), which included 734 lung cancer patients. They observed a significant non-linear association existing between skeletal muscle index SMI and physical functions domains of QoL in both genders (men: p-value = 0.016, women: p-value = 0.004). Interestingly, they found that the cut point of skeletal muscle mass index (SMI) at which a significant association with physical function was observed, was similar to previously reported cut points associated with increased mortality. Specifically, the analysis revealed that associations occurred at similar lower levels of SMI values (male, SMI < 43 cm^2/m^2 when BMI <25 and female, SMI < 41 cm^2/m^2 for all BMI groups) [10]. It is very important to note that both of these studies evaluated physical function using patient reported questions, but performance-based tests were not used.

Although studies using performance-based measurement of physical functions in lung cancer patients are lacking, a longitudinal study by Naito et al. in 30 lung cancer patients who were receiving chemotherapy found positive linear association between decline in CT determined skeletal muscle mass and physical functions assessed using HSG and ISWD ($\beta = 8.8 \pm 2.4$, $p = 0.0005$). They concluded that low skeletal muscle leads to functional impairment and recommended early screening or treatment to possibly prevent further deterioration [9]. However in contrary to this, a study on community dwelling individuals aimed at examining association of skeletal muscle mass(measured by CT scan at three different groups of muscle at trunk, hip and mid-thigh) and physical performance (measured using TUG test) observed that there was poor association

between these two variables [46]. In 2017, a study in participants with various type of cancer also found no significant association of CT derived skeletal muscle mass measured at 3rd lumbar vertebra with physical functions [24]. They assessed physical functions using the Time up and Go test, the Karnofsky Performance Status scale and instrumental activities of daily living reported by the participants. Both performance

Table 3. Previous reports on associations between skeletal muscle mass(CT determined) and physical functions.

Author, population, type of study	**Physical functions measurement tool**	**Results**
Hanna et al. 2022 Metanalysis various cancer types (4 studies with lung cancer)	Patient reported physical functions as part of QoL	Patients with low SMI had reduced baseline physical functions as compared to normal SMM standardized (mean difference -0.4, 95% CI -0.74, -0.05, small-moderate effect size).
Wang et al. 2020 Community dwelling Cross sectional	TUG and HGS	No relationship between SMA and TUG and HGS (SMA was measured at different body parts, trunk, mid-thigh and gluteus)
Bye et al. 2017 Cross-sectional , 734 lung cancer patients	Patient reported physical functions as part of QoL	Decline in SMI below a given threshold was related to decline in physical function male, SMI < 43 cm2/m2 when BMI <25 and female, SMI < 41 cm2/m2 for all BMI groups)
Naito et al. 2017 Prospective cohort	HSG and ISWD	Decline in skeletal muscle mass showed a positive linear relation to decline in physical functions.
Williams et al. 2017 Various cancer types(20 % lung cancer) Cross-sectional	Both self-reported and performance-based measures (TUG)	No relationship between SMI and overall physical functions, instead found better association with SMD. Limited association with TUG

HGS= Hand Grip Strength, ISWD= Incremental shuttle walking distance TUG= Time Up and Go Test, SMD= Skeletal muscle density, SMI=Skeletal muscle mass

based and patient reported questionnaires were used to assess the physical functions. However, the participants included in this study were >65-year-old, only 20 % of participants were lung cancer patients and the assessment of physical functions were carried out as part of routine geriatric assessment. The above-mentioned studies have not specifically evaluated the gender differences in low skeletal muscle mass and its association to physical functions.

Gender difference in skeletal muscle mass and its outcome

As with any other disease the biological difference between male and female makes them differently susceptible for development of low skeletal muscle mass or decline in physical performance. In 2010 Baracos et al. evaluated 441 patients with lung cancer and reported 61 percent of men had loss of skeletal muscle mass as compared to 31 percent of women [27]. Later in 2015 in a longitudinal study of lung cancer patients receiving chemotherapy reported that male had much higher decline in skeletal muscle mass as compared to female [26] . Similar findings were reported in a recent article which found median skeletal muscle index (SMI) measured with CT at L3 lumbar vertebra was 43.1cm^2/m^2 for males, which was below the cut off used in the study (cut off for male was <55 m^2/m^2). In contrast, women had median SMI of 40.3 m^2/m^2 which was above the cut off for sarcopenia used in the study(cut off for female was <39 m^2/m^2) [47]. The exact cause for these differences is not well understood however it is thought that men have a higher susceptibility for weight loss, grip strength loss and muscle mass. Some studies in animal models have shown that biologically there are differences in muscle fiber composition and muscle mitochondrial metabolism. Males have a higher number of type 2 muscle fibers which are less resistant to fatigue and prone to cancer induced wasting. Some authors believe that sex hormone and muscle gene expression also play a role in these differences [29]. Table 4. shows different phenotypes of cancer cachexia in male and female.

More importantly researchers have observed it's not just the difference in skeletal muscle mass, but outcome associated with these differences also differs in male and female. Although studies specifically focused on lung cancer patients are lacking, a

study by Kilgour et al. on 88 patients with advanced gastrointestinal and lung cancer found that male patients with low skeletal muscle mass had a higher fatigue index, showing high frailty [28]. However, such an association was not seen in females, i.e., females with low or high skeletal muscle mass did not have association with frailty. Similarly, a study on B-cell lymphoma patients investigating the effect of sarcopenia and its outcomes found that males patients with low skeletal muscle mass had significant association with overall survival , which was not observed in females [48]. These studies suggests that the outcome associated with low skeletal muscle mass may differ according to the sex related differences. It is not well understood that such differences may exist when physical functions are evaluated as an outcome of low skeletal muscle mass. A better understanding of the effect of gender on the relationship of skeletal muscle mass and physical functions may aid in early identification of patients with highest risk of developing functional impairment and may guide targeted intervention. Therefore, we aim to explore gender differences in CT determined skeletal muscle mass and its association to physical functional limitation in lung cancer patients.

Table 4. Differences in different phenotypes of cancer cachexia in males and females [29].

	Male	Female
Cachexia prevalence		
Weight loss		
Grip strength loss		
Muscle mass loss		
Myofiber area loss		
Atrophy of Type 2 fibers		
Atrophy of Type 1 fibers		
Mitochondrial dysfunction	*Yes*	*Not tested*
Clinical outcome	*Worse*	*Better*
Normal mitochondrial quality	*Inferior*	*Superior*
Global normal gene expression	*Protein catabolism enriched*	*Mitochondrial function enriched*

Chapter 2

Research Methodology

2.1 Study design

Cross-sectional study.

2.2 Study location

Songklanagarind Hospital, Faculty of Medicine, Prince of Songkla University, Hat Yai, Thailand.

2.3 Target Population

Lung cancer patients before treatment, while on treatment or during surveillance after treatment.

2.4 Study Population

The study population consisted of lung cancer patients before treatment, had already undergone treatment, or were currently receiving treatment.

2.5 Inclusion criteria

1. Age >18 years old.
2. Lung cancer patients confirmed by histopathology at any stage.

2.6 Exclusion criteria

1. Unable to perform CT scan due to various reasons.
2. If unable to perform SPPB test due to physical disability or patient's refusal.
3. Pregnant patients.
4. Patients with physical deformities/neurological deficits.

2.7 Sample size calculation

The sample size calculation for the research was done according to objective of our research. We took the proportion of patients with SPPB score of less than or equal to 9 from previous literature i.e., 37 % in female and 63% in males [49].

$$n = \frac{\left[Z_{1-\alpha/2}\sqrt{p(1-p)(1+\frac{1}{r})} + Z_{\beta}\sqrt{p_1(1-p_1)+p_2(1-p_2)/r}\right]^2}{\Delta^2}$$

- $P1_{(female)} = 0.37$ $P2_{(male)} = 0.63$
- Ratio= 1
- Alpha (type 1 error) = 0.05
- Beta (type 2 error) = 0.20
- Power of the study = 0.8

  Output females =57, males = 57, sample size by using continuity correction

  Male =65, female=65

Total sample size N= 130.

Therefore, planned to include a minimum of 130 patients. Ultimately a total of 172 patients were enrolled in our study.

2.8 Study procedure

The study was conducted after consultation with Division of Respiratory Medicine, Songklanagarind Hospital. All participants who met the inclusion criteria were included in the study through primary chest physician of the patient on voluntary basis. The introduction of the research to patients was given by primary chest physician, and if participants agree to participate in the study, details of research were provided by our research team, following which informed written consent was obtained. Primary physicians were also requested to inform our research team about other new patients who meet our inclusion criteria, and the above steps were followed in every case. All the baseline data required for our study were recorded in Hospital Information System

(HIS) by our research team. After this, SPPB test was conducted in the chest clinic by our research team, which took about 7-10 minutes per patient. The CT scan was carried out as per routine schedule of patient which is based on advice of primary chest physician and appointment dates from the radiology department. The CT data were collected from PACS for assessing skeletal muscle mass in the Department of Radiology.

Recording of baseline characteristics

All the baseline characteristics were recorded from Hospital Information System (HIS) or directly taken from the participants.

Measurement of skeletal muscle mass

Patient's CT scan data were collected from picture archiving and communication system (PACS) for assessing skeletal muscle mass. The routine chest CT done on lung cancer patient is performed from thoracic inlet to lower margin of liver or iliac crest whichever is easily visible for the radiotechnologist in Songkalagarind Hospital. CT scan is gold standard test for non-invasive measurement of muscle mass [12]. Measuring skeletal muscle area (SMA) at L3 vertebral level using CT scan is used to estimate total body skeletal muscle mass [33,12,34] by different methods. A method using deep learning U-Net algorithm described by Ronneberger et al in 2015 provides accurate measurement of skeletal muscle mass. It has been previously employed by many other investigators in measuring skeletal muscle mass [36–38].

We have carefully selected a single CT slice of the third lumbar vertebra (L3) and saved in the form of Digital Imaging and Communications in Medicine (DICOM) data (Figure 1). To calculate body composition from DICOM data, in-house software was developed using MATLAB (The MathWorks, Natick, MA, USA) and freeware Python 3.6.13 (Anaconda, Inc.). This software generated a measurement model based on the deep learning algorithm mentioned above. This is a validated model that has been used previously with an accuracy of 99.17% and validity over union co-efficiency of 89.40% [39]. (More detail about the deep learning model in Appendix A).

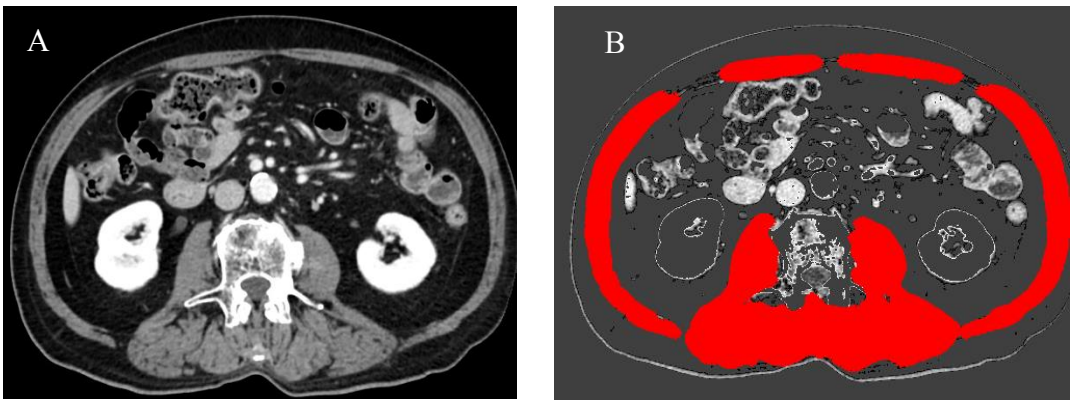


Figure 1. Method for measuring skeletal muscle mass at 3rd lumbar vertebra. (A) The computed tomography image taken from the PACS and saved in DICOM format. (b) The image is post processed using in-house developed software for calculation of cross-sectional area of abdominal wall muscles as delineated in red . The sum of the muscle areas is calculated as 3rd lumbar vertebra skeletal muscle area (L3SMA).

Evaluation of physical functions using SPPB

SPPB is considered among the most reliable and valid tests for assessment of functional capability [13,40]. It provides an objective assessment of physical functions enabling it to be used in measuring changes in functional limitation overtime [12,13]. SPPB can be easily performed by health workers after a basic training and it doesn't require expensive equipment [18]. SPPB consists of three tests including balance test, gait test and 5 times chair stand test. Patients are asked to stand side-by-side, semi-tandem and tandem to measure balance and are asked to walk 4 meters to assess gait speed. Chair stand test is performed by asking the patient to fold their arms and stand up from seated position for five times. Each component of the test is given a maximum of 4 points by measuring time required to perform the task. At the end of the test, total points given will range from 0 to 12 (4 points each for balance, gait and chair stand), where 0 is worst performance and 12 is best performance as shown in following table SPPB test was conducted in division of respiratory medicine by research assistant. The detailed parts of SPPB test with corresponding points are given in Table 5.

Table 5. Three different sets of SPPB test and corresponding scoring system[43].

Balance test	
Side-by-side-stand	
Held for 10 seconds	1 point
Not held for 10 seconds	0 points
Semi-Tandem Stand	
Held for 10 seconds	1 point
Not held for 10 seconds	0 points
Tandem Stand	
Held for 10 seconds	2 points
Held for 3 to 9.99 seconds	1 point
Held for < than 3 seconds	0 points
Total Balance Tests score	4 points
Gait test	
If unable to perform test	0 points
If time is more than 8.70 seconds	1 point
If time is 6.21 to 8.70 seconds	2 points
If time is 4.82 to 6.20 seconds	3 points
If time is less than 4.82 seconds	4 points
Chair stand test	
If unable to complete 5 chair stands or completes stands in >60 seconds	0 points
If chair stand time is 16.70 seconds or more	1 point
If chair stand time is 13.70 to 16.69 seconds	2 points
If chair stand time is 11.20 to 13.69 seconds	3 points
If chair stand time is 11.19 seconds or less	4 points

Karnofsky Performance Scale (KPS)

The Karnofsky Performance Scale (KPS) is a tool used to assess the functional status and overall performance of individuals, particularly those with chronic illness or advanced stages of disease. The scale consists of ten categories, each representing a different level of functional ability. These categories range from complete disability (score of 0) to full independence and normal functioning (score of 100).

2.9 Variables and operational definitions

Outcome (dependent) variables

1. Physical functional limitation using SPPB test score

As described above SPPB consists of three parts: - 1) balance test, 2) gait test and 3) chair stand test. Each part is given points from 0 to 4 according to time (in seconds) required to perform the test. Total score for the whole test will be from 0 to 12, where 0 represents the worst and 12 the best performance.

The interpretation of SPPB score to define physical functional limitation(PFL) in this study will be defined as score of less than or equal to 9 points (based on reports of AGWS as described above).

Independent variable

1. Skeletal muscle mass using CT scan

CT determined skeletal muscle area (SMA) at L3 lumbar vertebra (L3SMA)was used to calculate skeletal muscle index at L3 vertebra (L3SMI) by dividing with patient's height square. The units for L3SMA and L3SMI are cm^2 and cm^2/m^2 respectively.

2. Patient characteristics- sex (male/female), weight (in kg) and height (in meters), BMI(kg/m^2)

3. Age in years was taken as age of participants on day of SPPB test.

4. Type of treatment- Chemotherapy or targeted therapy.

5. Laboratory parameters : Hemoglobin(g/dl), HCT %, WBC(count), platelet (count), blood urea and nitrogen(mmol/l) and serum creatinine(mg/dl).

6. Karnofsky Performance Score (KPS): score from 0-100 divided in 10 categories.

7. Stage of lung cancer

Operational definitions

1. Physical functional limitation(PFL) is defined as SPPB score of less than or equal to 9 points for both males and females.
2. CT- defined sarcopenia will be defined as SMI of values of 42 cm^2/m^2 and 38 cm^2/m^2 in males and females respectively.

2.10 Ethical aspects

The study was performed in an ethically safe and sound procedure. Patient's CT scan data were taken from routine scans done as part of patient management (done on every advanced lung cancer patient) in Songklanagarind Hospital. The routine chest CT done on lung cancer patients is performed from thoracic inlet to lower margin of liver or iliac crest whichever is easily visible for the radiotechnologist in Songklanagarind Hospital. There was small variation in radiation dose to the participants during the study period, however this variation was not large enough to cause harm to the participants.

SPPB tests were conducted by a trained research assistant. The training was based on videos and documents provided by the founder of the test which included detailed information explaining about the test and associated safety concerns to prevent falls. All the important procedures were adopted to prevent falls.

This study was approved by Human Research Ethics Committee, Prince of Songkla University, Hatyai, Thailand, Ethics Committee approval number: REC. 65-080-7-1.

2.11 Statistical Analysis

Descriptive statistics

The baseline characteristics are presented with n (%) and mean (SD) as appropriate. Chi-square test (or Fisher Exact test) and Student t-test was used to calculated differences of baseline data between male and female groups. The frequency and percentage were used for the categorical variables simultaneously. The Wilcoxon rank sum test was used to calculate the difference between SMI and SPPB scores.

Inferential statistics

Logistic regression was used to assess the effect of SMI, gender and age on physical functional limitation with the following logistic model :

- Model 1 - Prob(score<=9) = exp(a + b1(smi))
- Model 2- Prob(score<=9) = exp(a + b1(smi) + b2(sex)+b3(age)

The best fitted line between SPPB and SMI was calculated using quadratic polynomial regression upon the best fit by visualized, AIC and BIC criteria.

The p-value of less the 0.05 was considered statistically significant. The analysis and graphically figures was analyzed on R software, version 4.2.0 (R foundation, Vienna, Austria).

Chapter 3

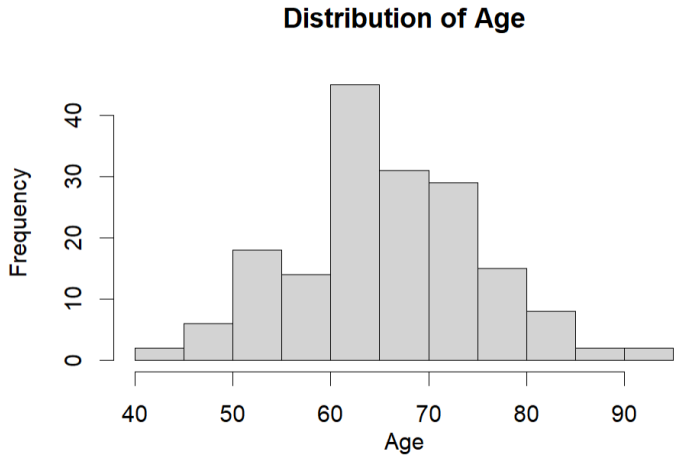
Results

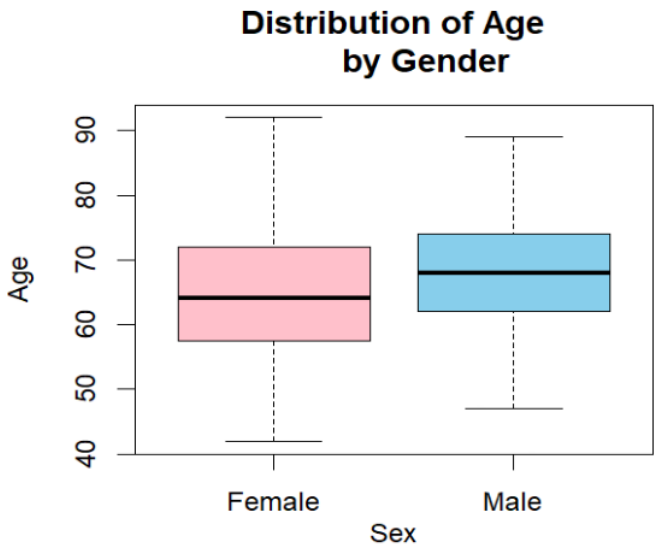
3.1 Patients characteristics

The descriptive statistics for age, weight, and BMI of participants are shown in Table 6. The sample size for the study was 172 individuals, with 95 females and 77 males. The mean (SD) age for female participants was 65 (10.1) years, and for males, it was 68 (9.6) years. The distribution age (one of the predictor variables) is shown in Figure 3. The Shapiro-Wilk test showed normal distribution of the age data (W = 0.99399, p-value = 0.7081). There was no statistically significant difference observed between the age of female and male participants (p = 0.080).

Female participants had a mean (SD) weight of 53 kg (10.4 kg), while males had a mean (SD) weight of 59 kg (12.8 kg). There was a significant difference observed in weight between female and male participants (p = 0.003). However, no significant difference was observed between the BMI of female and male participants, with a mean (SD) of 23 kg/m² (4.1 kg/m²) for females and 22 kg/m² (4.1 kg/m²) for males (p = 0.2). No significant differences were found in the Karnofsky Performance Score (KPS). The mean KPS was 81.3 for males and 84.9 for females (p = 0.2).

A.





B.

Figure 2. Distribution of age is represented by (A) Histogram and (B) Boxplot for both males and females.

3.2 Status and types of treatment

Three groups of patients were enrolled in the study, most participants were enrolled before starting treatment (59.9 %). In this group of participants treatment was started right after enrollment. Remaining participants were enrolled during surveillance after treatment (27.9%) with various types of lung cancer therapy including surgery, CCRT, chemotherapy or targeted therapy depending on stage of disease. The last group of patients were enrolled while participants were receiving treatment (12.2%). There was no significant difference in the status of treatment between male and female participants (p=0.6).

First-line treatment was the most frequently employed treatment option, with 67% of patients receiving it. 28.8% of females received second-line treatment, which was slightly more common compared to males. Third-line treatment was the least commonly used modality. Overall, there was no significant difference in the choice of treatment between males and females. The use of different therapies is listed in the same table. The drugs or drug combinations included the following medications: Afatinib, Carboplatin plus Etoposide, Ceritinib, Cisplatin plus Etoposide, Cisplatin and Gemcitabine, Crizotinib, Docetaxel, Erlotinib, Gefitinib, Gemcitabine plus Cisplatin,

Table 6. Demographics

Characteristic	Female, N = 95[1]	Male, N = 77[1]	Total,N=172[1]	p-value[2]
Age	65 ± 10.1	68 ± 9.0	66 ± 9.7	0.080
Weight	53 ± 10.4	59 ± 12.8	56 ± 11.8	0.003
BMI	23 ± 4.1	22 ± 4.1	22 ± 4.1	0.2
KPS	85 ± 19.1	81 ± 19.6	83 ± 19.4	0.2
Hb	12 ± 1.6	12 ± 1.9	12 ± 1.8	0.003
WBC	7 ± 3.1	8 ± 3.4	8 ± 3.3	0.009
PLT	278 ± 77.9	307 ± 102.0	291 ± 90.1	0.2
BUN	12 ± 4.1	13 ± 4.4	13 ± 4.2	0.3
Cr	1 ± 0.2	1 ± 0.3	1 ± 0.3	<0.001
Albumin	4 ± 0.4	4 ± 1.0	4 ± 0.8	0.7
Status of treatment				0.6
Before treatment	54 (56.8%)	49 (63.6%)	103 (59.9%)	
During surveillance	28 (29.5%)	20 (26.0%)	48 (27.9%)	
During treatment	13 (13.7%)	8 (10.4%)	21 (12.2%)	
Stage				0.2
1	11 (11.6%)	9 (11.7%)	20 (11.6%)	
2	5 (5.3%)	0 (0.0%)	5 (2.9%)	
3	7 (7.4%)	5 (6.5%)	12 (7.0%)	
4	72 (75.8%)	63 (81.8%)	135 (78.5%)	
Type of treatment				0.006
Chemotherapy	32 (47.8%)	41 (71.9%)	73 (58.9%)	
Targeted therapy	35 (52.2%)	16 (28.1%)	51 (41.1%)	
Line of treatment				0.6
1st line	37 (62.7%)	38 (71.7%)	75 (67.0%)	
2nd line	17 (28.8%)	12 (22.6%)	29 (25.9%)	
3rd line	5 (8.5%)	3 (5.7%)	8 (7.1%)	
Name of therapy				0.052
Afatinib	1 (1.5%)	0 (0.0%)	1 (0.8%)	
Cb Eto	1 (1.5%)	1 (1.8%)	2 (1.6%)	
Ceritinib	3 (4.5%)	3 (5.3%)	6 (4.8%)	
Cis Eto	0 (0.0%)	1 (1.8%)	1 (0.8%)	
Cisplatin, Gemcitabine	1 (1.5%)	0 (0.0%)	1 (0.8%)	
Crizotinib	3 (4.5%)	3 (5.3%)	6 (4.8%)	
Docetaxel	10 (14.9%)	11 (19.3%)	21 (16.9%)	
Erlotinib	20 (29.9%)	5 (8.8%)	25 (20.2%)	
Gefitinib	0 (0.0%)	2 (3.5%)	2 (1.6%)	
Gem Cis	1 (1.5%)	1 (1.8%)	2 (1.6%)	
Osimertinib	8 (11.9%)	3 (5.3%)	11 (8.9%)	
Pac Cb	16 (23.9%)	25 (43.9%)	41 (33.1%)	
Pemetrexed	2 (3.0%)	2 (3.5%)	4 (3.2%)	
Pemetrexed Cb pembrolizumab	1 (1.5%)	0 (0.0%)	1 (0.8%)	

[1] Mean ± SD; n (%),[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test
BMI= Body Mass Index, KPS= Karnosfky Performance Score, Hb=Hemoglobin(g/dl), WBC= White Blood Cell, PLT= Platelet, BUN=Blood Urea Nitrogen, Cr=Serum Creatinine.

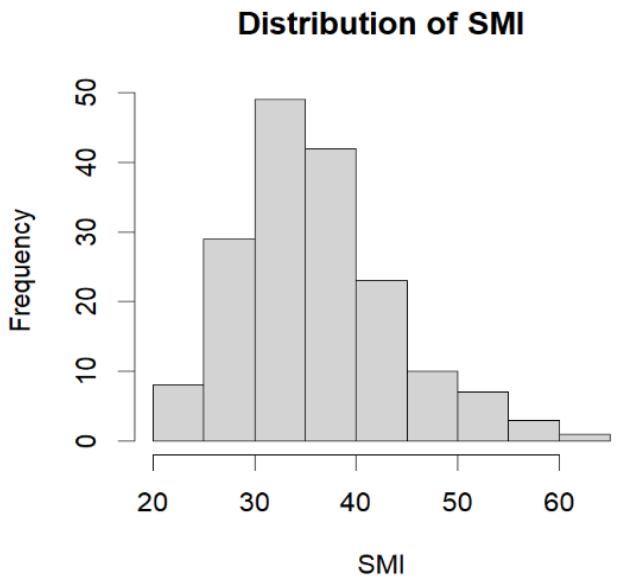
Osimertinib, Paclitaxel plus Carboplatin, and Pemetrexed. 41 patients (33.1%) received paclitaxel with carboplatin, with of those 16 (23.9%) being female and 25 (20.2%) being male. Erlotinib was the most commonly prescribed targeted therapy with a total of 25 patients receiving it.

3.3 Laboratory findings

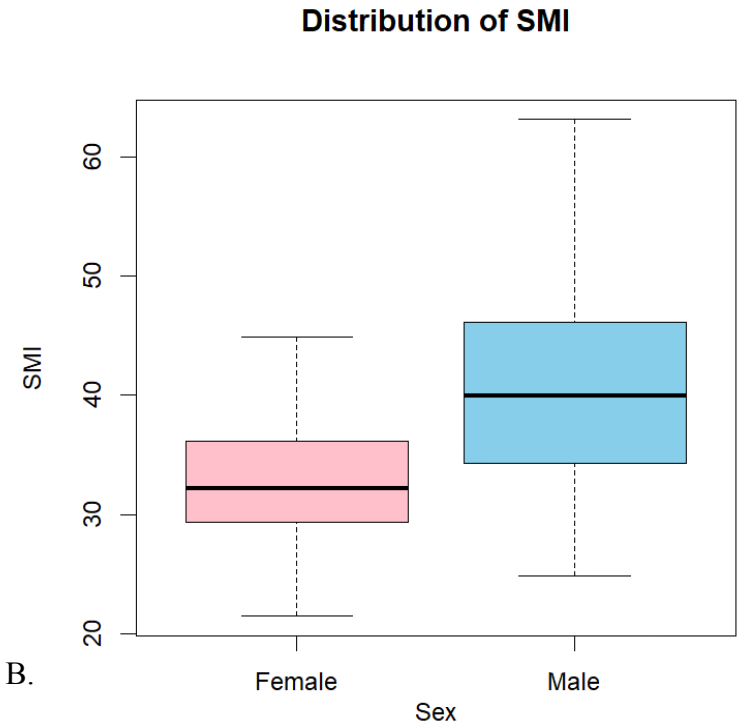
The laboratory findings showed that the male participants exhibited higher hemoglobin and white blood cell count levels compared to the female group, with a statistically significant difference (Hb: $p = 0.003$, WBC: $p = 0.009$). The platelet count did not differ significantly between males and females. Blood urea nitrogen levels were similar in both groups, while serum creatinine levels were significantly higher in males ($p < 0.001$). Albumin levels showed no significant difference between males and females ($p = 0.7$).

3.4 CT determined skeletal muscle mass

The distribution SMI(variable of interest) at 3rd lumbar vertebra (L3SMI) is shown in Figure 2. The Shapiro-Wilk test showed that the distribution of the data is non-normal ($W = 0.95797$, p-value = >0.001). Therefore, Wilcoxon test, which is a non-parametric test suitable for analyzing non-normally distributed data.



A.



B.

Figure 3. Distribution of SMI values are represented by (A) Histogram and (B) Boxplot for both females and males.

The mean (SD) SMA value was 110 cm^2 (24.4 cm^2) in males, compared to a mean (SD) of 77 cm^2 (13.5 cm^2) in females, demonstrating a statistically significant difference ($p < 0.001$). Similarly, the mean (SD) SMI value also exhibited a statistically significant difference, with males having a mean (SD) of 41 cm^2/m^2 (8.3 cm^2/m^2) and females having a mean (SD) of 33 cm^2/m^2 (5.1 cm^2/m^2) ($p < 0.001$). Summary of CT-determined skeletal muscle mass is shown in Table 7.

Table 7. Summary of CT determined skeletal muscle mass findings.

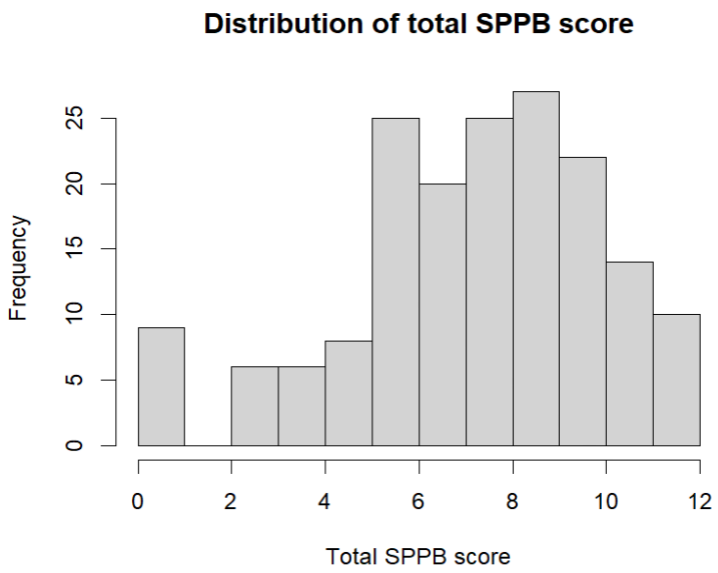
Characteristic	Female, N = 95[1]	Male, N = 77[1]	Total[1]	p-value[2]
SMI	33 ± 5.1	41 ± 8.3	36 ± 7.9	<0.001
SMA	77 ± 13.5	110 ± 24.4	92 ± 25.3	<0.001

[1] Mean ± SD, [2] Wilcoxon rank sum test

3.5 Physical performance and functional limitation (SPPB score)

The distribution total SPPB score (outcome variable) are shown in Figure 3. The Shapiro-Wilk test showed that the distribution of the data is non-normal (W = 0.93853, p-value = >0.001). Therefore, similar to SMI we used Wilcoxon test for analyzing the differences in males and females. The mean standing time was 10.0 seconds for both males and females, with no significant difference between the sexes (p = 0.9) as shown in Table 8. Similar results were observed for both standing, semi tandem and tandem

A.



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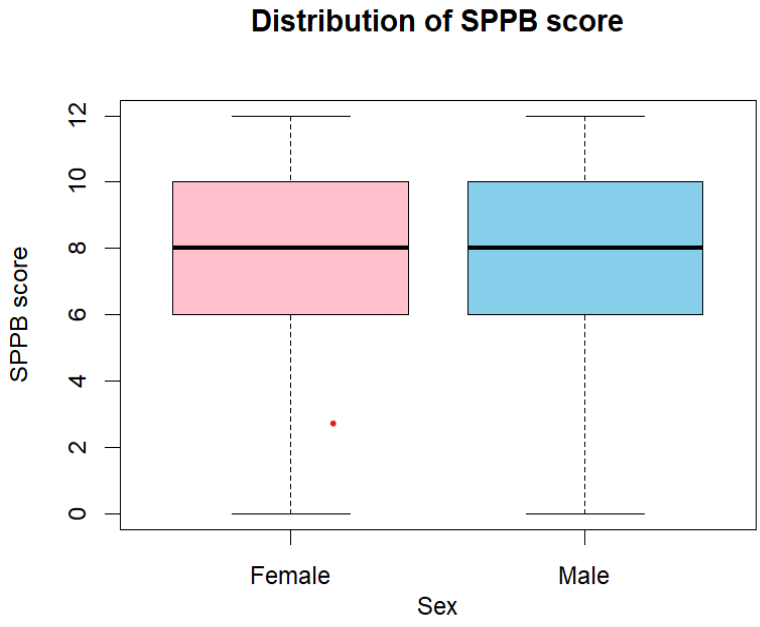

Figure 4. Distribution of total SPPB score is represented by (A) Histogram and (B) Boxplot for both males and females.

balance tests. The mean total balance score was 4 (1.0) for males and females, without statistically difference (p = 0.853). The average time taken to walk a 4-meter distance during the gait test was 8 seconds (6.5 seconds) for females and 8 seconds (6 seconds) for males, without significant difference (p=0.8). Chair stand test averaged (SD) at 14 seconds for both groups. The mean(SD) total score across all tests was 8 (2.7) for females and 8(2.9) for females, with no significant difference (p = 0.9). This values are comparatively low as compared to mean of community dwelling individuals(male=11.6±1.1, female=11.7±1.2) found in another study in Asian population [50].

Table 8: Summary of SPPB score

Characteristic	Female, N = 95[1]	Male, N = 77[1]	Total[1]	p-value[2]
Standing(sec)	10 ± 2.0	10 ± 1.6	10 ± 1.8	0.7
Standing(score)				0.7
0	5 (5.3%)	3 (3.9%)	8 (4.7%)	
1	90 (95%)	74 (96%)	164 (95%)	
Semi-tandem(sec)	9 ± 2.3	9 ± 2.6	9 ± 2.4	>0.9
Semi-tandem(score)				>0.9
0	7 (7.4%)	6 (7.8%)	13 (7.6%)	
1	88 (93%)	71 (92%)	159 (92%)	
Tandem(sec)	9 ± 2.9	9 ± 2.9	9 ± 2.9	0.7
Tandem(score)				0.6
0	9 (9.5%)	8 (10%)	17 (9.9%)	
1	6 (6.3%)	2 (2.6%)	8 (4.7%)	
2	80 (84%)	67 (87%)	147 (85%)	
Total balance score	4 ± 1.0	4 ± 1.0	4 ± 1.0	0.5
Gait speed (sec)	8 ± 6.5	8 ± 6.0	8 ± 6.2	0.8
Gait speed(score)				0.8
0	6 (6.5%)	5 (6.5%)	11 (6.5%)	
1	28 (30%)	19 (25%)	47 (28%)	
2	20 (22%)	23 (30%)	43 (25%)	
3	24 (26%)	19 (25%)	43 (25%)	
4	15 (16%)	11 (14%)	26 (15%)	
Chair stand(sec)	14 ± 7.3	14 ± 7.3	14 ± 7.3	>0.9
Chair stand(points)				0.9
0	12 (13%)	10 (13%)	22 (13%)	
1	31 (33%)	24 (31%)	55 (32%)	
2	17 (18%)	19 (25%)	36 (21%)	
3	20 (22%)	14 (18%)	34 (20%)	
4	13 (14%)	10 (13%)	23 (14%)	
Total score	8 ± 2.9	8 ± 2.7	8 ± 2.8	0.9

[1] Mean ± SD; n (%), [2] Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test

3.6 Prediction of physical functional limitation using SMI, gender and age

We initially performed an Ordinary Least Squared (OLS) to understand the relationship between the variables which revealed that the data met the assumption of homoscedasticity (chi-square value = 1.600369, p-value of 0.20585) and there was no evidence of multicollinearity as well (VIF SMI=1.442158, Sex=1.443591 and Age=1.061576). These findings supported the reliability of using the SMI variable in the regression analysis (details in Appendix B).

The logistic regression was performed for interaction of sex and SMI in predicting our main outcome of physical functional limitation i.e. total SPPB score of less than or equal to 9 points. Initially the analysis was performed with SMI as the only predictor which showed a statistically significant odds ratio of 0.96 (CI=0.91- 1.00, p= 0.034). Following this, when sex was added as predictor, no interaction was seen with female odd ratio of 0.5 as referred to males (CI 0.21, 1.15, p=0.11). An interaction term of sex and SMI also did not show significant interaction (OR=1.01, CI=0.91-1.13, p=0.8). This showed that the relationship between SMI and the outcome does not vary significantly between males and females.

As it is known that with increasing age there is decline in both skeletal muscle mass and physical functions[50–52], therefore we added age in our analysis together with SMI and sex as predictors. The age odds ratio of 1.14(CI=1.09-1.21, p<0.001) was observed, showing that age is a statistically significant predictor of the outcome . The model was further tested for effect size of age by including variables stage of disease and types of treatment received (details in Appendix B), which showed consistent significant odds ratio of age (OR=1.12, CI=1.06, 1.20, p=<0.001). However, these variables were not included in the final model.

Furthermore, the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were employed to compare the predictive performance of the models in relation to the outcome:

- Model 1 - Prob(score<=9) = exp(a + b1(smi))
- Model 2 - Prob(score<=9) = exp(a + b1(smi) + b2(sex)
- Model 3- Prob(score<=9) = exp(a + b1(smi) + b2(sex)+b3(age)

Table 9. Comparison of models with AIC and BIC criteria.

	OR	95% CI	p-value	AIC	BIC
Model 1				**199.21**	**205.50**
SMI	0.96	0.91,1.00	0.034		
Model 2				**198.57**	**208.01**
SMI	0.93	0.88,0.98	0.009		
Sex					
Male	—	—	—		
Female	0.50	0.21,1.15	0.11		
Model 3				**165.43**	**178.02**
SMI	0.96	0.90,1.01	0.14		
Sex					
Male	—	—	—		
Female	0.93	0.35,2.37	0.9		
Age	1.14	1.09,1.21	<0.001		

OR = Odds Ratio, AIC= Akaike Information Criterion, BIC= Bayesian Information Criterion, CI = Confidence Interval

Model 1 included only the predictor variable SMI, Model 2 included both sex and SMI as predictors, and Model 3 included SMI, sex, and age as predictors (the interaction term of SMI and sex was omitted as it was not significant).

For Model 1, as already mentioned the odds ratio (OR) for SMI was 0.96 (95% CI: 0.91-1.00, p = 0.034), indicating that for each unit increase in SMI, the odds of the outcome decreased by 4%. The AIC and BIC values for Model 1 were 199.21 and 205.50, respectively.

Model 2, which included both sex and SMI as predictors, showed OR of 0.50 (95% CI: 0.20-1.23, p = 0.11) for sex, suggests that the inclusion of sex as a predictor in the model does not provide strong evidence of a significant impact on the outcome. The AIC and BIC values for Model 2 were 198.57 and 208.01, respectively.

Finally, Model 3, which included SMI, sex, and age as predictors, revealed an OR of 1.14 (95% CI: 1.09-1.21, p < 0.001) for age, indicating that for each year increase in age, the odds of the outcome increased by 14%. The AIC and BIC values for Model 3 were 165.43 and 178.02, respectively. These results suggest that Model 3, which includes all three predictors (SMI, sex, and age), provides the best fit to the data based

on the lowest AIC and BIC values. The inclusion of sex and age in addition to SMI helps to capture the complexity of the relationship between these variables and the outcome. The relationship between sex, SMI and probability of functional limitation is graphically represented in Figure 5.

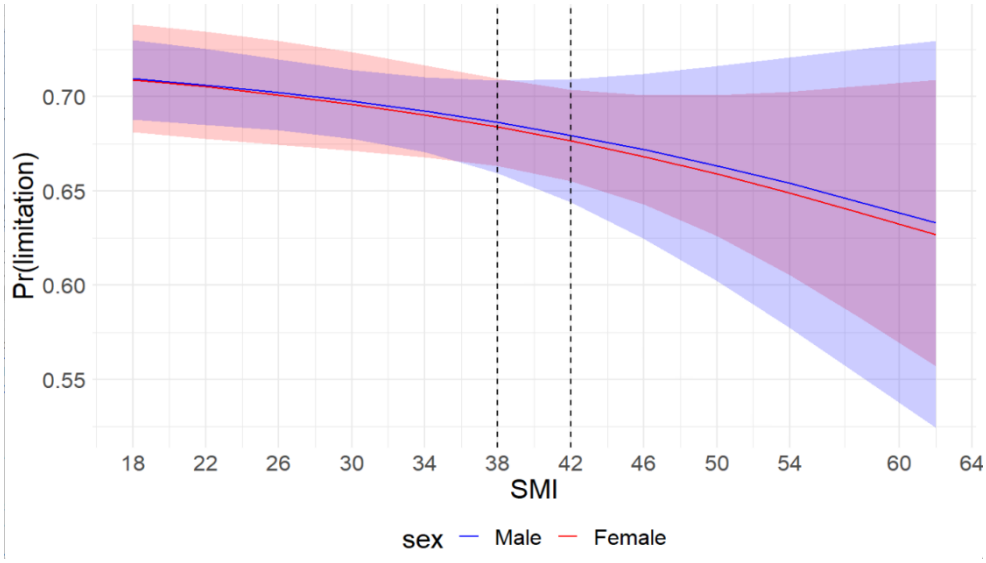

Figure 5. Relationship between skeletal muscle mass and sex in predicting physical functional limitation. These blue and red lines represent average predicted probability of functional limitation for males and females respectively. The vertical lines represent cut point used in this to define low SMI . SMI= skeletal muscle index. Pr(limitation)= probability of functional limitation

Chapter 4

Discussion

Our study aimed to examine the effect of gender differences in skeletal muscle mass and its association to physical functional limitation in lung cancer patients. Through our analysis, contrary to our hypothesis, we identified some evidence to suggest that the gender differences in skeletal muscle does not affect the probability of developing physical functional limitation in lung cancer patients . Age, on the other hand, emerged as a significant predictor of the outcome (OR = 1.14, 95% CI: 1.09-1.21, $p < 0.001$), with each year increase in age associated with 14% higher odds of experiencing physical functional limitation. This highlights the importance of considering these factors together when assessing the risk and understanding the complexities of physical functional limitations in relation to skeletal muscle mass. Our study also showed that the probability of physical functional limitations becomes more pronounced at lower levels of skeletal muscle mass which is consistent with previous report[10].

To our knowledge, this is the first study to explore the effects of gender on the association between CT determined skeletal muscle mass and physical functions measured using SPPB in this population. Although there are limited studies evaluating such associations using a performance-based measurement of physical functions, a longitudinal study of lung cancer patients demonstrated linear association between decline in CT determined skeletal muscle mass and decline in physical functions. They investigated the association between physical function, measured by handgrip strength and incremental shuttle walking distance, in individuals aged over 70 years [9]. Our findings support their observation of older lung cancer patients experiencing a significant decline in physical functions together with the decline in skeletal muscle mass. The age-related decline in skeletal muscle mass and physical function has been well-documented [50–52]. Furthermore existing reports indicate expediated decline of skeletal muscle mass and physical function among older cancer patients when compared to the general aging population [20]. This emphasizes the challenges faced

by cancer patients, who experience the combined effects of both aging and cancer in developing sarcopenia.

Low skeletal muscle mass correlating with low physical functions was also reported in a recent meta-analysis, which included 14 oncologic studies (4 studies with lung cancer). They observed that in comparison to participants with normal skeletal muscle mass, participants with low skeletal muscle mass have low baseline score in physical functions domains of quality-of-life scores (Standardized mean difference -0.4, 95% CI -0.74, -0.05, small-moderate effect size) [23]. Similarly, a study of 734 lung cancer patients reported a significant non-linear association existing between skeletal muscle mass and physical functions in both genders (men: $p = 0.016$, women: $p = 0.004$). Interestingly, they found that the cut point of skeletal muscle mass index (SMI) at which this significant association was observed, was similar to previously reported cut points associated with increased mortality. Specifically, the analysis revealed that associations occurred at lower levels of SMI values (male, SMI < 43 cm^2/m^2 when BMI <25 and female, SMI < 41 cm^2/m^2 for all BMI groups) [10]. This observation is consistent with our finding as we also observed that at lower levels of skeletal muscle mass the probability of predicting physical functional limitation increased. This highlights the clinical importance of maintaining skeletal muscle mass above specific threshold values may prevent functional limitations. Consistent with previous research, low skeletal muscle mass has been associated with adverse outcomes such as poor prognosis, treatment-related complications, impaired quality of life, and reduced survival [6–11]. Therefore, targeting interventions to preserve optimal skeletal muscle mass may have the potential to prevent such adverse outcomes in lung cancer patients.

The important difference in our study as compared to the latter two studies mentioned above is the type of functional assessment used. They used self-reported questionnaires as compared to a performance based measured, we have employed. Performance-based measures are better at identifying higher-level changes like decline in gait speed while self-reported measures are believed to be more adept at detecting lower-level changes in functioning like needing help with basic daily activities [53]. Nonetheless lower physical functions assessed with either of these measures are found to be associated

with negative outcomes in cancer patients. Self-reported functional limitation is shown to be independent risk factor for morbidity and mortality, on the other hand performance based measures gives a more detailed information about global health highlighting combined effects of multiple factors like disease condition, aging and nutrition [42]. SPPB has be shown to be associated with all-cause mortality in community dwelling population and in lung cancer SPPB has been shown to be a potential tool in predicting completion of chemotherapy and post-surgical complications [18,19]. In our study the mean SPPB score for females were 8 ± 2.7 and for males it was 8 ± 2.9, these values are comparatively low as compared to mean of community dwelling individuals (male=11.6±1.1, female=11.7±1.2) [50]. This implies that patients with lung cancer commonly experience functional impairment compared to individuals without cancer.

In contrary to our findings, a study by Williams et al in participants with different cancer types found no significant association of skeletal muscle mass measured using CT with overall physical functions [24]. Both performances based (using Time up and Go test) and patient reported questionnaires were used to assess the physical functions as part of routine geriatric assessment. The reason for weak negative association observed with TUG is uncertain, it may be due to different cancer types included in their study or due to different type of functional assessment. Moreover, it is worth noting that this study found a stronger association with skeletal muscle density (SMD) rather than skeletal muscle mass, which was not evaluated in our study. Likewise a stronger correlation between SMD with physical function has also been observed in community-dwelling elderly populations [25]. Further investigation of relationships between SMD and SMI with physical functions in lung cancer patients could offer a more comprehensive understanding of the associations we have identified in our study.

The biological difference between male and female makes them differently susceptible for development of low skeletal muscle mass or decline in physical performance. Studies in lung cancer patients have shown that higher proportion of males have low skeletal muscle mass as compared to female counterparts [26,27,47]. The exact cause for these differences is not well understood however it is thought that men have a higher

susceptibility for developing sarcopenia, which may be attributed to biological differences in muscle fiber composition and muscle mitochondrial metabolism, sex hormone and muscle gene expression [58]. However, our study provides some evidence that the gender differences in developing low skeletal muscle mass doesn't necessarily result into differential outcome in physical functions. In contrary to this, differential outcomes were observed when fatigue was evaluated as outcome by Kilgour et al. on 88 patients with advanced lung and gastrointestinal cancer .They reported that male patients with low skeletal muscle mass had a higher fatigue index, showing high frailty index (measured using the Brief Fatigue Inventory) as compared to female counterparts. However it was thought the limited sample size in females group could have caused such differences in fatigue score [28].

Strengths and limitations

We have used CT scan to measure the skeletal muscle mass, which is considered standard in oncologic patients. This allowed for an accurate measurement of skeletal muscle mass. The physical function measurement we employed in our study is a reliable and widely used performance-based assessment tool. To the best of our knowledge, this study is the first to perform a gender-based analysis of the association between skeletal muscle mass and physical functions in lung cancer patients.

Our study has several limitations. This study is a cross sectional study which does not provide information about causation, although the findings show that a more accurate prediction of physical functional limitations can be achieved by considering combined effects of skeletal muscle mass, gender and age. Age in the study was determined based on participants' age during the SPPB test. Age at diagnosis of cancer was not considered as some participants had missing age data at the time of cancer diagnosis. This could have potentially influenced the analysis while using age as predictor. However, the lack of significant age differences between genders suggests minimal impact on the gender analysis. To maintain the meaningful power of the study, other important predictors such as co-comorbidities, stage of disease, type of cancer treatment and skeletal muscle density were not included in in our analysis. Including these predictors may help to provide a more comprehensive understanding.

Chapter 5

Conclusion

We showed that low skeletal muscle mass and increasing age is associated with declining physical functions in lung cancer patients . In addition, this study provides some evidence that the association between skeletal muscle mass and physical function is not influenced by gender, further prospective studies are required to confirm this finding. The relationship between skeletal muscle mass and physical function is complex. A more comprehensive understanding may be achieved by considering additional variables, such as co-morbidities, skeletal muscle density, and treatment types.

Conflict of Interest

No conflict of interest declared.

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APPENDICES

Appendix A

Measurement of skeletal muscle mass at 3rd lumbar vertebra

The segmentation was performed on CT images obtained from the Picture Archiving and Communication System (PACS). We carefully selected single CT slice at the level of third lumbar vertebra (L3) and archived as Digital Imaging and Communications in Medicine (DICOM) data. The images were preprocessed to include the pixel values between -29 to 150 HU. The skeletal muscle area (SMA) using these images were calculated using an in-house software developed by MATLAB (The MathWorks, Natick, MA, USA) and freeware Python 3.6.13 (Anaconda, Inc.)

The in-house software we employed was based on a model which was initially trained using 215 CT images and their binary counterparts. These images were carefully prepared using MATLAB with the help of an experienced radiation technologist. The dataset was divided into three groups for training, validation, and verification to ensure that the model performed well. Deep learning model development was carried out in Python with the specialized architecture called the 2D dilated residual attention U-net. Thresholding based solutions were used to address potential issues over-detection of model's exterior muscle area.

This approach allowed for the accurate segmentation of skeletal muscle mass in the CT images This is a validated model that has been used previously with an accuracy of 99.17% and validity over union co-efficiency of 89.40%.

Appendix B

Associations between SMI and physical functions (OLS model)

We initially used an Ordinary Least Squared (OLS) model to understand the relationship between skeletal muscle mass and the outcome. The OLS model as shown in Figure shows that the relationship between the variables is non-linear.

Furthermore, due to non-linearity and non-normal distribution of SMI data, the assumption of homoscedasticity and the absence of multicollinearity were assessed for the SMI. The analysis revealed that the data met the assumption of homoscedasticity (chi-square value = 1.600369, p-value of 0.20585) indicating that the variability of the SMI data is approximately constant across different levels of the predictor. There was no evidence of multicollinearity as well (VIF SMI=1.442158, Sex=1.443591 and Age=1.061576) suggesting that the variables of interest were not highly correlated with other predictors in the model. These findings supported the reliability of using the SMI variable in the regression analysis. We proceeded to perform a logistics regression for prediction of outcome.

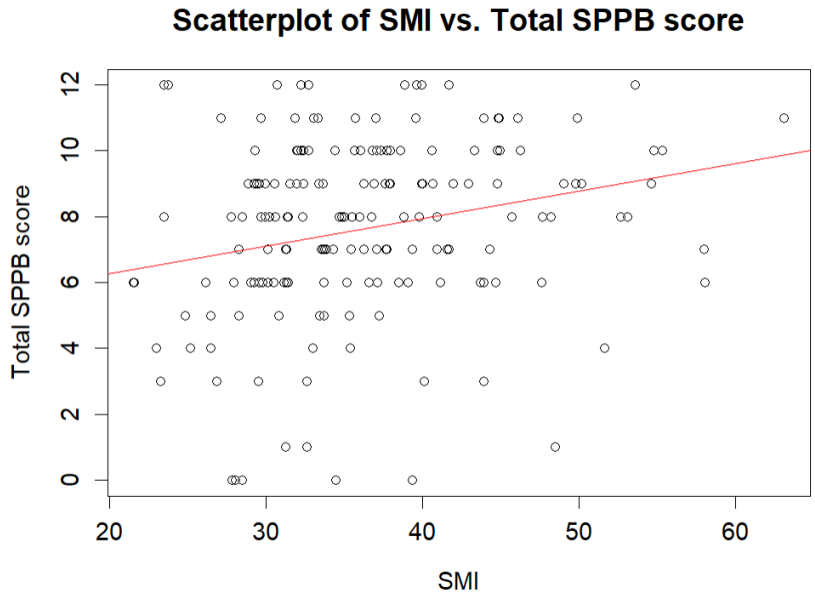

Figure 6. Scatterplot showing a non-linear relationship between SMI and total SPPB score.

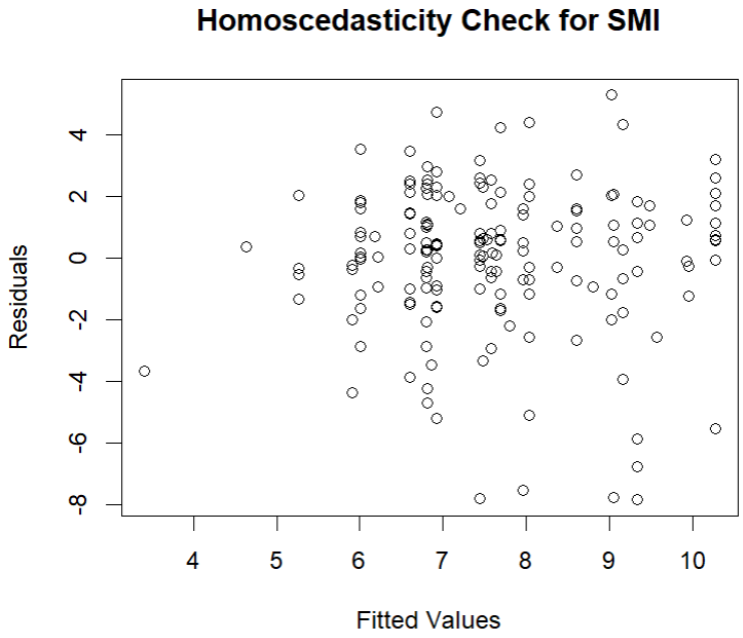

Figure 7. Homoscedasticity check for SMI showing no clear systematic pattern or significant deviation from the horizontal line.

Appendix C

Table 10. Result of model with predictors including type of treatment and stage of disease.

Characteristic	OR[1]	95% CI[1]	p-value
SMI	0.96	0.90, 1.03	0.3
sex			
Male	—	—	
Female	0.96	0.28, 3.20	>0.9
Stage	0.96	0.17, 3.11	>0.9
Type of treatment	0.62	0.23, 1.69	0.3
Age	1.12	1.06,1.20	<0.001

[1] OR = Odds Ratio, CI = Confidence Interval

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