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Sarcopenia and its Influencing Factors in Patients with Stage IIIB-IV Non-Small Cell Lung Cancer

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Abstract

Objective: To investigate the incidence and influencing factors of sarcopenia in patients with stage IIIB-IV Non-Small Cell Lung Cancer (NSCLC).

Methods: A total of 152 patients with IIIB-IV NSCLC were enrolled and their body composition were measured.

Results: The incidence of sarcopenia in IIB-IV NSCLC patients was 40.13%, which related to age, diabetes mellitus, Body Mass Index (BMI), and other body component. Besides, age and diabetes mellitus were independent risk factors, while high BMI was opposite.

Conclusion: Patients with IIIB-IV NSCLC generally have decreased muscle mass, it's necessary to early evaluate the muscle mass and to provide early nutritional intervention.

Keywords: Non-small cell lung cancer; Sarcopenia; Muscle mass; Influencing factors.

Introduction

Lung cancer, also known as primary bronchogenic carcinoma, originates from the trachea, bronchial mucosa or glands, and is a common primary lung malignancy [1] with high morbidity and mortality rates [2]. In 2015, the number of lung cancer cases in China reached 730 thousands, and the number of deaths reached 610 thousands, ranking first among all malignant tumors [3]. Lung cancer can be divided into small cell lung cancer and NSCLC according to its pathological characteristics, with NSCLC accounting for about 85% cases [2]. NSCLC can be divided pathologically into adenocarcinoma, squamous cell carcinoma, adenoid carcinoma, large cell carcinoma, and other subtypes [4]. Adenocarcinoma is more common clinically. Most patients diagnosed as stage IIIB and stage IV lung cancer lose the best treatment opportunity.

Sarcopenia [5] is a syndrome characterized by extensive and progressive decline in muscle strength and content. Sarcopenia was originally considered to be age-related skeletal muscle decline. The most common manifestations are decreased skeletal muscle mass and strength and associated loss of physical function. However, research has shown that sarcopenia can occur throughout the human life cycle. Sarcopenia in cancer patients is different from that in normal elderly people and belongs to secondary sarcopenia, often aggravated by increased physical expenditure, inadequate nutritional intake, reduced exercise, and treatment-related toxic reactions. Moreover, cancer patients may experience a systemic inflammatory response, abnormal endocrine regulation, and tumor-related hypermetabolic state, which accelerate muscle decomposition [6,7]. Decreased skeletal muscle mass is the most prominent clinical manifestation of sarcopenia. Sarcopenia is significantly associated with cachexia [8] and increases the risk of chemotherapy toxicity, postoperative complications, and death in cancer patients [9,10]. However, there are few studies on sarcopenia in patients with NSCLC. This study aimed to investigate the muscle loss in patients with NSCLC and its influencing factors to provide data to delay sarcopenia progression, improve the quality of life, reduce complications and mortality rate in NSCLC patients.

Materials and methods

Study design

A cross-sectional study design was used to analyze patients diagnosed with NSCLC in the Department of Oncology of the Sixth Affiliated Hospital of South China University of Technology from January 2020 to December 2021. Inclusion criteria: (1) age ≥18 years; (2) NSCLC diagnosed by cytology or pathology; (3) NSCLC patients with stage IIIB-IV according to the Tumor Node

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Metastasis (TNM) classification 8th edition of the American Cancer Society; (4) no other malignancies; (5) agreed to participate in the study. Exclusion criteria: (1) unclear cytological or pathological diagnosis or non-NSCLC; (2) unclear TNM staging or stage I-IIIA; (3) other malignant tumors and severe cachexia; (4) severe hypertension, heart disease, or liver and kidney disease; (5) poor compliance, inability to complete the study, or refusal to participate in the study.

The study was reviewed by the Ethics Committee of the Hospital. Informed consent was obtained from the enrolled patients. According to the rough estimation method of sample size proposed by Kendall, the number of study cases needed is 10-20 times the study variables. Considering a case loss rate of 10% of the sample size, 152 patients were finally included, including 72 men and 80 women. The general information of patients is shown in Table 1.

Data collection

The potential risk factors of sarcopenia were selected based on a literature search.

Demographics questionnaire

The demographics questionnaire was developed specially for the study. The following demographic variables were collected: Name, sex, age, height, weight, education level, marital status, monthly income, and smoking status. Educational level was classified as primary school or below, middle school and high school, and junior college or above. Marital status was classified as unmarried, married, divorced or widowed. Monthly income was classified as ≤¥1000, ¥1001–3000, ¥3001–6000, ¥6001–10000, >¥10000; most of the participants in this study were elderly patients. No income was defined as monthly income ≤¥1000, minimum income was defined as ¥1001–3000, Guangdong middle income was defined as ¥3001–6000, middle and higher income was defined as ¥6000–10000, and high income was defined as >¥10,000.

Clinical examination data

Clinical data such as the presence of diabetes, cell type, TNM stage, hemoglobin and albumin levels of the patients were obtained from the case records. The disease course was classified into: short disease course (0-6 months), middle disease course (6-2 months), and long disease course (>12 months). Cell type was classified into adenocarcinoma, squamous cell carcinoma, and others; the prognosis of patients with different cell types was inconsistent. Furthermore, 2 mL of fasting peripheral blood sample was collected in the morning and the patient's hemoglobin and albumin levels were detected by an automatic biochemical analyzer.

Body composition data

The Korean Inbody570 body composition analyser (InBody Co., Ltd. Seoul, Korea) was used to detect the body composition, which is based on the principle of bioelectrical impedance. The specific operation is as follows: the patient stands barefoot on the detector naturally and holds the hand electrode with both hands. The body composition analysis results are directly obtained after inputting the information of the patient, including the BMI, protein, minerals, Soft Lean Mass (SLM), Body Fat Mass (BFM), Fat Free Mass (FFM), Percent Body Fat (PBF), Waist Hip Ratio (WHR), Arm Muscle Circumference (AMC), and Visceral Fat Area (VFA). The criteria for judging sarcopenia were based on the criteria recommended by the Asian Working Group on Sarcopenia (AWGS) in 2014 [11], the corrected muscle mass or Appendicular Skeletal Muscle Mass Index (ASMI) is less than 7.0 kg/m^2 in men and less than 5.7 kg/m^2 in women, which can be judged as muscle mass deficiency. In this study, Inbody570 was used to directly measure the muscle mass according to the principle of bioelectrical impedance. BMI was obtained by dividing the weight in kilograms by the square of the height in meters. BMI can be divided into three groups according to the Chinese standard, lean group (≤18.4 kg/m^2), normal group (18.5 kg/m^2 –23.9 kg/m^2), and overweight/obesity group (≥24.0 kg/m^2) [12].

Statistical analysis

The body composition analysis data were exported to EXCEL form and then imported to SPSS for analysis. All the data were analyzed by SPSS20.0 statistical software. Age, body weight, BMI, and other data that had a normal distribution were described by ±S, whereas non-normally distributed data were expressed as medians or quartiles. Categorical variables (such as disease stage, sex, and cell type) were described by percentages or ratios. Normally distributed data were compared by the t-test or Pearson correlation analysis. Non-normally distributed data were compared by non-parametric tests, including the chi-square test and rank-sum test. Missing values were processed by substitution. Multicollinearity was assessed using the Pearson correlation coefficient statistic and by checking the Variance Inflation Factor in a multiple regression model with the same dependent and independent variables [13]. A variance inflation factor <5 was included in the binary logistic regression analysis. Binary logistic regression entry method was used for multivariate analysis of sarcopenia in patients with NSCLC. The difference was statistically significant when $p<0.05$.

Quality control

In line with the rigor of scientific research design and to avoid selective bias, the research participants were selected strictly according to the inclusion and exclusion criteria.

The purpose, significance, and methods of the study were clearly explained to the patients before the investigation was performed to obtain their trust and cooperation and all patients voluntarily participated in the study.

The human body composition analysis instrument was uniformly configured by the hospital, passed the quality inspection, and was calibrated before performing measurements. All investigators were trained and tested before using the human body composition analysis instrument.

To ensure the accuracy of the results, the same researcher operated the same machine to measure each time.

To ensure the accuracy of data, all data entry was carried out by two persons, one for entry and one for verification.

Results

Comparison of general and clinical examination data between the normal muscle mass and low muscle mass groups of patients with stage IIIB-IV NSCLC

A total of 201 patients were initially included in this study. Subsequently, 16 patients with small cell lung cancer, 18 patients with stage I-IIIA, eight patients with other malignant tumors, and seven patients with missing data were excluded. Finally, 152 patients with NSCLC were included, including 91 patients with normal muscle mass (59.87%) and 61 cases with low mus-

cle mass (40.13%), among which there were 72 men (47.37%) and 80 women (52.63%). The average age was 56.59±10.59 years. Additionally, the educational level was primary school and below in 31.58% participants, junior high school and senior high school in 52.63% participants, and junior college or above in 15.79% participants; 17.11% had a monthly income ≤¥1000, 31.58% between ¥1000 and ¥3000, 23.68% between ¥3000 and ¥6000, 16.45% between ¥6000 and ¥10000, and 11.18% >¥10000. Furthermore, 26.32% participants were smokers; 34.21% had diabetes; and 77.63% were in TNM stage IV. Participants with BMI<18.5 accounted for 12.50%; BMI 18.5-23.9 accounted for 50.66%; and BMI ≥24.0 accounted for 36.84%.

The muscle mass of the patients was selected as the dependent variable, and the general and clinical data, including sex, age, education level, marital status, smoking, diabetes, monthly income, TNM stage, disease course, cell type, hemoglobin, albumin, and BMI were selected as the independent variables. Univariate analysis of muscle mass was performed by Chi-square test and t-test. $p<0.05$ was statistically significant. We found that age (p=0.000), diabetes (p=0.000), disease course (p=0.007), cell type (p=0.015), and BMI (p=0.000) of NSCLC patients with sarcopenia showed statistically significant differences.

Pearson correlation analysis between ASMI and body composition in patients with stage IIIB-IV NSCLC

The body composition of 152 patients with stage IIIB-IV NSCLC was analyzed. ASMI was negatively correlated with the patients' age (p=0.000), and positively correlated with the BMI (p=0.000), protein (p=0.000), mineral (p=0.000), SLM (p=0.000), BFM (p=0.000), FFM (p=0.000), WHR (p=0.000), AMC (p=0.000), and VFA (p=0.000). A variance inflation factor>10 can be considered to indicate multicollinearity and multicollinearity was detected in the relationship of ASMI with the protein, mineral, SLM, BFM, FFM, PBF, AMC, and VFA.

Binary logistic regression analysis of patients with NSCLC

The influential factors with statistical significance ($p<0.05$) in the univariate analysis were included as independent variables (excluding multicollinearity variables), and muscle mass was taken as the dependent variable in the binary multivariate logistic regression. The results showed that older age (odds ratio [OR] = 1.108, 95% Confidence Interval [CI]: 1.039 - 1.182, p=0.002) and diabetes (OR=3.728, 95% CI: 1.371-10.139, p=0.010) were independent risk factors for low muscle mass, while high BMI (OR=0.048, 95% CI: 0.012-0.183, p=0.000) was a protective factor for low muscle mass, but disease course, cell type, and WHR did not demonstrate significant differences ($p>0.05$).

Discussion

In recent years, due to population aging, environmental deterioration, and other reasons, the incidence rate of tumors has been increasing. The incidence of sarcopenia is higher in tumor patients, with a reported incidence rate between 15-61% [14,15], especially can be as high as 78% in gastrointestinal cancer patients [16]. Sarcopenia is reportedly an independent risk factor for postoperative complications, chemotherapy toxicity, and adverse reactions in tumor patients, and can be used to predict the prognosis [17]. In China, the incidence rate and mortality of lung cancer rank first among all malignant tumors, with NSCLC accounting for 85% of lung cancers. It has a high incidence at all ages and the incidence rate continues to rise; however the treatment remains less than satisfactory [18]. Sarcopenia is an age-related clinical syndrome. It has attracted increasing attention recently because the decrease in muscle quality can cause multiple health problems and dysfunctions, such as falls, fractures, disability, and death [19]. Additionally, low muscle quality can affect the quality of life of cancer patients, even impacting their survival [15]. Therefore, it is particularly important to conduct a cross-sectional study on patients with NSCLC complicated with sarcopenia and implement targeted intervention measures on its influencing factors.

Low muscle mass in patients with stage IIIB-IV NSCLC

According to our results, there were 61 patients with low muscle mass, with an incidence rate of 40.13%, which was much higher than that in the general population (17.9%), but similar to the incidence in patients with digestive tract and breast tumors [15]. However, it was lower than the results of Murphy [20] who evaluated computer tomography images. Computer tomography is considered the gold standard for determining the content of skeletal muscles. The bioelectrical resistance analysis method used in this study to assess sarcopenia has certain limitations. Moreover, the sample size was small and this study lacks a large-scale cross-sectional survey design. Furthermore, the selected participants must be willing to cooperate with the examination. To avoid unnecessary risks such as falls and injuries, we excluded patients with severe tumor cachexia and some elderly patients. Therefore, the incidence rate of sarcopenia in this study is lower than that in foreign studies.

Factors influencing low muscle mass in patients with stage IIIB-IV NSCLC

The single factor analysis showed that age, diabetes mellitus, disease course, cell type, BMI, protein, mineral, SLM, BFM, FFM, WHR, AMC, and AFA were the influencing factors of low muscle mass in patients with NSCLC; especially, age, diabetes mellitus, and BMI are independent risk or protective factors for low muscle mass revealed by Binary logistic regression analysis. Sarcopenia is one of the symptoms of the aging syndrome associated with increasing age. Normal people begin to lose muscle mass slowly at the rate of 1-2% per year from the age of 30. After entering old age, the rate gradually accelerates, and from the age of 60-80 years, the loss of muscle mass reaches 30% or more [21]. With increasing age, the body functions deteriorate, physiological metabolic functions decline, the intake of protein, amino acids, vitamins, calcium, and other nutrients becomes insufficient, while the absorption of nutrients in the intestinal tract is decreased, which increases the accumulation of fat while the quality and function of muscle decline [22]. Increasing age can also lead to chronic inflammation. The increase in inflammatory factors promotes protein decomposition and inhibits protein synthesis through various signaling pathways, which ultimately leads to metabolic imbalance of muscle tissue [23]. Moreover, aging leads to an increase in reactive oxygen species, which damage the cell signal transduction pathways, thus leading to oxidative damage of mitochondrial DNA, mitochondrial dysfunction, and ultimately imbalance between cell generation and differentiation, decrease in muscle tissue content, and decline in muscle mass [24].

Many studies have shown that chronic diseases such as diabetes mellitus and chronic obstructive pulmonary disease affect sarcopenia, which is consistent with the results of the present study. Yoon [25] from Korea found that diabetic patients had a 3.5-fold increased risk of low muscle mass, and the National Health and Nutrition Examination Survey reported that diabetic

patients had a lower grip strength than non-diabetic patients. This may be closely related to insulin, because insulin can transport amino acids and glucose through the PI3K/Akt and mTOR signaling pathways, thus affecting muscle metabolism and protein synthesis, and ultimately increasing muscle mass [26,27].

BMI is commonly used worldwide to measure the degree of obesity and health. Our results showed that the incidence of sarcopenia in thin patients (BMI≤18.4) was as high as 94.74%, which is much higher than the incidence in overweight/obese patients (BMI≥24.0). Low BMI indicates malnutrition and many studies [19] have shown that the decline in muscle mass and strength in cancer patients precedes malnutrition; consequently, skeletal muscle can be used as an indicator of malnutrition and maintaining a high BMI can prevent the occurrence and development of sarcopenia.

Targeted treatment and nursing to prevent sarcopenia

Patients with NSCLC have a lower nutritional intake and reduced physical activity due to surgery, radiotherapy, chemotherapy, targeted drugs, complications, and other reasons, which lead to the occurrence of sarcopenia. Therefore, increasing the intake of high-quality protein and ensuring sufficient energy supply in patients is the key to ensure adequate nutrition. According to the latest guidelines at home and abroad [28], the target intake amount of a tumor patient is determined after measuring the basal metabolic energy consumption or is directly calculated as 104.7-125.6 KJ/(kg. D). The protein requirement of lung cancer patients is 1.2-1.8 g/(kg. D), but the protein supply of the elderly (>65 years), those with mobility difficulties, and systemic inflammatory response can be increased to 2 g/(kg. D), while the protein supply of patients with renal insufficiency can be reduced to less than 1.2 g/(kg. D). Fat should account for 30-50% of the total energy intake, and additional vitamins and minerals should be supplemented according to the individual needs [29].

Although exercise intervention cannot increase the muscle mass, it can improve physical function, improve immunity, and increase muscle strength of patients [30]. Clinical practice guidelines issued in 2018 suggest that exercise intervention can effectively treat sarcopenia. Resistance exercise not only helps to increase the skeletal muscle strength, but also improves the quality of the skeletal muscle [31].

Conclusion

Although many studies have found that the occurrence of sarcopenia in cancer patients is related to age, BMI, diabetes, and other chronic diseases, which is consistent with the results of this study, there are some shortcomings of this study. Firstly, the sample size was small, as some elderly patients and those with severe cachexia were excluded for safety; therefore, there were fewer statistically significant variables. In addition, the variables in the body composition analysis had the problem of multicollinearity, because of which they could not be included in the logistic regression analysis. The next step is to continue to collect patient data and carry out a large-scale multi-center prospective cohort study.

Declarations

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