Prognostic value of sarcopenia and nutritional status in early or mid-term non-small cell lung cancer (POSE)

Research Protocol

Main researchers: Zhao Ting, Zhu Yinggang

Clinical research department: Respiratory and Critical Care Medicine

Sponsor: Zhao Ting

Ethics Review No.:2021K125

Scheme Version No: 02

Plan Preparation date: October 15, 2021

CONTENT

I Research background

Lung cancer is the leading cause of cancer related death all over the world [1]. Although the existing treatment methods and technologies, such as new targeted gene detection and chemoradiotherapy, have brought great hope to improve the survival rate of patients, many patients with advanced non-small-cell lung cancer (NSCLC) are difficult to achieve disease control, and the overall survival rate of lung cancer is still unsatisfactory. In recent years, many clinical studies have confirmed that the prognosis of lung cancer patients is not only related to the stage of the tumor itself, but also closely related to the basic situation and physiological and psychological state of the patients. A poor prognosis of patients is associated with cardiovascular events, anxiety and depression or fatigue to varying degrees [2]. Identifying and assessing these combined factors aggressively and manage with interventions and treatment measures may have an important impact on improving the survival prognosis and quality of life of lung cancer patients.

Malignant tumors are often associated with weakness and cachexia. The clinical characteristic changes of tumor cachexia are continuously skeletal muscle reduction, which can not be corrected by routine dietary supplement, which may cause progressive functional decline and disorder [3]. Sarcopenia is defined as skeletal muscle mass (SMM) combined with skeletal muscle dysfunction. Now it is considered that the occurrence of primary sarcopenia is mainly related to age, and the occurrence of secondary sarcopenia is related to systemic acute and chronic diseases. In recent years, according to the latest definition of the Asian Working Group for Sarcopenia, the definition of sarcopenia has been clarified, the ICD code of the disease has been defined, and a unified diagnosis has formed [4]. Clinical studies on sarcopenia and cancer have also attracted more attention, such as digestive tract tumor, pancreatic cancer, gastric cancer, urologic tumors and rectal cancer [5][6]. Data had show that the prevalence of sarcopenia in lung cancer patients can reach as high as 43%, although sarcopenia is an elderly syndrome closely related to age, clinical rehabilitation or dietitian intervention diet can improve the nutritional status of patients with lung cancer to a certain extent. Although the diagnostic criteria of sarcopenia have been confirmed, most of the research are limited to the toxic and side effects of chemotherapy, postoperative complications and the survival rate of sarcopenia and other malignant tumors. There are few studies that have attempted to

investigate the impact of sarcopenia on the prognosis of lung cancer. Previous studies have also found that nutritional status plays an important role in tumor cachexia of other systems [7]. Loss of appetite, weight loss and fatigue caused by tumor will lead to poor nutritional status or even malnutrition. Poor nutritional status will further reduce patients' appetite and physical activity, thus forming a vicious circle. Nutrition is also an important factor in the progression of sarcopenia disease. Therefore, it is also of great clinical significance to determine whether nutritional status will affect the prognosis of patients with tumor sarcopenia, so it is absolutely valuable to investigate the risk factors associated with sarcopenia in lung cancer patients and confirm the impact of nutritional status on prognosis among these patients.

It has been reported that the prevalence of malnutrition in cancer patients varies from 30% to 80% according to the different distribution characteristics of the enrolled population in different studies [8]. A systematic review from 2006 to 2017 found that the Physical function and nutritional status were the most predictive domains for mortality [9]. At the same time, MNA score is widely used in tumor research of all ages [10], and it has been proved that MNA nutritional assessment can simply and quickly evaluate the nutritional status of patients according to anthropometric values, basic activity ability and eating conditions, and form a relatively complete evaluation system combined with blood albumin and other values [11], The score is also used to evaluate the baseline nutritional status of a variety of tumors and has good prognostic value in clinical outcome [12]. In rectal cancer, head and neck cancer and even non solid tumors such as acute lymphoblastic leukemia, higher MNA score has been proved to be an independent risk factor of prognosis [13]. Regarding the close relationship between this evaluation method and multiple clinical complications and prognostic factors, in recent years, people have gradually realized that early screening of the nutritional status of tumor patients and further receiving an appropriate intervention are particularly important to improve the influences on the outcomes of tumors. The American Society of Clinical Oncology also recommended the routine application of MNA score in the basic evaluation of nutritional status of 65 year old patients receiving chemotherapy in 2020 [7]. However, the application of this scoring system in early and mid-term lung cancer is very limited, studies examining the clinical features and nutritional status of patients in early mid-term NSCLC are thus necessary.

Therefore, this study aims to observe the correlation between sarcopenia and the

prognosis of patients with early mid-term non-small cell lung cancer, clarify the value of sarcopenia and nutritional status in predicting the overall survival rate and progression-free survival rate of patients with non-small cell lung cancer, and explore the value of early screening and nutritional intervention in predicting the prognosis of patients with lung cancer, To provide evidence-based research for alleviating the social and economic burden of lung cancer patients.

2、Research purpose

1. Identify the prevalence of sarcopenia in patients with early and mid-term non-small cell lung cancer as well as the anthropometry, clinical characteristics, tumor stage and treatment methods of this population, to compare and analyze the differences of clinical characteristics such as smoking status, tumor stage, EGFR gene expression, nutritional score and physical endurance with patients with non-small cell lung cancer.
2. Multivariate logistic analysis aim to explore the related risk factors of sarcopenia in patients with early and mid-term non-small cell lung cancer.
3. To clarify the impact of sarcopenia on the overall survival rate and progression-free survival rate of early and mid-term non-small cell lung cancer, and its clinical value as a predictor of the prognosis of patients.

3、Type of experimental design, grouping method

1) Study case collection scope: including respiratory ward, respiratory intensive care unit and respiratory outpatient department of Huadong Hospital Affiliated to Fudan University.
2) This study was a prospective, and observational cohort study. The follow-up results were grouped according to the diagnostic criteria of sarcopenia.

4、Case inclusion criteria and exclusion criteria

1. inclusion criteria

(1) The patients with non-small cell lung cancer diagnosed by cytology or pathology meet the standards of clinical diagnosis and treatment guidelines for lung cancer of Chinese Medical Association (2018 Edition), and the TNM staging diagnosis of lung cancer meets the stage IA-IIIA.

(2) The medical records are complete.

2. exclusion criteria

(1) Severe heart failure, acute progressive pulmonary inflammation ,acute liver and kidney dysfunction in recent 2 weeks;

(2) Incomplete clinical and follow-up data or disagreement or inability to conduct regular follow –up CT imaging evaluation;

(3) Patients with other malignant tumors and a history of related tumor chemotherapy within half year, previous history of radiotherapy;

(4) Unable to stand or walk, unable to cooperate to complete the walking test, and patients with past unconscious fall history and fall risk;

(5) Unable to complete BIA examination due to pacemaker implantation and other reasons;

(6) Those who withdraw from the study for subjective reasons, regardless of the patient's loss of follow-up caused by any reason, shall be regarded as patients who withdraw from the study.

5、Estimation of case sample size

Prevalence of lung cancer in China is about 36.09/10 million, with mortality of 28.41/10 million. The prevalence of sarcopenia in Asia is 25.2%. Combined with reported correlation coefficient OR3.2 of tumor and sarcopenia, GPOWER is used to calculate the incomplete information and missing value below 10%. α Less than or equal to 0.05 and statistical inspection force 1- β When it is 0.8, it is estimated that the final required numbers for this study includes about 66 patients with lung cancer complicated with sarcopenia. According to the 1:1 ratio of sarcopenia and non sarcopenia, the overall sample size is about 132, so as to ensure that the efficiency of the control test is 80%.

6、 Research process

1. Demographic data

The gender, age, height, weight, body mass index and skeletal muscle mass index were recorded.

2. Clinical data

According to the Electronic Medical Record, system image record data, face-to-face or

telephone follow-up records, clinical data were collected: oral drugs, smoking status(no smoking history, past smoking history, now smoking), tumor stage at the time of diagnosis, other chronic diseases, tumor pathological type and stage. According to the definition of tumor, lymph node and metastasis TNM stage in the eighth edition of American Lung Cancer joint staging. ECOG (Eastern Cooperative Oncology Group performance status, PS), MNA (mini nutritional assessment) nutrition score, quality of life depression score and treatment strategy.

3. Examination data

Serological samples: blood routine, C-reactive protein, blood cholesterol level, albumin level, tumor markers CEA, cyfra211, NSE, SCC, EGFR gene expression.

Imaging examination: chest CT.

4. Diagnostic criteria of sarcopenia

The diagnosis process of sarcopenia complies with the provisions of the Asian sarcopenia working group. The specific information collected for diagnosis includes: skeletal muscle mass of limbs: the skeletal muscle mass index (ASMI) is measured by Korea inbody570 (Korea Biospace) human composition analyzer. The decrease of skeletal muscle mass is defined as the decrease of male < 7.0kg/m^2 and female < 5.7kg/m^2; The Jamar hand dynamometer (USA) is used to measure the grip strength in the grip strength test. Patients are required to hold the grip strength tester in the dominant hand with standing position for 3 times, the maximum value were recorded. Male < 28kg and female < 18kg are defined as reduced grip strength; The time required for patients to walk at normal pace was measured by 6-meter distance pace measurement; If the walking speed is less than 0.8m/s, it is defined as the decline of walking function; The decrease of ASMI accompanied by the decrease of grip strength or gait speed was diagnosed as sarcopenia.

5. Follow up endpoint

The primary endpoint was progression free survival (PFS) within 2 years, defined as the time from diagnosis to clinically recorded disease progression or death from any cause. The patients were followed up according to the outpatient and electronic medical records and telephone calls. The tumor treatment strategy and the time of clinical outcome or disease progression were followed up. The disease progression was defined as the 20% increase in sum of longest diameters from nadir (and a minimum absolute increase of 5 mm), or unequivocal increase in nontarget lesions according to RECIST solid tumor standard. The progress needs to be confirmed by at least one imaging and one clinical expert. The deadline for follow-up is 2 years. The secondary endpoint was overall survival time (OS), defined as

the outcome of patient death from diagnosis to any cause or the final follow-up time. During the follow-up, the researchers conducted disease evaluation, follow up of disease progress, grip strength test, walking test, muscle density measurement and nutritional score (MNA) at 6, 12, 18 and 24 months after enrollment. If feasible, the paticipants will continue to be followed up for up to five years.

7、Adverse events

1. During the walking test, trained doctors and nurses were trained to detect the exercise safety in the whole process. This study will practically implement the safety work and safety equipment in the implementation of the scheme, including oxygen inhalation, oximeter, defibrillator, cardiopulmonary resuscitation drugs, bronchodilators and nitroglycerin; In case of the following conditions, the test will be terminated strictly: 1. Reaching 85% of the maximum heart rate; 2. Arrhythmia events; 3. Blood pressure exceeding 180 / 100mmhg; 4. Chest pain; 5. Blurred vision; 6. Cold sweat syncope; 7. Abnormal limb coordination; 8. Blood oxygen saturation lower than 85%.
2. This study is an observational study and does not involve new drugs and traumatic testing, so there is basically no additional research risk. In case of acute exacerbation or condition change during the study, the patient may not be affected by the study and be treated in accordance with the medical principles. The end point of observation and disease progress indicators are the objective state of the development of the disease itself. The study does not involve any research methods and drugs for intervention and diagnosis measures, so there will be no serious adverse events related to the study.

8、Statistical analysis

The patients were divided into two groups according to whether they were diagnosed as sarcopenia, and the differences of clinical data between the two groups were analyzed. The statistical analysis will be calculated by spss24.0 statistical analysis software.

1. Demographic characteristics and clinical data analysis: describe the age and gender distribution of patients, group patients according to whether they are diagnosed as sarcopenia, and analyze the differences of clinical data such as age distribution, smoking, tumor type and clinical stage between the two groups. Continuous variables are represented by mean standard deviation, classified variables are represented by

percentage, students t-test analysis and Mann-Whitney U test are used according to data type differences, and chi square test is used for component comparison of classified data.

2. Analysis of risk factors of non-small cell lung cancer combined with sarcopenia: univariate and multivariate logistic analysis of relevant variables of patients with sarcopenia, including clinical data variables, nutritional status, tumor stage, serum C-reactive protein, cholesterol level, albumin level, EGFR gene expression, etc, Logistic regression was used to analyze the risk factors of sarcopenia in non-small cell lung cancer.

3. Prognostic value of sarcopenia in non-small cell lung cancer: progression free survival time PFS and overall survival time OS were statistically analyzed by Kaplan-Meier, and the difference was tested by log-rank method.

9、 Ethics related to experiment

The risk of patients participating in this study comes from the risk of tumor itself and tumor complications. It is an observational study without any intervention means such as drugs. The study itself does not increase the disease risk of patients. Patients can still stop treatment or withdraw from the study at any time, and subjects can stop the study at any time or for any reason at their own request or at the request of the investigator. For all subjects who withdrew from the study for any reason, contact themselves or their families or health care providers 24 weeks after withdrawal to determine the subject's life status. Subjects may voluntarily stop participating in the study at any time without affecting further treatment.

At the same time, ensure that after the end of the study and midway suspension, all participants continue to accept the disease medical measures recommended in the guidelines, do not change the follow-up further treatment, and do not intervene in the outcome of the disease.

10、Recruitment methods and informed consent of subjects

This study used the recruitment method of clinical case collection, including respiratory ward, respiratory intensive care unit and respiratory clinic. All patients must

obtain informed consent and sign the informed consent form.

11、Expected progress and completion time of the study

Study period: October 15, 2021 to October 15, 2024

From October 2021 to November 2021, the research group collected personnel training and enrolled cases.

From November 2021 to November 2023, the case observation indexes, clinical data and follow-up data were collected.

From November 2023 to January 2024, the final follow-up was completed and the outcome events were collected and sorted out.

From January 2024 to October 2024, statistics and data sorting, writing papers, accepting results and publishing articles.

12、Follow up and medical measures after the study

After the study, continue to accept the disease medical measures recommended by the guidelines, do not change the follow-up further treatment, and do not intervene in the outcome of the disease.

13、Responsibilities of each party and other relevant provisions

1. Research Division of labor: before the beginning of the research, the researchers shall be trained to be familiar with the research scheme and the principles of data collection. The researcher shall record the contents truthfully, in detail and carefully as required. The specific division of labor is as follows:

- Zhao Ting, attending physician, research plan formulation, data collection and article writing
- Zhu Yinggang, deputy chief physician, supervision and training of research program
- Zhao Hongyu, resident patient follow-up and data management
- Lu Yuntao, attending physician, data collection, statistics and article writing

2. Expected goals

1) The purpose of this study is to clarify the impact of skeletal sarcopenia on the overall survival rate and progression free survival rate of early and mid-term non-small cell lung

cancer, as well as its clinical value in predicting the prognosis of patients.

2) The research results will provide high-quality evidence-based medicine evidence for the formulation, revision and optimization of international and domestic lung cancer clinical guidelines and expert consensus, and the research has certain social value.

3) While further cultivating the clinical trial research team, the research team will publish at least 2 clinical research papers as the first / corresponding author in the International Journal of respiratory medicine consistent with the funding direction of the project.

4) At least one provincial and municipal project in the direction of relevant disciplines of the new project.

5) Make special or general assembly speeches at important international conferences in this field.

14、References

[1]Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA: a cancer journal for clinicians, 2018,68(6):394-424.doi:10.3322/caac.21492.

[2]Choi S, Ryu E. Effects of symptom clusters and depression on the quality of life in patients with advanced lung cancer[J]. European journal of cancer care, 2018,27(1).doi:10.1111/ecc.12508.

[3]Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus[J]. The Lancet Oncology, 2011,12(5):489-95.doi:10.1016/s1470-2045(10)70218-7.

[4]Chen LK, Woo J, Assantachai P, et al. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment[J]. Journal of the American Medical Directors Association, 2020,21(3):300-7.e2.doi:10.1016/j.jamda.2019.12.012.

[5]Ozola Zalite I, Zykus R, Francisco Gonzalez M, et al. Influence of cachexia and sarcopenia on survival in pancreatic ductal adenocarcinoma: a systematic review[J]. Pancreatology : official journal of the International Association of Pancreatology (IAP) [et al], 2015,15(1):19-24.doi:10.1016/j.pan.2014.11.006.

[6]Sun G, Li Y, Peng Y, et al. Can sarcopenia be a predictor of prognosis for patients with non-metastatic colorectal cancer? A systematic review and meta-analysis[J]. 2018,33(10):1419-27.doi:10.1007/s00384-018-3128-1.

[7]Roeland EJ, Bohlke K, Baracos VE, et al. Management of Cancer Cachexia: ASCO Guideline[J]. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2020,38(21):2438-53.doi:10.1200/jco.20.00611.

[8]Caillet P, Liuu E, Raynaud Simon A, et al. Association between cachexia, chemotherapy and outcomes in older cancer patients: A systematic review[J]. Clinical nutrition (Edinburgh, Scotland), 2017,36(6):1473-82.doi:10.1016/j.clnu.2016.12.003.

[9]Bruijnen CP, van Harten-Krouwel DG, Koldenhof JJ, et al. Predictive value of each geriatric assessment domain for older patients with cancer: A systematic review[J]. Journal of geriatric oncology, 2019,10(6):859-73.doi:10.1016/j.jgo.2019.02.010.

[10]Torbahn G, Strauss T, Sieber CC, et al. Nutritional status according to the mini nutritional assessment (MNA) ® as potential prognostic factor for health and treatment outcomes in patients with cancer - a systematic review[J]. BMC cancer, 2020,20(1):594.doi:10.1186/s12885-020-07052-4.

[11]Aprile G, Basile D, Giaretta R, et al. The Clinical Value of Nutritional Care before and during Active Cancer Treatment[J]. Nutrients, 2021,13(4).doi:10.3390/nu13041196.

[12]Vasilopoulos G, Makrigianni P. Pre- and Post-Operative Nutrition Assessment in Patients with

Colon Cancer Undergoing Ileostomy[J]. 2020,17(17).doi:10.3390/ijerph17176124.
[13]Yoo KH, Cho J, Han B, et al. Outcomes of decitabine treatment for newly diagnosed acute myeloid leukemia in older adults[J]. PloS one, 2020,15(8):e0235503.doi:10.1371/journal.pone.0235503.