

Received: 2024.10.01
Accepted: 2024.10.23
Available online: 2024.11.04
Published: 2024.12.18

Association Between Body Mass Index and Survival in Patients with De Novo Metastatic Non-Small Cell Lung Cancer

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Financial support: None declared
Conflict of interest: None declared

Background: This retrospective study from a single center included 289 patients diagnosed with advanced non-small cell lung cancer (NSCLC) between 2010 to 2017 and aimed to evaluate the effects of body mass index (BMI) on overall survival.

Material/Methods: This retrospective study involved 289 patients diagnosed with metastatic-stage NSCLC at a single institution between January 2010 and December 2017. Patients were categorized into 2 groups based on their BMI at diagnosis: those with a BMI <25 kg/m² and those with a BMI ≥25 kg/m². Univariate and multivariate Cox regression analyses were conducted to identify factors associated with overall survival.

Results: A total of 289 patients (241 men, 48 women) were included in the study, with a mean age of 60.1±11.1 years. Among them, 175 patients (60.6%) had a BMI less than 25 kg/m². Multivariate analysis revealed that BMI, pathological diagnosis, and complete response after first-line treatment were independently associated with survival in patients with lung cancer. Predicted survival time was significantly shorter in the BMI <25 group than in the BMI ≥25 group (9.3 months vs 13.0 months, *P*<0.05).

Conclusions: The study demonstrated that a higher BMI at the time of diagnosis is associated with improved overall survival in patients with de novo metastatic NSCLC. BMI may serve as an important prognostic factor in this patient population. Future prospective, multi-center studies are necessary to further validate the role of BMI in predicting survival outcomes in NSCLC patients across different treatment modalities.

Keywords: **Body Mass Index • Carcinoma, Non-Small-Cell Lung • Obesity • Survival**

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/946751>

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Introduction

Lung cancer is a severe illness that can be life-threatening. Lung cancer caused an estimated 1.8 million deaths worldwide in 2020 [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer diagnoses, with a 5-year survival rate of 25% [2].

Surgical intervention remains the most favorable approach for achieving sustained remission and prolonged survival in patients with resectable NSCLC [3]. About half of patients with lung cancer receive a diagnosis at an advanced stage [4]. Patients with metastatic NSCLC harboring driver mutations receive targeted therapies, while those without such mutations but exhibiting high programmed cell death-ligand 1 (PD-L1) expression are treated with immunotherapy. In patients with low PD-L1 expression, a therapeutic regimen that combines chemotherapy with immunotherapy is used [3,5,6].

In addition to biomarkers such as PD-L1 and microsatellite instability, which are used for tumor response and survival in NSCLC, several straightforward clinical and demographic factors, including Eastern Cooperative Oncology Group Performance Status (ECOG PS) and body mass index (BMI), have been traditionally used for prognostic evaluation [6-10].

The pathophysiology of obesity involves a complex interaction between genetic, hormonal, metabolic, and environmental factors that disrupt energy balance. Obesity occurs when energy intake consistently exceeds expenditure, leading to fat accumulation. Genetic predisposition, hormonal imbalances (such as leptin resistance), and insulin resistance contribute to increased appetite and altered metabolism. Additionally, environmental influences, such as high-calorie diets and sedentary behavior, amplify these effects. This multifactorial process results in chronic inflammation and metabolic dysfunction, sustaining and exacerbating obesity [11,12]. Excess bodyweight is associated with a dramatic reduction in life expectancy, especially among those who develop obesity under the age of 40 [13]. In particular, a meta-analysis of 230 cohort studies involving more than 30 million individuals found that overweight and obesity were associated with an increased risk of all-cause mortality [14]. The association between obesity and cancer is highly controversial. Being overweight is associated with an increased risk of more than one type of cancer. It is estimated that overweight and obesity caused 40% of all cancers in the United States in 2014 [15]. Obesity has been linked to a higher incidence of various cancers and increased mortality rates among cancer patients. However, in certain types of cancer, obesity may confer some beneficial effects [16]. Several studies have indicated that an elevated BMI is associated with prolonged survival in patients with NSCLC [17-20]. In another study, obesity negatively influenced prognosis in both NSCLC and small cell lung cancer (SCLC) [21].

BMI is one of the factors investigated for its prognostic effect in lung cancer. Although a BMI above normal is associated with many diseases, it may have a positive effect on survival, especially in metastatic solid organ tumors with short survival. Therefore, this retrospective study from a single center included 289 patients who received a diagnosis of advanced NSCLC between 2010 to 2017 and aimed to evaluate the effects of BMI on overall survival (OS).

Material and Methods

Study Design and Ethical Issues

This retrospective study included patients who were followed and treated in the Oncology Clinic of Dursun Odabaşı Medical Center, Faculty of Medicine, Van Yüzüncü Yıl University between January 2010 and December 2017. Patient consent was waived due to the retrospective observational design of the study. This study was conducted in accordance with the Declaration of Helsinki. The required approval for conducting the study was obtained from the Ethics Committee of Van Yüzüncü Yıl University (date: 02.16.2024, decision no: 2024/02-10).

Participants and Data Collection

Patients who were older than 18 years of age, had metastatic disease at the time of diagnosis, had a cytologic or histologic diagnosis of NSCLC, and had complete data were included in the study. Patients younger than 18 years of age, patients with more than one primary malignancy, patients with SCLC histology, patients who developed recurrence after curative treatment, patients who received immunotherapy or targeted therapy, and patients with missing data were excluded. Tumor staging was performed according to tumor, nodes, and metastases (TNM) classification 8th edition. Overall survival was determined by measuring the time interval from the initial diagnosis to either the date of death or the most recent follow-up. The height and weight values of the patients before treatment were measured and recorded by an oncology nurse using calibrated instruments. BMI was calculated using these measured height and weight values. The formula for BMI is weight in kilograms divided by height in meters squared ($BMI = kg/m^2$). Patients were divided into 2 groups according to BMI at the time of diagnosis, as $BMI < 25 kg/m^2$ and $BMI \geq 25 kg/m^2$. Demographic data such as sex, age, smoking, height, weight, ECOG PS, histological subtype, lung lobe of origin, site of metastasis at the time of diagnosis, response to treatment, and outcome were obtained from written archival files.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 28 (IBM Corp, Armonk, NY, USA).

Table 1. Clinical and demographic data.

Characteristics	Total (n=289)	Characteristics	Total (n=289)
Age (mean±SD)	60.1±11.1	1	70 (24.2)
Age (n, %)		2	80 (27.7)
<60	145 (50.2)	3	47 (16.3)
≥60	144 (49.8)	Patologic diagnosis (n, %)	
Sex (n, %)		Squamous cell carcinoma	79 (27.3)
Female	48 (16.6)	Adenocarcinoma	146 (50.5)
Male	241 (83.4)	NOS	64 (22.1)
Height, cm (mean±SD)	167.5±8.1	The site of metastasis (n, %)	
Weight, kg (mean±SD)	68.7±13	Brain	76 (26.3)
BMI, kg m ² (mean±SD)	24.5±4.5	Liver	49 (17)
BMI, kg m ² (n, %)		Bone	128 (44.3)
<25	175 (60.6)	Surrenal	62 (21.5)
≥25	114 (39.4)	Pleura	42 (14.5)
Smoking (n, %)		Counter-Lung	62 (21.5)
Yes	246 (85.1)	Other	31 (10.7)
No	43 (14.9)	Final situation	
ECOG PS (n, %)		Alive	63 (21.8)
0	92 (31.8)	Dead	226 (78.2)

Results were presented as mean±standard deviation or n (%). SD – standard deviation; BMI – body mass index; ECOG PS – Eastern Cooperative Oncology Group performance status; NOS – not otherwise specified.

Categorical variables were presented as numbers (percentages), while continuous variables with normal distribution were presented as mean±standard deviation (SD); non-normal variables were reported as median (minimum-maximum). Kaplan-Meier survival estimates were calculated. The possible factors identified with univariate analysis were further entered into the Cox regression analysis, with backward selection, to determine independent predictors of survival. Among correlated factors with similar effects on survival, only those with clinical significance were included. The proportional hazards assumption and model fit was assessed by means of residual (Schoenfeld and Martingale) analysis. A *P* value <0.05 was considered statistically significant.

Results

Patient Demographics and Characteristics

A total of 289 patients (241 men, 48 women) were included. The mean age of the patients was 60.1±11.1 years. The BMI

of 175 (60.6%) patients was less than 25 kg/m². About 50.5% of the patients had non-squamous histology. Approximately 85.1% of the patients had a history of smoking. The ECOG PS was 0 or 1 in 162 patients (55%). Clinical and demographic characteristics of the patients are summarized in **Table 1**.

BMI and OS

The median OS was significantly lower in the BMI <25 group than in the BMI ≥25 group (9.3 months vs 13.0 months, *P*<0.05; **Figure 1**).

Univariate and Multivariate Analysis of Prognostic Factors

Univariate analysis and multivariate analysis for OS are presented in **Table 2**. Multivariate analysis showed that BMI, pathologic diagnosis, and complete response after the first line treatment were independently associated with the survival of patients with lung cancer.

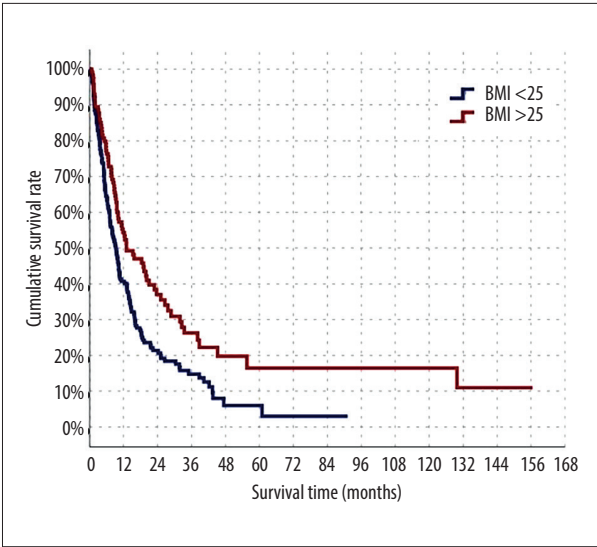


Figure 1. Overall survival according to body mass index (BMI) groups.

Discussion

In our study, we found that the OS of patients with metastatic NSCLC who had a BMI above normal at the time of diagnosis was statistically significantly longer. In addition, we found 2 factors, pathologic diagnosis and complete response after first-line treatment, were the independent prognostic factors for lung cancer.

In an analysis involving 225 patients with a diagnosis of stage III and IV NSCLC and SCLC, the group with underweight had worse survival than the group with normal weight [22]. A retrospective study evaluated 233 patients with metastatic NSCLC treated with first-line platinum-based chemotherapy and found that a BMI ≥ 25 was associated with more favorable progression-free survival (PFS) and OS [19]. In a multicenter study, Nie et al conducted a retrospective analysis of data from 7 cohorts involving 7021 patients with advanced NSCLC who underwent chemotherapy, immunotherapy, or a combination of both (chemoimmunotherapy). The findings indicated that obesity was correlated with

Table 2. Univariate and multivariate analysis for overall survival (OS).

	Univariate analysis for OS			Multivariate analysis for OS		
	HR	95% CI for HR	P	HR	95% CI for HR	P
Age	1.018	1.005-1.030	0.005			
Sex	1.399	0.962-2.036	0.079			
Height	1.001	0.985-1.016	0.920			
Weight	0.982	0.971-0.993	0.001			
BMI	0.941	0.911-0.973	0.000	0.958	0.924-0.994	0.021
Smoking status	1.931	1.263-2.954	0.002			
ECOG PS	2.212	1.942-2.519	0.000			
Pathologic diagnosis	0.669	0.569-0.786	0.000	0.672	0.565-0.799	0.000
Localization	1.018	0.913-1.136	0.745			
Pleural effusion	1.137	0.835-1.547	0.416			
Brain metastasis	0.893	0.738-1.081	0.247			
Counter-lung metastasis	0.844	0.655-1.088	0.191			
Liver metastasis	0.907	0.731-1.125	0.373			
Surrenal metastasis	0.977	0.791-1.206	0.827			
Bone metastasis	1.308	1.074-1.594	0.008			
Pleural metastasis	0.922	0.691-1.231	0.584			
Other metastasis	1.591	1.075-2.354	0.020			
Complete response after first-line therapy	0.060	0.015-0.243	0.000	0.056	0.014-0.228	0.000

OS – overall survival; HR – hazard ratio; CI – confidence interval; BMI – body mass index; ECOG PS – Eastern Cooperative Oncology Group performance status.

prolonged OS in male patients receiving chemotherapy, while no significant association was observed between obesity and survival outcomes in those treated with immunotherapy or chemioimmunotherapy [23]. In another study, patients with resectable lung cancer were categorized based on BMI. Underweight was associated with lower survival than was normal weight, while overweight and obesity were associated with improved survival. The effect of BMI was validated when stratified by sex and the Charlson comorbidity index. BMI emerged as a robust and independent predictor of survival in patients undergoing surgery for NSCLC [24]. In a meta-analysis examining the relation of BMI and mortality in patients with lung cancer, it was found that patients with lung cancer with a higher BMI had a longer survival than those with a lower BMI [25]. While overweight is associated with shorter survival in a typical individual, there are different reasons why it is associated with better survival in this patient group. Research indicates that this effect may be linked to immune system alterations caused by malnutrition, higher levels of smoking exposure, reduced treatment tolerance, and mechanisms associated with cancer-related cachexia [26-29].

A meta-analysis of 5000 patients from 10 studies showed that immunotherapy was significantly more effective in NSCLC patients with a higher BMI than in those with a lower BMI [30]. In a meta-analysis including 9 studies and involving 4602 NSCLC patients treated with immune checkpoint inhibitors, there was no notable distinction in PFS or OS between the low-BMI group and the high-BMI group. However, in subgroup analysis, compared with patients with normal weight, patients with overweight and obesity achieved longer PFS and OS [31]. The inflammatory state can precede or accompany lung cancer and is responsible for increased energy expenditure, contributing to malnutrition and thus catabolic processes. Similarly, fat and muscle loss can occur as a result of reduced caloric intake resulting from malignancy-related symptoms and treatments. In contrast to the immune defense in lean patients, high body fat may promote a good immune defense status against NSCLC. The density of dendritic cells and cytotoxic CD8+ lymphocytes, which are important components of immune cells, is directly related to good nutritional status [32,33]. In our study, patients who received immunotherapy were not included, to ensure homogeneity of the patient group.

While overall mortality was higher in cancer patients with obesity, those with obesity and diagnosed with lung cancer, renal cell carcinoma, and melanoma exhibited a reduced risk of death than did patients without obesity who had the same types of cancer [20]. In an analysis of patients with an NSCLC diagnosis, obesity was recognized as a protective factor at baseline when comparing patients with obesity with patients with normal-overweight. However, for patients with a follow-up period exceeding 16 months, obesity was associated with an increased risk of death, compared with the normal or overweight categories [18]. In a study that sought to develop an equation to predict OS in

advanced-stage patients, obesity or being overweight was not identified as either a protective or risk factor [34].

In contrast to these studies, there are also studies showing that there is no association between BMI and survival. In another study, no significant difference in the risk of death was observed between stage III and stage IV NSCLC patients with a normal BMI and those who had overweight or obesity. Moreover, the study revealed that sex, smoking status, and race interact with the association between BMI and survival in patients with NSCLC [35]. Taking into account the aforementioned studies, it can be concluded that research and meta-analyses on the topic have produced varying results. This study did not assess the effectiveness of any specific treatment or compare the superiority of different treatments. Patients who received immunotherapies and targeted therapies with higher survival were not included.

Our study has limitations that must be acknowledged. First, its retrospective design inherently carries the potential for selection bias, as the data were collected from medical records. Second, the study was performed at a single center, which can restrict the applicability of the findings to wider populations, especially given the regional differences in patient demographics and treatment protocols. While the study has certain limitations, such as its retrospective and single-center nature, the homogeneity of our study population is enhanced by the consistent administration of treatments within the same clinic and the exclusion of patients receiving treatments other than chemotherapy.

Conclusions

Higher BMI at the time of diagnosis was associated with improved OS in de novo metastatic NSCLC. This finding suggests that BMI, a readily measurable and simple clinical parameter, may serve as an important prognostic factor in this patient population. More studies are needed in which all BMI categories are sufficiently represented and patients receiving different treatment options are included. Future prospective, multi-center studies incorporating a broader range of therapies and patient variables are needed to further clarify the role of BMI in predicting survival in patients with NSCLC.

Department and Institution Where Work Was Done

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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