Effect of Pulmonary Functions on Survival in Patients with Operable Non-small Cell Lung Cancer

Melek Cihanbeylerden[1], Merve Yumrukuz[2], Bahar Kurt[3], Cise Tuccar[4] and Cagla Safak[5]

[1]*Department of Pulmonology, Hacettepe University Hospital, Ankara, Turkey*
[2]*Department of Pulmonology, Balikesir State Hospital, Balıkesir, Turkey*
[3]*Department of Pulmonology, Faculty of Health Sciences, Diskapi Yildirim Beyazit Research and Training Hospital, Ankara, Turkey*
[4]*Department of Pulmonology, Baskent University Hospital, Ankara, Turkey*
[5]*Ankara University School of Medicine, Biostatistics, Ankara, Turkey*

ABSTRACT

Objective: To investigate the prognostic importance of pulmonary functions and their effect on survival in patients with operable non-small cell lung cancer (NSCLC), who underwent surgical resection and/or received medical treatment.

Study Design: Cohort study.

Place and Duration of Study: University of Health Sciences, Diskapi Training and Research Hospital, Ankara, Turkey, between June 2013 and March 2020.

Methodology: The study included a total of 70 patients diagnosed with non-small cell lung cancer (NSCLC), comprising 35 who underwent surgical treatment and 35 who were treated medically. The effects of age, gender, additional comorbidities, smoking status, complications after surgery and/or radiotherapy, and pulmonary function test values on survival were investigated.

Results: The median overall survival time of the patients was 1973±769.1 (466-3.480) days. According to the univariate Cox regression analysis, the preoperative and postoperative values of the forced expiratory volume in 1 second were not important risk factors affecting survival (p=0.752 and p=0.878) respectively. A statistically significant difference was observed in survival probability between the patients with and without coronary artery disease (CAD) (p=0.005). There was also a statistically significant difference between the Eastern Cooperative Oncology Group (ECOG) performance groups in terms of survival probability (p<0.001).

Conclusion: There was no relationship between pulmonary functions and survival in patients with operable NSCLC, but this evaluation should be undertaken in larger patient groups. This study demonstrated the importance of patients' performance status and comorbidities, such as CAD in survival.

Key Words: *Non-small cell lung cancer, Survival, Respiratory function test.*

How to cite this article: Cihanbeylerden M, Yumrukuz M, Kurt B, Tuccar C, Safak C. Effect of Pulmonary Functions on Survival in Patients with Operable Non-small Cell Lung Cancer. *J Coll Physicians Surg Pak* 2022; **32(05)**:606-612.

INTRODUCTION

Lung cancer is one of the leading causes of cancer-related mortality in the world.[1] According to the World Health Organisation (WHO) data, every year approximately 1.2 million new lung cancer cases are diagnosed. It is estimated that this number will have reached 26 million by 2030. Despite advances in screening, diagnosis, and molecular genetics, the overall five-year survival remains around 18%.[2] In patients with non-small cell lung cancer (NSCLC), which is considered to be resectable, the accurate preoperative staging of mediastinal lymph nodes is of great importance in the success of treatment.[3]

Correspondence to: Dr. Melek Cihanbeylerden, Department of Pulmonology, Hacettepe University Hospital, Ankara, Turkey
E-mail: ytse_jammm@hotmail.com

Received: October 22, 2021; Revised: January 11, 2022; Accepted: January 22, 2022
DOI: https://doi.org/10.29271/jcpsp.2022.05.606

In staging, non-invasive (computed tomography, positron emission tomography-computed tomography, and magnetic resonance imaging) and invasive (mediastinal lymph node sampling) methods are used. Currently, the most effective method in the treatment of early-stage NSCLC is surgery. Surgical treatment is preferred for locally advanced tumors in selected patients with NSCLC. Metastasis to ipsilateral mediastinal and/or subcarinal lymph nodes (N2 disease) constitutes 15% of NSCLC cases.[4] However, the treatment of N2 disease is still controversial, and a multidisciplinary approach is important in the treatment of these patients. In induction therapy, better response rates and survival outcomes are achieved with concomitant chemoradiotherapy compared to chemotherapy alone. It is stated that long-term survival is better when complete resection is achieved in patients who have benefited from induction therapy. Therefore, diagnosis and treatment modalities in lung cancer are very important.

Many different prognostic factors have been revealed in patients with NSCLC.[5] Lung function has been shown to be an important prognostic determinant in patients with NSCLC who have undergone surgery.

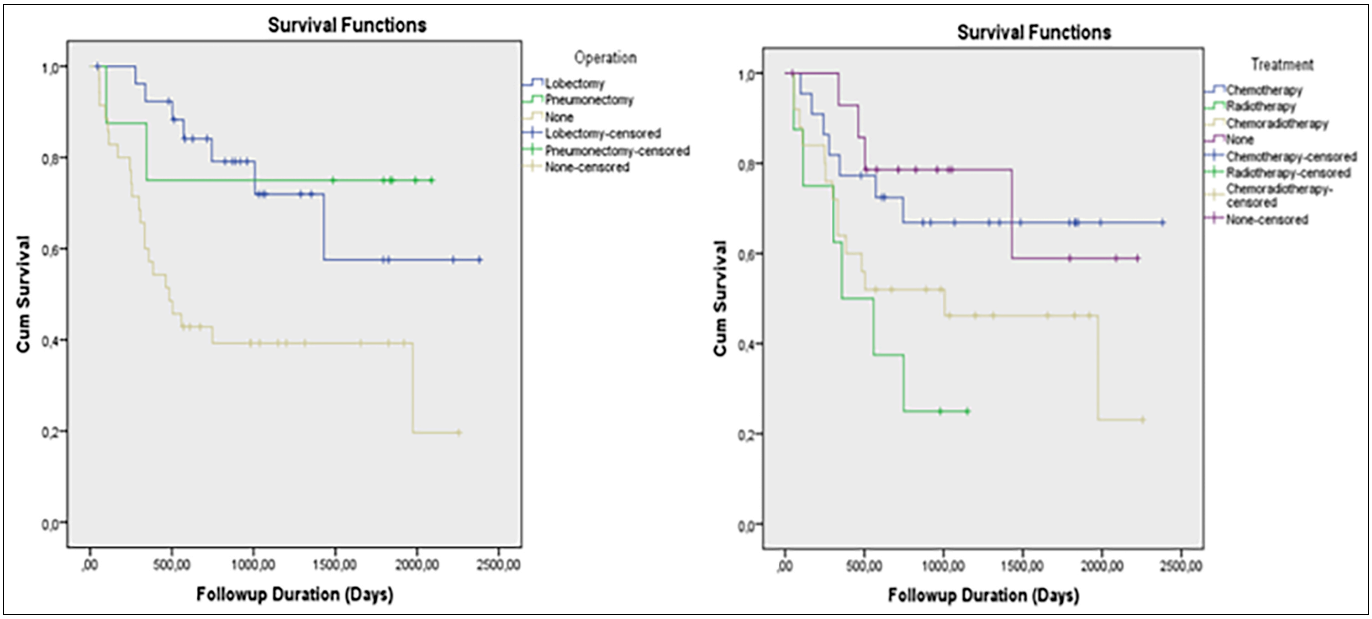

Figure 1: Right: relationship between surgery type and survival/Left: Relationship between non-surgical treatment method and survival.

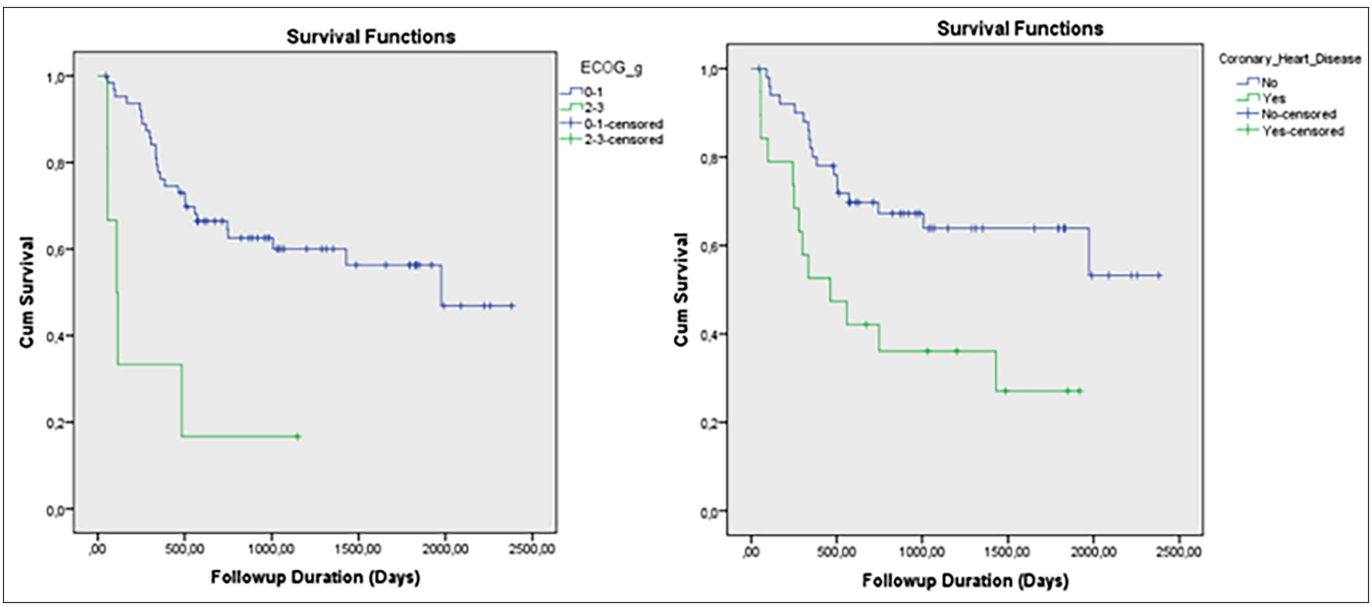

Figure 2: Right: Relationship between eastern cooperative oncology group (ECOG) performance status and survival/Left: Relationship between coronary heart disease and survival.

In some of the previous studies in the literature, increased mortality was demonstrated in patients with a lower than expected pulmonary function test value, which is an indicator of poor lung function. The pulmonary function test is a standard method used to evaluate lung reserve and risk preoperatively in patients recommended for surgery. Previous research has also shown that this test is a determining factor in mortality in patients treated with chemotherapy. The forced expiratory volume in one second (FEV_1), which is determined by spirometry, is a parameter used in the physiological determination of pulmonary function, and has been reported to be successful in predicting mortality in the evaluation of lung reserve in patients who have undergone surgery and received chemotherapy.[6,7]

In light of this information, the aim of this study was to evaluate the importance of prognostic factors by examining the relationship between survival and FEV1, a spirometric parameter that is reported to change after surgery in patients with operable NSCLC.

METHODOLOGY

The files of 70 patients who presented to the Chest Diseases Clinic of Health Sciences University Ankara Diskapi Yildirim Beyazit Training and Research Hospital, between June 1, 2013 and March 1, 2020, received a diagnosis of lung cancer, and had complete records, were retrospectively analyzed.

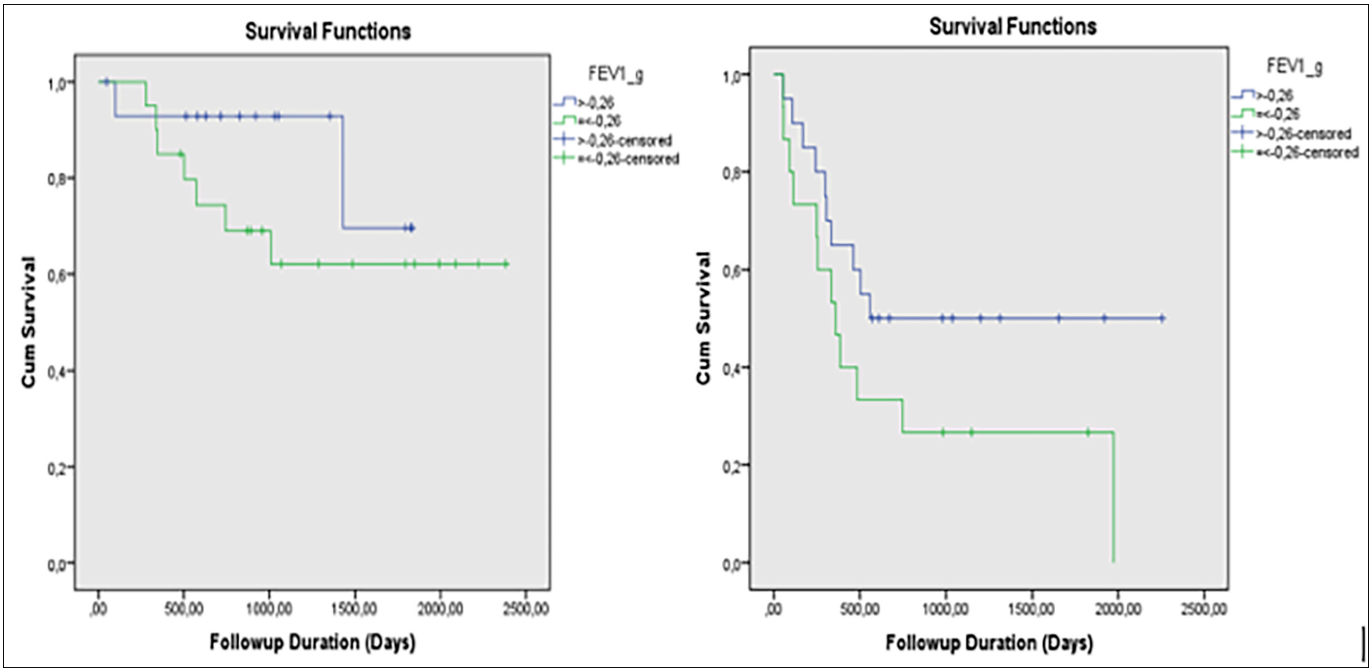

Figure 3: Left: Relationship between forced expiratory volume in 1 second (FEV1) and survival in the operated group/Right: Relationship between FEV1 and survival in the non-operated group.

Table I: Demographic characteristics of the patients included in the study.

	Total n (%)	Operated n (%)	Non-operated n (%)
Gender			
Female	6 (8.6)	4 (11.4)	2 (5.7)
Male	64 (91.4)	31 (88.6)	33 (94.3)
Age			
≤60 years	23 (32.9)	15 (42.9)	8 (22.9)
>60 years	47 (67.1)	20 (57.1)	27 (77.1)
ECOG performance status			
Group 1 (ECOG 0 and 1)	64 (91.4)	35 (100.0)	29 (82.9)
Group 2 (ECOG 2 and 3)	6 (8.6)	0 (0.0)	6 (17.1)
Active smoker			
No	4 (5.7)	1 (2.9)	3 (8.6)
Yes	66 (94.3)	34 (97.1)	32 (91.4)
Type of cancer			
Squamous carcinoma	45 (64.3)	19 (54.3)	26 (74.3)
Adenocarcinoma	25 (35.7)	16 (45.7)	9 (25.7)
Treatment method			
Chemotherapy	22 (31.4)	19 (54.3)	3 (8.6)
Radiotherapy	8 (11.4)		8 (22.9)
Chemoradiotherapy	25 (35.7)	2 (5.7)	23 (65.7)
None	15 (21.5)	14 (40.0)	1 (2.9)
Type of surgery			
Lobectomy	27 (38.6)		
Pneumonectomy	8 (11.4)		
None	35 (50.0)		

ECOG: Eastern cooperative oncology group.

Patients with early-stage and selected locally advanced NSCLC, who agreed to participate in the study and underwent spirometry evaluation at the time of diagnosis were included in the study. Patients under 18 years, those with neurodegenerative disease, those diagnosed with small cell lung cancer (SCLC) or advanced metastatic lung cancer were excluded from the sample. Ethics committee approval was obtained with the decision numbered 106/15 from the Planning and Coordination Committee of the hospital.

The histological diagnosis of NSCLC was made based on pathological analysis of tumor tissue obtained through a biopsy, and the staging of the patients was performed following the International Association for the Study of Lung Cancer staging system, which is the eighth edition of stage classification.[8] Accordingly, Stage I and Stage II cases were included in Group 1 and Stage 2 cases in Group 2. The patients were also evaluated in two groups depending on the severity of airflow limitation considering the percent of predicted FEV_1 being ≥80% and <80%. The median value of the difference in FEV_1 before and after the operation was compared according to the survival times. The total survival time (lifetime) of the patients was calculated in days. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. The patients were evaluated in two BMI groups as <25 Kg/m^2 and ≥25 Kg/m^2. Patients, age, gender, BMI, Eastern Cooperative Oncology Group (ECOG) performance status, exposure to tobacco smoke, tumor histology and stage, lung function measurements, treatment method, post-treatment complications, and comorbidities [chronic obstructive pulmonary disease (COPD), diabetes mellitus, hypertension, coronary artery disease (CAD), and heart failure] were recorded. The operated patients were followed up at three-month intervals after surgery, and the non-operated patients receiving medical treatment were followed up at varying intervals of 15-30 days. The data from all the visits of our patients from 2013 to 2020 were retrospectively reviewed.

Table II: Results of the Cox regression analysis.

Variable	Mortality/ Total n (%)	Univariate HR (95% CI of HR)	p	Multivariate HR (95% CI)	p
Gender					
Female	1 (16.7)	1			
Male	30 (46.9)	2.635 (0.359-19.368)	0.341		
Age					
≤60 years	(39.1)	1			
>60 years	22 (46.8)	1.092 (0.502-2.377)	0.824		
BMI, kg/m^2					
<25	15 (44.1)	1			
≥25	16 (44.4)	0.881 (0.433-0.790)	0.725		
Smoking status					
Non-smoker	1 (25.0)	1			
Smoker	30 (45.5)	1.612 (0.219-11.846)	0.639		
Type of cancer					
Squamous cell carcinoma	18 (40.0)	1			
Adenocarcinoma	13 (52.0)	1.420 (0.694-2.906)	0.338		
ECOG performance status					
Group 1 (ECOG 0+1) 0-1)	26 (40.6)	1		1	
Group 2 (ECOG 2+3) 2-3)	5 (83.3)	4.969 (1.878-13.153)	0.001*	4.786 (1.591-14.397)	0.005*
Stage					
Group 1 (1 2 1-2)	15 (37.5)	1			
Group 2 (3)	16 (53.3)	1.763 (0.871-3.570)	0.115		
Type of surgery					
Lobectomy	7 (25.9)	1	0.007*	1	0.113
Pneumonectomy	2 (25.0)	0.848 (0.174-4.126)	0.839	0.623 (0.125-3.093)	0.563
None	22 (62.9)	3.339 (1.423-7.835)	0.006*	2.105 (0.840-5.277)	0.112
COPD					
Absent	21 (40.4)	1			
Present	10 (55.6)	1.523 (0.716-3.239)	0.274		
Cardiovascular disease					
Absent	18 (35.3)	1			
Present	13 (68.4)	2.733 (1.325-5.636)	0.006*	2.994 (1.343-6.677)	0.007*
Preoperative FEV_1, %					
≥80	13 (41.9)	1			
<80	18 (46.2)	1.122 (0.549-2.295)	0.752		
Postoperative FEV_1, %					
≥80	7 (38.9)	1			
<80	24 (46.2)	1.068 (0.458-2.491)	0.878		
FEV_1 difference**liter					
≥-0.26	12 (34.3)	1			
<-0.26	19 (54.3)	1.533 (0.741-3.171)	0.250		

*BMI: Body mass index, ECOG: Eastern cooperative oncology group, FEV_1: Forced forced expiratory volume in 1 second, COPD: Chronic obstructive pulmonary disease, CI: Confidence interval, HR: Hazard ratio. *p <0.05, **Median difference between the preoperative and postoperative FEV_1*

In this study, quantitative variables were described as median, while qualitative variables were shown as n (%). Survival time was defined as the time from the patient's arrival at the clinic to the date of death of any cause. The Kaplan-Meier method was used to estimate survival, and the log-rank test was used to compare survival according to clinical parameters. The multivariate analysis was performed using the Cox proportional hazards regression model to examine important prognostic factors independently associated with survival. The multivariate analysis was applied to the ECOG, operation and CAD variables, which were determined to be significant in the univariate analysis. Results were defined as hazard ratio and 95% confidence interval. P <0.05 was considered statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences v. 11.5 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Seventy patients with stage I, II or III NSCLC were included in the study. Twenty-five (35.7%) patients had adenocarcinoma and 45 (64.3%) had squamous cell carcinoma. Thirty-five (50%) of the 70 patients underwent surgery due to lung cancer. Pneumonectomy was applied in eight (11.4%) patients, and lobectomy was performed in 27 (38.6%) patients. Of the 70 patients, 31 (44.2%) died, of whom 9 (12.8%) were in the operated group and 22 (31.4%) were in the non-operated group. Patient ages ranged from 45 to 89 years (median:63.5), 64 (91.4%) were male, 6 (8.6%) were female. The main characteristics of the patients, such as age, gender, smoking status, comorbidities, ECOG performance status, surgery status, cancer type, and additional treatment methods are shown in Table I.

The median initial measurement values were FEV_1, 2.1; forced vital capacity (FVC), 2.6 liters; and FEV_1/FVC, 79.4%. The median second measurement values were FEV_1, 1.6 liters; FVC, 2.3 ~~4~~ liters; and FEV_1/FVC, 75%.

The median follow-up period of the 70 patients included in the study was 1973.1 (95% CI 465.578-380.422) days. During the follow-up period, 31 patients (44.3%) died. The effect of investigated variables on survival was analyzed with the Kaplan-Meier method. In the statistical analysis, there was a significant difference between the operated and non-operated groups in relation to the probability of survival (p = 0.004, Figure 1). There was also a statistically significant difference between the treatment types in terms of survival rates (p = 0.042, Figure 1). Survival probability statistically significantly differed between the patients with and without CAD (p = 0.005, Figure 2). There was also a statistically significant difference between the ECOG groups in terms of survival probability (p <0.001, Figure 2). However, no statistically significant difference was found in FEV_1 spirometry difference between the survivors and non--survivors (p = 0.246).

Survival did not significantly differ according to the preoperative percent of predicted FEV1 being ≥80% and <80% (p = 0.752). There was also no significant difference in daily median survival between the patients with adenocarcinoma and those with squamous cell carcinoma (p = 0.335). Survival time was not significantly affected by gender, smoking status, or BMI (p=0.725).

When the relationship between the median FEV1 spirometry difference values and survival was investigated in the operated and non-operated groups, there was no statistically significant difference between these two groups (p >0.05, Figure 3).

According to the results of the univariate Cox regression analysis, a patient with ECOG 2-3 had a 4.969 times greater risk of mortality than a patient with ECOG 0-1 (p = 0.001). The risk of death of a patient undergoing lobectomy was not different from a patient undergoing pneumectomy (p=0.838), having no surgery resulted in 3.339 times greater risk of mortality compared to undergoing pneumonectomy (p = 0.006). In addition, the patients with CAD had 2.733 times higher risk of mortality than those without this comorbidity (p = 0.006).

In the multivariate Cox regression model, only ECOG performance status and the presence of CAD were determined to be significant factors for survival. Accordingly, the patients with ECOG 2-3 had 4.786 times higher risk of mortality than those with ECOG 0-1 (p = 0.005). The patients with CAD had 2.994 times higher risk of mortality than those without this comorbidity (p = 0.007, Table II).

DISCUSSION

Several studies have investigated the effects of pneumonectomy on lung function and found that the decrease in FEV_1 after pneumonectomy follows the decrease in vital capacity (VC).[9] In many studies involving a small number of patients (10-20), permanent functional deficit ranged from 26.7% to 40.7% for FVC and from 22.7% to 36.1% for FEV_1 at six months after pneumonectomy.[10] It has been reported that there is no difference in overall survival between surgically treated lung cancer patients with and without COPD.[11] In the current study, There was no significant relationship between 1% change in FEV_1 before surgery and NSCLC survival with or without surgery. The present study showed that <80% predicted FEV_1 was not an independent predictor of mortality for advanced NSCLC according to both univariate and multivariate analyses. Decreased FEV_1 was not determined to be a predictor of mortality.

A prospective study conducted with 688 cases reported no difference in overall survival between the patients with normal lung function who underwent surgery for stage I and II NSCLC and those with mild to moderate COPD.[12] In another study investigating surgically treated lung cancer cases, no difference was found in the overall five-year survival between the patients with and without COPD.[10] Similarly, Lee *et al*. retrospectively reviewed the spirometry results of 449 patients with stage IV NSCLC (n = 313) or SCLC (n = 136) at the time of diagnosis and showed that the survival of patients with metastatic NSCLC and SCLC-extensive stage was not related to COPD.[13]

In a different study, all-cause mortality was investigated in 4,439 patients, and it was emphasised that the risk of mortality increased in those with a low FEV_1 value and CAD.[14] In the current study, the risk of mortality was found to be 3.341 times higher in patients with CAD (p = 0.006) compared to those without this comorbidity. Smoking is considered a risk factor for all-cause mortality. However, we detected no significant relationship between smoking and mortality in patients with NSCLC who underwent surgery. In a similar study, while no significant survival difference was observed between smoking and non-smoking patients with lung cancer, short survival was predicted in those with a low FEV_1 value.[14]

In a study evaluating 148 patients who underwent surgery for NSCLC, Roth *et al*. reported that according to the univariate analysis of 30-day mortality and complications, age over 70 years, advanced preoperative stage, and FEV1 <80% were predictors of long-term survival. In that study, a significant difference in survival was found between the patients with FEV_1 ≥80% and those with FEV_1 <80%. However, the authors emphasised that the study being conducted in a small hospital and some high-risk cases being referred to the regional hospital might have contributed to longer survival in the patient group with high FEV_1.[15]

In some studies, it was observed that the survival rate of patients with non-squamous cell lung cancer who received surgical treatment increased compared to those with squamous cell lung cancer who received surgical treatment. According to some studies, a low BMI value can also predict a shorter survival time.[16] Contrary to previous studies, we did not determine age, gender and BMI to be prognostic markers in our study. We found that the cause of mortality due to lung cancer was not related to a lower percent of FEV_1, smoking status, age, or gender.

In a study by Rancic *et al*., FEV_1 was shown to be an important independent factor that could predict survival in patients with advanced NSCLC receiving chemotherapy, and a decrease in tumor size was accompanied by a statistically significant improvement in FEV_1 and FVC in these patients.[17] In this study, no significant correlation was observed between FEV_1 and survival in the patients with NSCLC who received only chemotherapy (p = 0.068).

The main limitation of our study may be the small number of patients with lung cancer who underwent surgery. The statistical difference between previous studies and our study is related to the present sample size. Bolliger *et al*. performed the functional evaluation of lobectomy and pneumonectomy with the pulmonary function and exercise tests and showed that three months after lobectomy, FVC, FEV_1, and total lung capacity were significantly lower compared to the preoperative values, while these parameters significantly increased at six months after resection. The authors observed that at three months after pneumonectomy, all the parameters were significantly lower than their preoperative values and post-lobectomy values, and there was no improvement at six months after resection.[18] In the present study, a single pulmonary function test was performed in the preoperative evaluation and postoperative follow-up of the patients. The authors consider that if the relationship would be evaluated between FEV_1 and survival time by repeating this test at the third and sixth months postoperatively, there could have been significant results.

CONCLUSION

Pulmonary functions did not affect survival in patients with operable NSCLC, but the patients' comorbidities and performance values were associated with survival. Further studies with more patients are needed to clarify the relationship between operable lung cancer cases and prognostic risk factors.

ETHICAL APPROVAL:
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was conducted in the Chest Diseases Clinic of Health Sciences University Ankara Diskapi Yildirim Beyazit Training and Research Hospital, between June 1, 2013 and March 1, 2020. Ethical approval was obtained from the Planning and Coordination Board with the decision No.106/15.

PATIENT'S CONSENT:
Informed consents were obtained from all patients to publish their clinical data.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
MC: Design the work and the acquisition, analysis, and interpretation of data for the work. Drafting the work, revising it critically for important intellectual content.
BK: Conception and design of the work. Final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.
MYS: Conception and design of the work. Final approval of the version to be published. Revising it critically for important intellectual content.
CT, CS: Design the work and the acquisition, analysis, and interpretation of data for the work.
All authors approved the final version of the manuscript to be published.

REFERENCES

1. Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rate and trends-an update. *Biomarkers Prev* 2016; **25(1)**:16-27. doi: 10.1158/1055-9965.EPI-15-0578.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. 13. *CA Cancer J Clin* 2016; **66(1)**:7-30. doi: 10.3322/caac.21340.
3. De Leyn, P, Dooms, C, Kuzdzal J, Lardinois D, Passlick B, Rami-Porta R, *et al*. Preoperative mediastinal lymph node staging for non-small cell lung cancer. *Transl Lung Cancer Res* 2014; **3(4)**:225-33. doi: 10.3978/j.issn.2218-6751.2014.08.05.
4. James BY, Decker RH, Detterbeck FC, Wilson LD. Surveillance epidemiology and end results evaluation of the role of surgery for stage I small cell lung cancer. *J Thorac Oncol* 2010; **5(2)**: 215-9. doi: 10.1097/JTO.0b013e3181cd3208.
5. Liptay MJ, Basu S, Hoaglin M, Freedman N, Penfield Faber L, Warren WH, *et al*. Diffusion lung capacity for carbon monoxide (DLCO) is an independent prognostic factor for long-term survival after curative lung resection for cancer. *J Surg Oncol* 2009; **100(8)**: 703-7.doi: 10.1002/jso.21407.
6. Deepak Aggarwal , Prasanta R Mohapatra , Ashok K Janmeja , Varinder Saini . Evaluation of spirometry as a parameter of response to chemotherapy in advanced lung cancer patients: A pilot study. *J Cancer Res Ther* 2020; **16(4)**:788-92. doi: 10.4103/jcrt.JCRT_919_17.
7. Maas KW, der Lee IV, Bolt K, Zanen P, Lammers JWJ, Schramel FMNH. Lung function changes and pulmonary complications in patients with stage III non-small cell lung cancer treated with gemcitabine/cisplatin as part of combined modality treatment. *Lung Cancer* 2003; **41(3)**: 345-51. doi: 10.1016/s0169-5002(03)00237-x.
8. Rami-Porta R, Bolejack V, Giroux DJ, Chansky K, Crowley J, Asamura H, *et al*. The IASLC lung cancer staging project:

The new database to inform the eighth edition of the TNM classification of lung cancer. *J Thorac Oncol* 2014; **9(11)**: 1618-24. doi: 10.1097/JTO.0000000000000334.

9. Tronc F, Grégoire J, Leblanc P, Deslauriers J. Physiologic consequences of pneumonectomy. Consequences on the pulmonary function. *Chest Surg Clin N Am* 1999; **9(2)**: 459-73. PMID: 10365276.
10. Brunelli A, Charloux A, Bolliger CT, Rocco G, Sculier JP, Varela G, *et al*. European respiratory society and european society of thoracic surgeons joint task force on fitness for radical therapy. *Eur Respir J* 2009; **34(1)**:17-41. doi**:** 10. 1183/09031936.00184308.
11. López-Encuentra A, Astudillo J, Cerezal J, Gonzalez-Aragoneses F, Novoa N, Sánchez-Palencia A. Bronchogenic carcinoma cooperative group of the Spanish society of pneumology and thoracic surgery (GCCB-S). *Eur J Cardiothorac Surg* 2005; **27(1):**8-13. doi: 10.1016/j.ejcts.2004.09.010.
12. Bugge A, Lund MB, Brunborg C, Solberg S, Kongerud J. Survival after surgical resection for lung cancer in patients with chronic obstructive pulmonary disease. *Ann Thorac Surg* 2016; **101(6)**: 2125-31. doi: 10.1016/j.athoracsur. 2015. 12.057.
13. Lee SY, Choi YJ, Seo JH, Lee SY, Kim JS, Kang EJ. Pulmonary function is implicated in the prognosis of metastatic non-small cell lung cancer but not in extended disease small cell lung cancer. *J Thorac Dis* 2019; **11(11)**: 4562-72. doi: 10. 21037/jtd.2019.10.77.
14. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: Findings from the Renfrew and paisley prospective population study. *BMJ* 1996; **313(7059)**:711-5; Discussion 715-6. doi: 10.1136/bmj.313.7059.711.
15. Roth K, Nilsen TI, Hatlen E, Sørensen KS, Hole T, Haaverstad R. Predictors of long time survival after lung cancer surgery: A retrospective cohort study. *BMC Pulm Med* 2008; **8**:22. doi: 10.1186/1471-2466-8-22.
16. Sekine Y, Suzuki H, Yamada Y, Koh E, Yoshino I. Severity of chronic obstructive pulmonary disease and its relationship to lung cancer prognosis after surgical resection. *Thorac Cardiovasc Surg* 2013; **61(2)**:124-30. doi: 10.1055/s-0032-1304543.
17. Rančić M, Ristić L, Rančić S, Radović M, Ćirić Z. Pulmonary function parameters as prognostic factors in advanced non-small cell lung cancer. *Med Glas (Zenica)* 2014; **11(1)**: 58-65. PMID:24496342.
18. Bolliger CT, Jordan P, Solèr M, Stulz P, Tamm M, Wyser C, *et al*. Pulmonary function and exercise capacity after lung resection. *Eur Respir J* 1996; **9(3)**:415-21. doi: 10.1183/ 09031936.96.09030415.

• • • • • • • • • •