Are predicted postoperative function values similar to actual postoperative values in patients with chronic obstructive pulmonary disease and which of the values are most useful in predicting complications?

Kronik obstrüktif akciğer hastalığında öngörülen ameliyat sonrası fonksiyon değerleri ameliyat sonrası gerçek değerlere benzer midir ve hangi değer komplikasyonları öngörmede en faydalıdır?

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ABSTRACT

Background: This study aims to investigate if predicted postoperative lung function values are similar to actual postoperative values in patients with chronic obstructive pulmonary disease and which of the values are most useful in predicting complications. Also, we aimed to show whether there is a difference in outcomes of patients with or without chronic obstructive pulmonary disease who undergo lung resection surgery on the basis of postoperative lung function values.

Methods: Out of 151 lung cancer patients who underwent lung resection between January 2010 and June 2011, 23 male patients (mean age 62.0 ± 6.9 years) with chronic obstructive pulmonary disease were included in the study group, while 24 patients (22 males, 2 females; mean age 55.9 ± 9.7 years) without chronic obstructive pulmonary disease were randomly selected as the control group. Fourteen of the patients with chronic obstructive pulmonary disease underwent a lobectomy and nine underwent a pneumonectomy. Lobectomies were performed on 18 patients without chronic obstructive pulmonary disease, while the other six patients underwent pneumonectomies. The predicted postoperative lung functions of the patients were measured and evaluated postoperatively on the first, fifth, and 10^{th} days and in the first, third, and sixth months. Features of the surgical process, complications, mortality, and related data were recorded.

Results: On the fifth postoperative day, actual lung capacity values were lower than the baseline and predicted postoperative values. There were no significant differences in terms of postoperative lung function in patients with or without chronic obstructive pulmonary disease. The occurrence of pneumonia was associated with chronic obstructive pulmonary disease and low diffusing capacity for carbon monoxide(p=0.007).

Conclusion: Our study showed that level of <45% postoperative diffusing capacity for carbon monoxide may increase complications. Through a meticulous evaluation, lung cancer patients with chronic obstructive pulmonary disease may be operated with similar morbidity rates as in those without this condition.

Keywords: Chronic obstructive pulmonary disease; pulmonary resection; akciğer kanseri.

ÖΖ

Amaç: Bu çalışmada kronik obstrüktif akciğer hastalığında öngörülen ameliyat sonrası akciğer fonksiyonu değerlerinin ameliyat sonrası gerçek değerlere benzer olup olmadığı ve hangi değerin komplikasyonları öngörmede en faydalı olduğu araştırıldı. Ayrıca, akciğer rezeksiyonu geçiren, kronik obstrüktif akciğer hastalığı olan ve olmayan hastaların sonuçlarında ameliyat sonrası akciğer fonksiyonu değerleri açısından farklılık olup olmadığı gösterildi.

Çalışma planı: Ocak 2010 - Haziran 2011 tarihleri arasında akciğer rezeksiyonu geçirmiş 151 akciğer kanseri hastası içerisinden kronik obstrüktif akciğer hastalığı olan 23 erkek hasta (ort. yaş 62.0±6.9 yıl) çalışma grubuna dahil edilir iken kronik obstrüktif akciğer hastalığı olmayan 24 hasta (22 erkek, 2 kadın; ort. yaş 55.9±9.7 yıl) rastgele kontrol grubu olarak seçildi. Kronik obstrüktif akciğer hastalığı olan hastalardan 14'ü lobektomi, dokuzu pnömonektomi geçirdi. Kronik obstrüktif akciğer altı hasta pnomonektomi geçirdi. Öngörülen ameliyat sonrası akciğer fonksiyonları ameliyat sonrası bir, beş ve 10. günlerde ve bir, üç ve altıncı aylarda ölçüldü ve değerlendirildi. Cerrahi sürecin özellikleri, komplikasyonlar, mortalite ve ilgili veriler kaydedildi.

Bulgular: Ameliyat sonrası beşinci günde gerçek akciğer kapasitesi değerleri eşik değerden ve öngörülen ameliyat sonrası değerlerden düşük idi. Kronik obstrüktif akciğer hastalığı olan ve olmayan hastalar arasında ameliyat sonrası akciğer fonksiyonu açısından anlamlı farklılık yok idi. Pnömoni varlığı kronik obstrüktif akciğer hastalığı ve düşük karbon monoksit difüzyon kapasitesi ile ilişkili idi (p=0.007).

Sonuç: Çalışmamız ameliyat sonrası <%45 karbon monoksit difüzyon kapasitesi düzeyinin komplikasyonları artırabileceğini gösterdi. Titiz bir değerlendirme ile kronik obstrüktif akciğer hastalığı olan akciğer kanseri hastaları, bu hastalığı olmayanlara benzer morbidite oranları ile ameliyat edilebilir.

Anahtar sözcükler: Kronik obstrüktif akciğer hastalığı; akciğer rezeksiyonu; pulmonary neoplasm.



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Lung resection is the optimum treatment modality to cure patients with early stage non-small-cell lung cancer (NSCLC). However, only 20 to 30% of individuals with lung cancer are suitable candidates for lung resection, due to either late stage of their disease or associated comorbidities.^[1,2] Even though 37% of lung cancer cases are anatomically resectable, some patients are not surgically suitable due to inadequate lung function or other physiological causes.^[3] Preoperative pulmonary evaluation is important to estimate the potential loss of lung function after resection as well as early morbidity connected with resection.^[4-6]

Many studies provide evidence that the expected values of forced expiratory volume in 1 second (FEV₁) and diffusing capacity for carbon monoxide (DLCO) are more relevant than the preoperative absolute values. Patients with chronic obstructive pulmonary disease (COPD) are at higher risk for surgical morbidity and mortality if they have NSCLC and are candidates for surgery. Therefore, in this study, we aimed to investigate if predicted postoperative lung function values are similar to actual postoperative values in patients with chronic obstructive pulmonary disease and which of the values are most useful in predicting complications. Also, we aimed to show whether there is a difference in outcomes of patients with or without COPD who undergo lung resection surgery on the basis of postoperative lung function values.

PATIENTS AND METHODS

Out of 151 lung cancer patients who underwent lung resection between January 2010 and June 2011, 23 male patients (mean age 62.0 ± 6.9 years) with COPD were included in the study group, whereas 24 patients (22 males, 2 females; mean age 55.9 ± 9.7 years) without COPD were randomly selected as the control group.

Of patients with COPD, 14 underwent lobectomy and nine underwent pneumonectomy, while lobectomies were performed on 18 patients without COPD and the other six underwent pneumonectomy.

Chronic obstructive pulmonary disease patients who were diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease criteria and whose preoperative - post COPD treatment ratio of FEV₁ to forced vital capacity (FEV₁/FVC ratio) was <70% were included.^[15] Patients with previous pulmonary surgery, FEV₁ and DLCO values of <30%, comorbidities like diabetes or coronary disease, and patients who received neoadjuvant therapy were excluded.

Patients were under treatment for COPD during their preoperative cancer evaluation. All patients in

the study were performed chest X-rays, thorax and upper abdomen computed tomography (CT) scans, biochemical tests, pulmonary function tests, and arterial blood gas analysis. Additionally, all patients were evaluated using fiberoptic bronchoscopy. Magnetic resonance imaging scans were performed on 38 patients, and 10 patients had CT scans for the detection of cranial metastases. Diffusing capacity for carbon monoxide and quantitative lung perfusion scintigraphy were performed in both groups of patients. Perfusion percentages and postoperative FEV₁ values were calculated for each lung and all lung segments. Positron emission tomography (PET)-CT was used in 38 patients, whereas 10 patients were staged using conventional screening tests because of insurance problem. Tumor node metastasis evaluation was performed according to the criteria of the International Association for the Study of Lung Cancer.^[7-9]

Study patients were prohibited from smoking or using bronchodilators as of 24 hours prior to the DLCO measurements. They were also prohibited from smoking for a minimum of one week preoperatively.

Postoperative FEV₁, DLCO, FEV₁%, and DLCO% values were calculated by perfusion scintigraphy for all patients with COPD. The presumed FEV₁, DLCO, FEV₁%, and DLCO% values for patients without COPD were calculated using the formulas developed by Wernly et al.^[10]

The duration of hospitalization, features of the surgical process, complications, mortality, and related data were recorded. During the postoperative period, on the first, fifth, and 10th days and in the first, third, and sixth months, the patients were evaluated using physical examination, chest x-rays, pulmonary function tests, arterial blood gas analysis, and thorax CTs.

Statistical analysis

Statistical analyses were performed using SPSS for Windows version 15.0 software program (SPSS Inc., Chicago, IL, USA). Categorical numerical variables were analyzed using mean and standard deviation. Comparison of categorical values within multivariate groups was done using the Chi-square test. The Monte Carlo simulation was also used when data were unsuitable for other statistical tests. When comparing the two groups, normally distributed variables were compared using an independent samples t-test, while non-normally distributed variables were compared using the Mann-Whitney U-test. Independent non-normally distributed numerical variables were compared using a Spearman correlation test. Multivariate logistic regression analysis was used to determine prediction factors. The statistical significance value was set at p<0.05. The cut-off value was determined by receiver operating characteristic (ROC) analysis.

RESULTS

Average rate of cigarette consumption was higher in COPD patients than it is in patients without COPD (p<0.001). The T and N tumor stages and the American Society of Anesthesiologists, physical status classification were not significantly different between lung cancer patients with or without COPD (p=0.748, p=0.812, and p=0.459, respectively).

Mean preoperative baseline values of $FEV_1\%$, FEV_1/FVC , and DLCO% in lung cancer patients with COPD were significantly lower than patients without COPD (p<0.001 for all parameters). There were no significant differences between the blood gas parameters (PaO₂, PCO₂, pH) of patients with or without COPD (p=0.757, p=0.218, p=0.409, p=0.923, respectively). Mean postoperative predicted values of FEV₁%, FEV₁, and DLCO% in patients with COPD were significantly lower than those without COPD (p=0.018, p=0.008; p<0.001, respectively) (Table 1).

A comparison of the postoperative actual values of FEV₁ and FEV₁/FVC on the fifth and 10th days and in the first, third, and sixth months and DLCO in the first, third, and sixth months to baseline values revealed significant variations in FEV₁% and DLCO (p<0.001 for both parameters) (Figure 1). The actual values of FEV₁% and DLCO on the fifth day in patients without COPD were higher than in patients with COPD. There were no significant intra-group variations in FEV₁/FVC changes over time (p=0.052). However, there was a significant difference in the FEV₁/FVC values on the fifth and 10th days between patients with or without COPD (p=0.003, p=0.048).

When the calculated postoperative values of lung function tests were compared to the actual values observed on the 10^{th} day and in the first, third, and sixth months, there were no significant differences between the postoperative FEV₁ and the actual measurements on the 10^{th} day and in the first and third months (p=0.207, p=0.837, p=0.294). The postoperative FEV₁ values were higher than the actual measurements on the fifth day, whereas they were lower than the actual sixth-month measurements in both groups (lung cancer with COPD and without COPD) (p=0.001, p=0.001). The actual values of DLCO% observed in the first and

	NSCLC with COPD (n=23)		NSCLC without COPD (n=23)				
	n	%	Mean±SD	n	%	Mean±SD	р
Age (years)			62.0±6.9			55.9±9.7	0.018
Gender							
Male	23			21			0.489
Female	0			2			} 0.469
Smoking in pack (year)			53.5±23.5			32.0±18.5	< 0.001
Stage T							
0	0	00		1	4.3]
1	2	8.7		3	13.0		
2	14	60.9		14	60.9		0.748
3	5	21.7		5	21.7		
4	2	8.7		0	0.0		}
Stage N							
0	12	52.2		14	60.9]
1	9	39.1		8	34.8		0.812
2	2	8.7		1	4.3		J
ASA classification							
1	17	73.9		20	87.0] 0.450
2	_	_		3	13.0		} 0.459
Operation							
Pneumonectomy	9	39.1		5	21.7] 0.200
Lobectomy	14	60.9		18	78.3		} 0.200
Duration of hospitalization (days)			17.0±22.0			6.5±3.2	0.001

NSCLC: Non-small-cell lung cancer; COPD: Chronic obstructive pulmonary disease; SD: Standard deviation; ASA: American Society of Anesthesiologists.

Table 1. Patient chracteristics

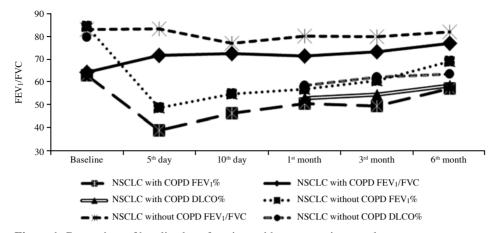


Figure 1. Comparison of baseline lung functions with postoperative actual measurements. NSCLC: Non-small-cell lung cancer; COPD: Chronic obstructive pulmonary disease; FEV₁: Forced expiratory volume in 1 second; DLCO: Carbon monoxide diffusing capacity; FVC: Forced vital capacity.

third months of follow-up visits were greater than the postoperative values (p=0.023, p=0.001) (Figure 2). The results were the same when the statistical analysis was performed after excluding the patients who died. Also, the duration of hospitalization of the patients with COPD was higher than for those without COPD (p=0.001).

The oxygen requirement on the first, second, and fifth days following surgery was higher in patients with COPD (p=0.001, p=0.004, p=0.022, respectively); however, on the 10^{th} day, there was no significant difference in oxygen requirement between patients with or without COPD.

In the group of patients with COPD; postoperative hypoxia, atelectasis, and pneumonia developed in 56.5%, 43.5%, and 39.1% of the group, respectively. These complications were more frequent in lung cancer patients with COPD than in patients without COPD

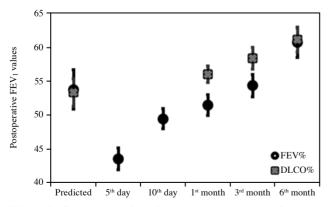


Figure 2. Comparison of predicted postoperative lung functions with actual postoperative measurements.

FEV: Forced expiratory volume; DLCO: Carbon monoxide diffusing capacity.

(p=0.001, p=0.001, p=0.007, respectively) (Table 2). All the patients who died were lung cancer patients with COPD (n=5, 21.7%), and the death rate was significantly different between the groups (p=0.049) (Table 3). Two patients died one month after surgery. One of the deaths was due to methicillin-resistant *Staphylococcus aureus* with respiratory insufficiency, and the other death was secondary to acute respiratory distress syndrome. The other three deaths occurred during the third, seventh, and 12th months after surgery and were due to pneumonia, pleural effusion with respiratory insufficiency, and pleural effusion leading to cardiac failure.

The average baseline $FEV_1\%$, FEV_1/FVC , DLCO% and the postoperative FEV_1/FVC and DLCO values

	Mean±SD	Mean±SD	р
Time			
5 th day	39.1±6.9	48.8±8.7	0.001
10 th day	46.5±8.0	54.8±9.5	0.001
1 st month	50.6±8.5	56.9±10.0	0.101
3 rd month	49.5±10.7	60.7±8.1	0.003
6 th month	57.3±13.7	69.1±13.7	0.073
Baseline FEV ₁ /FVC	64.1±5.4	81.9±9.0	< 0.001
5 th day	71.8±10.4	83.3±9.0	0.001
10 th day	72.7±9.3	76.9±11.1	0.087
1 st month	71.4±9.0	80.3±9.7	0.002
3 rd month	73.3±10.8	79.9±8.4	0.015
6 th month	77.0±9.7	82.1±10.1	0.021
Baseline DLCO%			
1 st month	53.1±8.6	58.6±6.5	0.022
3 rd month	54.5±10.8	62.4±9.0	0.010

SD: Standard deviation; FEV₁: Forced expiratory volume in 1 second; FVC: Forced vital capacity; DLCO: Carbon monoxide diffusing capacity.

	NSCLC with COPD (n=23)		NSCLC without COPD (n=24)	
n	%	n	%	р
13	56.5	2	8.7	0.001
9	39.1	0	0.0	0.001
10	43.5	2	8.7	0.007
4	17.4	0	0.0	0.109
3	13.0	0	0.0	0.233
3	13.0	3	13.0	1.000
2	8.7	1	4.4	1.000
2	8.7	2	8.7	1.000
5	21.7	0	0.0	0.049
	COPI n 13 9 10 4 3 2 2 2	with COPD (n=23) n % 13 56.5 9 39.1 10 43.5 4 17.4 3 13.0 3 13.0 2 8.7 2 8.7	$\begin{array}{c c} \text{with} & \text{wi} \\ \hline \text{COPD} (n=23) & \text{COPI} \\ \hline n & \% & \hline n \\ \hline 13 & 56.5 & 2 \\ 9 & 39.1 & 0 \\ 10 & 43.5 & 2 \\ 4 & 17.4 & 0 \\ 3 & 13.0 & 0 \\ 3 & 13.0 & 3 \\ 2 & 8.7 & 1 \\ 2 & 8.7 & 2 \\ \end{array}$	$\begin{array}{c cccc} with & without \\ \hline COPD (n=23) & COPD (n=24) \\ \hline n & \% & & \\ \hline 13 & 56.5 & 2 & 8.7 \\ 9 & 39.1 & 0 & 0.0 \\ 10 & 43.5 & 2 & 8.7 \\ 4 & 17.4 & 0 & 0.0 \\ 3 & 13.0 & 0 & 0.0 \\ 3 & 13.0 & 3 & 13.0 \\ 2 & 8.7 & 1 & 4.4 \\ 2 & 8.7 & 2 & 8.7 \end{array}$

Table 3.	Postoperative	complications
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NSCLC: Non-small-cell lung cancer; COPD: Chronic obstructive pulmonary disease.

in patients who had postoperative hypoxia were significantly lower than those without hypoxia (p=0.002, p=0.007, p=0.001, p=0.046, p=0.001, respectively). The duration of hospitalization was longer in patients with postoperative hypoxia (p=0.003). Baseline pH and postoperative FEV₁% and DLCO values were significant in predicting hypoxia using a multivariate analysis (p=0.033, p=0.046, p=0.017).

The average baseline FEV₁%, FEV₁/FVC, DLCO%, and the postoperative DLCO values in patients who had postoperative pneumonia were lower than in the patients without postoperative pneumonia (p=0.007, p=0.005, p=0.029, p=0.011, p=0.003, respectively). The duration of hospitalization was longer in patients with postoperative pneumonia (p=0.006). The presence of COPD and the predicted DLCO% values were predictive of postoperative pneumonia (p=0.029, p=0.046).

The average baseline FEV₁%, FEV₁/FVC, and DLCO% values in patients who had postoperative atelectasis were lower than in those without atelectasis (p=0.009, p=0.016, p=0.009), but the postoperative values were the same (p>0.05). The baseline and postoperative lung function tests were not predictive factors for atelectasis using the logistic regression model.

The mortality rates were 21.4% in patients who had a pneumonectomy and 6.3% in patients who had a lobectomy. The mortality rate was 12.7% in all lung cancer patients, regardless of whether the patient had COPD. Patients who died within the first year were more likely to have had a N₂-stage tumor than patients who remained alive in the first year (p=0.038). There was no association between mortality and other parameters such as the presence of lymph node metastasis, type of surgery, and duration of hospitalization (p=0.637, p=0.157, p=0.166, respectively). The average postoperative DLCO was higher in patients who did not die within the first year (p=0.050). FEV₁%, FEV₁/FVC, postoperative FEV₁, DLCO, and N-stage classification were not significantly predictive of mortality. Using ROC analysis, it was determined that the postoperative DLCO% cut-off value of 45% was predictive of postoperative pneumonia and hypoxia. The cut-off value had 77.4% 1-sensitivity and 40% 1-specificity (area under the curve [AUC] 0.795) for hypoxia and 77.8% 1-sensitivity and 22.2% 1-specificity (AUC 0.742) for pneumonia.

DISCUSSION

This study demonstrated that postoperative values of FEV_1 were higher than the actual measurements for five days postoperatively. Similarly, in the study by Varella et al.,^[11] $FEV_1\%$ was lower on the first postoperative day and increased gradually up to day six, but the mean values never reached the postoperative $FEV_1\%$ values. The Varella study also reported that the pain scores decreased from day one to day six and that the postoperative FEV_1 ratio was inversely associated with preoperative FEV_1 and with postoperative pain score.

Pulmonary function of patients who underwent lobectomy continued to recover for approximately six months after surgery. In patients who underwent pneumonectomy, improvement was generally limited to postoperative three months.^[12,16] Loss of lung function may vary significantly depending on the location of resection. For example, resection of the emphysematous portion of the lung probably results in less loss of function.^[19]

Complications such as hypoxia, atelectasis, and pneumonia were more frequent in lung cancer patients with COPD than in patients without COPD. Additionally, the oxygen requirement on the fifth postoperative day and the duration of hospitalization were higher in patients with COPD. Similarly, postoperative pulmonary complications were more frequent in lung cancer patients with COPD than in patients without COPD.^[20]

A study by Nakajima et al.^[21] demonstrated that 30% of patients with COPD had worse dyspnea and 20% of patients acquired pneumonia within the first three postoperative months.^[21] In that study, all the patients who died were lung cancer patients with COPD (21.7%). Volpino et al.^[22] determined that acute respiratory failure leading to death in patients with COPD was caused by pneumonia, pulmonary

embolism, acute pulmonary edema, acute myocardial ischemia, or cerebrovascular events during the first 30 postoperative days. The mortality rate was 12.9%. Their findings suggest that postoperative cardiovascular and respiratory deaths may be expected in patients with COPD and advanced stage lung carcinoma or in patients undergoing a pneumonectomy or partial resection of the bilateral lung for a second primary tumor by meticulous evaluations.

Similar to the results of our study, the study by Seok et al.^[23] found that COPD and preoperative pneumonia were risk factors for postoperative pneumonia in patients who underwent any type of resection.

Bobbio et al.^[24] also reported that the mean preoperative DLCO was significantly lower in patients who had postoperative cardiopulmonary complications than in the complication-free population.

We determined that the baseline pH and postoperative FEV_1 and DLCO were important in predicting hypoxia. Additionally, the presence of COPD and the predicted DLCO were important in predicting pneumonia. Recent evidence has shown that postoperative FEV_1 is not a reliable predictor of complications in patients with obstructive pulmonary disease when used alone and that DLCO predicts complications even in patients with normal FEV_1 values.^[22] The study by Ferguson et al.^[25] demonstrated that postoperative DLCO was the strongest predictor of postoperative complications in patients with or without COPD.

In a study by Schussler et al.^[26] showed that underlying COPD was a risk factor for the development of pneumonia and that a prolonged hospital stay was associated with a higher incidence of pulmonary complications. A postoperative FEV₁ value of 80% or higher has been proposed as the cut-off value that should be used to determine if a patient should proceed to resection without additional testing; however, this decision must be individualized for each patient.^[27] Similarly, it has been difficult to identify one cut-off value for DLCO.[19] A DLCO of <40% has been associated with an increased risk of postoperative respiratory complications, even in patients with postoperative FEV₁ values of >40%.^[28] While we determined that the postoperative DLCO cut-off value of 45% predicted postoperative hypoxia and pneumonia, we were unable to identify a value that predicted mortality. Based on the results of this study, we believe that there is a higher incidence of postoperative complications such as pneumonia and hypoxia when a patient has a postoperative DLCO value of <45%.

In conclusion, actual pulmonary function values on the fifth postoperative day were lower than the baseline and postoperative values. On the 10th postoperative day and beyond, all pulmonary function values began to gradually increase and reach the predicted values. There were no differences in the variations in postoperative lung function in lung cancer patients with or without chronic obstructive pulmonary disease. While the occurrence of pneumonia was associated with chronic obstructive pulmonary disease and low diffusing capacity for carbon monoxide, postoperative hypoxia was related to low pH and postoperative forced expiratory volume in 1 second and diffusing capacity for carbon monoxide. Atelectasis was not associated with any lung function parameters. The risk of these complications may increase when the postoperative diffusing capacity for carbon monoxide is <45%. Prior to attempting surgery, it is important to consider the presence of preoperative pneumonia, acidosis, and poor postoperative forced expiratory volume in 1 second and diffusing capacity for carbon monoxide percentages in patients with chronic obstructive pulmonary disease. If these conditions are met, patients with lung cancer and chronic obstructive pulmonary disease can undergo surgery in the same manner as patients without chronic obstructive pulmonary disease.

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