

## Risk factors for early mortality and morbidity after pneumonectomy

### *Pnömonektomi sonrasında erken morbidite ve mortalitenin risk faktörleri*

Gönül Sağıroğlu,<sup>1</sup> Elif Çopuroğlu,<sup>1</sup> Burhan Meydan,<sup>2</sup> Erdal Taşçı,<sup>3</sup>  
Y. Altumur Karamustafaoğlu,<sup>4</sup> Ayşe Baysal,<sup>5</sup> Yener Yörük<sup>4</sup>

*Institution where the research was done:*

Department of Thoracic Surgery, Medical Faculty of Trakya University, Edirne, Turkey

*Author Affiliations:*

Departments of <sup>1</sup>Anaesthesiology and Reanimation, <sup>4</sup>Thoracic Surgery,  
Medical Faculty of Trakya University, Edirne, Turkey

<sup>2</sup>Department of Anaesthesiology and Reanimation, <sup>3</sup>Department of Thoracic Surgery,

Süreyyapaşa Chest Disease and Thoracic Surgery Hospital Training and Research Hospital, İstanbul, Turkey

<sup>5</sup>Department of Anaesthesiology and Reanimation, Koşuyolu Yüksek İhtisas Training and Research Hospital, İstanbul, Turkey

**Background:** This study aims to investigate possible risk factors which affect the mortality and morbidity of pneumonectomy patients due to the non-small cell lung cancer (NSCLC).

**Methods:** Demographic, clinical and pathological features of 100 patients (96 males, 4 females; mean age 58.4±8.9 years; range 38 to 82 years) who underwent pneumonectomy between April 2008 and October 2009 were retrospectively analyzed.

**Results:** The morbidity and mortality rates were found to be 56% and 14%, respectively. The complications included cardiopulmonary in 46%, bleeding in 7%, and wound infection in 3% patients. There was no significant effect of age, sex, smoking habit, diabetes, hypertension, and coronary artery disease on 30-day morbidity and mortality. Neoadjuvant therapy (p=0.049), right pneumonectomy (p=0.01), and intraoperative blood transfusion (p=0.049) were associated with significantly increased morbidity. The duration of intensive care unit and hospital stays was significantly longer in patients with respiratory failure and bronchopleural fistula.

**Conclusion:** Pneumonectomy is a high-risk procedure in patients with neoadjuvant therapy, right pneumonectomy, and intraoperative blood transfusion. However, we believe that it is possible to reduce the risk factors with careful preoperative evaluation, rigorous anesthetic assessment and surgical interventions.

**Keywords:** Morbidity; mortality; pneumonectomy.

**Amaç:** Bu çalışmada küçük hücreli dışı akciğer kanseri (KHDAK) nedeni ile pnömonektomi yapılan hastalarda mortalite ve morbiditeyi etkileyen muhtemel risk faktörleri araştırıldı.

**Çalışma planı:** Nisan 2008 - Ekim 2009 tarihleri arasında kliniğimizde pnömonektomi yapılan 100 hastanın (96 erkek, 4 kadın; ort. yaş: 58.4±8.9 yıl; dağılım 38-82 yıl) demografik, klinik ve patolojik özellikleri retrospektif olarak incelendi.

**Bulgular:** Morbidite ve mortalite oranı sırasıyla %56 ve %14 olarak bulundu. Komplikasyonlar hastaların %46'sında kardiyopulmoner, %7'sinde kanama ve %3'ünde yara yeri enfeksiyonu idi. Yaş, cinsiyet, sigara kullanımı, diyabet, hipertansiyon ve koroner arter hastalığının 30 günlük morbidite ve mortalite üzerine anlamlı etkisi saptanmadı. Neoadjuvan tedavi (p=0.049), sağ pnömonektomi (p=0.01) ve ameliyat sırası kan transfüzyonunun (p=0.049) anlamlı düzeyde artmış morbidite ile ilişkilendirildi. Solunum yetmezliği ve bronkopleural fistülü olan hastalarda yoğun bakım ve hastanede kalış süresi anlamlı düzeyde daha uzundu.

**Sonuç:** Neoadjuvan terapi, sağ pnömonektomi ve ameliyat sırası kan replasmanı olan hastalarda pnömonektomi yüksek riskli bir işlem idi. Ancak, dikkatli ameliyat öncesi değerlendirme, titiz anestezi inceleme ve cerrahi girişimler ile risk faktörlerinin azaltılabileceği kanaatindeyiz.

**Anahtar sözcükler:** Morbidite; mortalite; pnömonektomi.



Available online at  
www.tgkdc.dergisi.org  
doi: 10.5606/tgkdc.dergisi.2014.8696  
QR (Quick Response) Code

Received: May 02, 2013 Accepted: June 19, 2013

Correspondence: Y. Altumur Karamustafaoğlu, M.D. Trakya Üniversitesi Tıp Fakültesi Göğüs Cerrahisi Anabilim Dalı 22030 Edirne, Turkey.

Tel: +90 542 - 414 81 92 e-mail: altumurk@hotmail.com

Lung cancer is the leading cause of cancer deaths in the world, and the most prevalent type of lung cancer is non-small cell lung cancer (NSCLC). Despite improvements in surgical methods and anesthesia, there has been little treatment. Postoperative cardiopulmonary complications associated with this type of cancer can often be detected and treated in the preoperative period.<sup>[1]</sup> In this retrospective study, we evaluated the risk factors that affect morbidity and mortality in patients who undergo a pneumonectomy for NSCLC.

## PATIENTS AND METHODS

We retrospectively evaluated 100 cases of elective pneumonectomies for NSCLC that were performed between April 2008 and October 2009. The 30-day morbidity and mortality rates were evaluated postoperatively, whereas the patients' age, gender, smoking habits, comorbid disease, histological type of cancer, clinical staging, and neoadjuvant therapy (chemotherapy, radiotherapy or both) were recorded preoperatively. In addition, the anesthesia risks were evaluated according to the American Society of Anesthesiologists (ASA) classifications. The most important guides for showing the extent of disease were the pathology reports and the clinical staging based on the American Joint Committee on Cancer (AJCC) tumor necrosis metastasis (TNM) classification.<sup>[2]</sup> For this study, the intraoperative data included the pneumonectomy side, anesthesia time, operation time, intraoperative blood/blood product transfusion, and extended pneumonectomy rate (intrapericardial, chest wall, superior vena cava (SVC), left atrium, and carina) while the postoperative data included the intubated transportation rate to the intensive care unit (ICU), mechanical ventilation time, total blood/blood product transfusion, need for reoperation, length of intensive ICU stay, and length of hospital stay. The need for postoperative mechanical ventilation for at least 24 hours or reintubation for controlled ventilation were signs of acute respiratory failure while the need for postoperative mechanical ventilation for the same length of time due to pulmonary complications signified respiratory failure. Leukopenia or leukocytosis, a fever of greater than 38 °C, purulent sputum, coughing, dyspnea, or tachypnea were indicative of pneumonia, and empyema was diagnosed when there was the presence of purulent material at the pneumonectomy site. Furthermore, when respiratory distress in the early postoperative period, rales, increased opacities in chest X-rays, and left ventricular dysfunction were noted, a diagnosis of post-pneumonectomy pulmonary edema was made. No premedication was used for

any of the patients, and all cases were monitored by electrocardiography (ECG) and a pulse oximeter. A catheter was inserted into a peripheral vein for fluid administration and the radial artery for invasive blood pressure monitoring and blood gas analysis. Anesthesia induction was done with fentanyl citrate 2 µg/kg<sup>-1</sup> (Fentanyl®, B. Braun Medikal Dış Ticaret A.Ş., İstanbul, Turkey), thiopental sodium 5-6 mg/kg<sup>-1</sup> (Pental Sodium® 0.5 g; İ.E. Ulagay İlaç Sanayi Türk A.Ş., İstanbul, Turkey), and vecuronium bromide 0.1 mg/kg<sup>-1</sup> (Blok-L® 10 mg 2 ml<sup>-1</sup>, Mustafa Nevzat İlaç Sanayi, İstanbul, Turkey), and intubation was carried out via a Robertshaw double-lumen endobronchial tube (Mallinckrodt Pharmaceuticals, Dublin, Ireland). For anesthesia maintenance, 0.03 mg/kg<sup>-1</sup> vecuronium bromide, sevoflurane 2-2.5% (Sevorane®, Abbott, Abbott Laboratories, Park, IL, USA) was given. Additionally, 100% oxygen was administered during single-lung ventilation, and a mixture of 80% oxygen and 20% air was given during normal ventilation.

The demographic data and results were calculated using the SPSS version 13.0 for Windows software program (SPSS Inc., Chicago, IL, USA). Pearson's chi-square test or Fisher's exact test were used to compare proportions, and Student's t-test was used to compare the means.

## RESULTS

The demographic and comorbidity data is provided in Table 1. We determined that age, gender, smoking status, histological type of cancer, ASA scores, the clinical cancer stage, neoadjuvant therapy, chronic obstructive pulmonary disease (COPD), hypertension, diabetes mellitus (DM), coronary artery disease (CAD), pneumonectomy side, forced expiratory volume in one second (FEV1), surgery duration, extended resection, and intraoperative blood transfusion were the risk factors that affected operative mortality and

**Table 1. Demographic and comorbidity data**

Demographics	%	Mean±SD
Total patients	100	
Age (years)		58.4±8.9
Male patients	96	
Smoking status	84	
Neoadjuvant therapy	11	
Chronic pulmonary obstructive disease	38	
Hypertension	23	
Diabetes mellitus	11	
Coronary artery disease	9	
Right pneumonectomy	42	

SD: Standard deviation.

**Table 2. Potential risk factors for operative mortality and cardiac and respiratory morbidity**

Risk factor	n	30-day mortality		Respiratory morbidity		Cardiac morbidity	
		%	<i>p</i>	%	<i>p</i>	%	<i>p</i>
Age (years)							
≥70	14	12	0.97	18	0.22	4	0.06
<70	86	2		5		1	
Gender							
Male	96	13	0.51	22	0.92	5	0.64
Female	4	1		1		0	
Smoking status							
Yes	83	12	0.77	18	0.49	4	0.85
No	17	2		5		1	
Histological type							
Squamous cell carcinoma	76	7		15	0.13	3	0.53
Adenocarcinoma	21	6	0.04	6		2	
Others	3	1		2		0	
ASA score							
I	38	5	0.96	7	0.53	3	0.51
II	43	6		10		1	
III	19	3		6		1	
Cancer stage							
I	52	5	0.40	8	0.06	3	0.69
II	36	7		8		2	
III	12	2		7		0	
Neoadjuvant chemotherapy							
Yes	11	3	0.17	4	0.26	0	0.42
No	89	11		19		5	
COPD							
Yes	38	6	0.68	13	0.03	2	0.92
No	62	8		10		3	
Hypertension							
Yes	23	3	0.88	5	0.87	2	0.35
No	77	11		18		3	
Diabetes mellitus							
Yes	11	2	0.67	3	0.72	0	0.42
No	89	12		20		5	
Coronary artery disease							
Yes	9	1	0.79	2	0.95	0	0.47
No	91	13		21		5	
FEV <sub>1</sub>							
≥60	21	3	0.87	4	0.73	1	0.74
<60	62	8		14		2	
Right pneumonectomy	42	9	0.06	14	0.03	2	0.92
Left pneumonectomy	58	5		9		3	
Duration of surgery (minutes)							
≥180	64	7	0.23	16	0.52	2	0.25
<180	36	7		7		3	
Extended resection							
Yes	20	2	0.56	5	0.81	0	0.25
No	80	12		18		5	
Intraoperative blood transfusion (U)							
Yes	66	9	0.88	17	0.36	3	0.77
No	34	5		6		2	

ASA: American Society of Anesthesiologists; COPD: Chronic obstructive pulmonary disease; FEV<sub>1</sub>: Forced expiratory volume in 1 second.

cardiac and respiratory morbidity. These are listed in Table 2. The mortality rate for males was higher than for females, but it was not statistically significant ( $p=0.51$ ). Moreover, we also found that gender was

not statistically significant for morbidity ( $p=0.87$ ), and we could not establish a relationship between age ( $\geq 70$ ) and pulmonary complications ( $p=0.22$ ), cardiovascular complications, or mortality ( $p=0.97$ ).

In addition, 84% of patients were smokers, and we noted that the duration of smoking was more than 20 pack-years for 95.2% of the smokers and 30-50 pack-years for 59.5%. The morbidity and mortality rates of those who had smoked for 20 pack-years or more were 34% and 9%, respectively, and there were no statistically meaningful results for smoking and morbidity ( $p=0.77$ ) or mortality ( $p=0.08$ ). The ASA scores also did not reflect postoperative morbidity or mortality, with a mortality rate of 14% and a morbidity rate of 56% for all of the cases. Cardiopulmonary complications occurred in 46% of the patients, hemorrhage in 7%, and wound infection in 3% (Table 3). Furthermore, neoadjuvant therapy, which was used to medicate 11% of the patients, was a risk factor for bleeding ( $p=0.002$ ) and bronchopleural fistulas (BPFs) ( $p=0.025$ ), but it did not influence postoperative mortality ( $p=0.17$ ). The comorbidities are given in Table 1. There were 38 cases of COPD and 10 of those (26%) were males. All COPD patients had at least one comorbid disease. Eight of the males (80%) also underwent a right pneumonectomy. The presence of COPD ( $p=0.68$ ), DM ( $p=0.67$ ), and CAD ( $p=0.79$ ) had no significant effect on mortality; however, COPD did show statistical significance with regard to the BPFs ( $p=0.01$ ). Furthermore, the ICU ( $40.56\pm 70.79$  hours;  $p=0.031$ ) and hospital stays ( $14.78\pm 10.57$  days;  $p=0.0001$ ) were longer for the cases that had pulmonary complications. The cases

with cardiovascular complications also had longer ICU stays (83.2 hours;  $p=0.0001$ ), but this did not hold true for the hospital stays (nine days;  $p=0.84$ ).

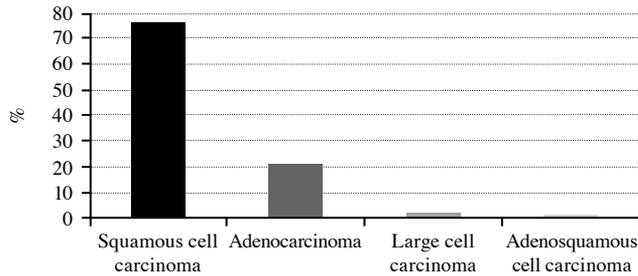
The BPFs for seven (16.6%) of the 42 right pneumonectomy cases and two (3.4%) of the 58 left pneumonectomy cases were statistically significant ( $p=0.006$ ). In addition, the patients who underwent a right pneumonectomy had higher rates of respiratory failure (28.5%;  $p=0.006$ ), and the mortality rate for this procedure (21.4%) was higher than for a left pneumonectomy (8.62%). However, the difference was not statistically significant ( $p=0.068$ ). Respiratory failure developed in 14% of the 100 cases, and the BPFs (28.5%;  $p=0.006$ ) and mortality rate (42.1%;  $p=0.001$ ) were significantly high in those cases. When analyzing the risk factors that affected the development of postoperative BPFs, age, gender, neoadjuvant therapy, COPD, CAD, DM, pneumonectomy side, and mechanical ventilation were evaluated, and we determined that age, gender, clinical cancer stage, DM, and cardiovascular comorbidity did not affect the BPF incidence rate. Neoadjuvant therapy ( $p=0.025$ ), COPD ( $p=0.01$ ), a right pneumonectomy ( $p=0.023$ ), and respiratory failure ( $p=0.006$ ) were, however, significant factors in the development of BPFs (Table 4), which were detected in 9% of the patients. Four of these were repaired with a thoracostomy, three with a thoracotomy, and two with a fiberoptic bronchoscope using adhesive fibrin. In addition, the length of the ICU (66.88 hours;  $p=0.0001$ ) and hospital stays (19.33 hours;  $p=0.0001$ ) of the cases with BPFs were statistically longer. Furthermore, the average FEV<sub>1</sub> was  $72.6\pm 16.6\%$  (range 32-119), the forced vital capacity (FVC) was  $76\pm 16.5$  (range 30-124), and the vital capacity was  $79\pm 20\%$  (41-128). The maximum oxygen consumption (VO<sub>2</sub> max.) value was evaluated for nine of the 21 cases with a preoperative FEV<sub>1</sub> value of 60% and under, but this had no statistically significant effect on morbidity ( $p=0.75$ ) or mortality ( $p=0.87$ ). Moreover, no complications or mortality were observed for the cases with poor VO<sub>2</sub> max cases ( $\leq 15$  mL/kg,  $n=2$ ). Finally, the mean partial pressure of O<sub>2</sub> (PaO<sub>2</sub>) was  $90.2\pm 46$  mmHg (range 48-260) and the

**Table 3. The causes of morbidity and mortality after the pneumonectomy**

Outcome	%
<b>Mortality</b>	14
Respiratory failure	8
Postoperative bleeding	5
Myocardial infarction	1
<b>Morbidity</b>	56
1. Cardiopulmonary complications	46
Respiratory complications	33
Respiratory failure	14
Bronchopleural fistulas	9
Atelectasis	4
Pneumonia	2
Empyema	1
Pneumothorax	1
Bronchoemphysema	1
Pulmonary edema	1
Cardiovascular complications	13
Arrhythmia	12
Myocardial infarction	1
2. Hemorrhage	7
3. Wound infection	3

**Table 4. Risk factors affecting the progress of bronchopleural fistulas**

Variable	<i>p</i>
Neoadjuvant therapy	0.043
Chronic obstructive pulmonary disease	0.028
Right pneumonectomy	0.01
Respiratory failure	0.001



**Figure 1.** Histological types of lung cancer.

partial pressure of CO<sub>2</sub> (PaCO<sub>2</sub>) was 46.9±12.2 mmHg (range 24-76).

The most frequently observed histological type of cancer was squamous cell carcinoma (SCC) (76%) (Figure 1). Despite a highly significant mortality ratio for adenocarcinoma ( $p=0.04$ ), the increased morbidity rate was not statistically significant ( $p=0.36$ ) with this type of cancer. The cases were classified according to the clinical stages used by the American Joint Committee on Cancer (AJCC), and no relationship was found between the cancer grade and morbidity ( $p=0.46$ ) or mortality ( $p=0.40$ ). The distribution of ratios for extended resection ( $n=20$ ) were the following: intrapericardial dissection in 11 cases, *en bloc* chest wall resection in five, SVC resection in two, resection of the left atrium in one and carinal resection in one. The effect of extended resection on morbidity ( $p=0.92$ ) and mortality ( $p=0.56$ ) was not statistically significant.

The average anesthesia time was 250.2±86.2 (range 120-660) minutes, and the average operation time was 220±85 (range 105-625) minutes. There were no significant increases in pulmonary (23.4%;  $p=0.5$ ,  $p=0.52$ ) and cardiovascular (3%;  $p=0.25$ ) complications or mortality (10.9%;  $p=0.23$ ) for operation time of three hours or longer (45.3%;  $p=0.85$ ). The average intraoperative blood transfusion rate was 64% in our study, and 2.42±1.45 (range 1-6) U/L packed red blood cells (RBC) and 2.35±1.09 (range 1-6) U/L fresh frozen plasma (FFP) solutions were given to each patient. Despite the statistically significant increase in the morbidity rate for the patients who had an intraoperative blood transfusion ( $p=0.049$ ), there were no significant increases in the mortality rate in these cases ( $p=0.88$ ). In addition, when we evaluated the intraoperative and early postoperative period together, 80% of all of the cases received a blood transfusion at a mean rate of 5.8 U per patient ( $n=3.1$  RBC;  $n=1.9$  FFP;  $n=0.8$  cryoprecipitate) but we found no statistically significant correlation between perioperative blood transfusions and morbidity ( $p=0.108$ ) or mortality ( $p=0.56$ ). The overall 30-day mortality rate was 14%

( $n=14$ ), and the cause of death was respiratory failure in eight cases, postoperative bleeding in five, and myocardial infarction (MI) in one. Ten of the 14 cases (71%) were male. Eight (57.1%) had at least one comorbidity disease, and eight (57.1%) underwent a right pneumonectomy. Additionally, the length of ICU stay was one day in 83% of the cases and two days in 10%. We also determined that the amount of bleeding did not affect mortality ( $p=0.56$ ), and a re-thoracotomy was performed on all the cases with this symptom. However, this procedure did not influence mortality ( $p=0.77$ ). Moreover, the amount of bleeding was statistically high in those patients who underwent prior neoadjuvant therapy ( $p=0.002$ ), but this also did not influence postoperative mortality ( $p=0.17$ ). The length of hospital stay was one week in 58 cases and two weeks in 31 cases. While the length of ICU stay was 38.84±35.87 hours ( $p=0.18$ ). However, the average length of hospital stay was 10±4.91 days;  $p=0.83$  for the patients with bleeding. Furthermore, the length of the ICU (36.35±30.04 hours; range 2-360 hours;  $p=0.02$ ) and hospital stays (42.86±36.19 days vs.  $p=0.005$ ) was significantly longer for patients with respiratory failure. Of the 16 patients who were transferred to the ICU with an intubation tube, nine (56%) were extubated in the first hour, but the other seven (44%) required two or more days of mechanical ventilation.

## DISCUSSION

It is important to evaluate preoperative risk factors in order to treat comorbidity and complications.<sup>[1]</sup> Pulmonary cancers are associated with age, male gender, smoking status, and comorbidities such as COPD or CAD,<sup>[1,3]</sup> and the increasing numbers of thoracic resections being performed have given rise to a corresponding increase in the number of complications. The 30-day mortality rate after a pneumonectomy ranges from 5.4-17.6%,<sup>[3,4]</sup> and the pneumonectomy complication rate is between 39 and 62%. Most of these complications can be attributed to cardiopulmonary causes.<sup>[3]</sup> Bernard et al.<sup>[5]</sup> suggested that complications occur at an overall rate of 43%, with 38% of these being cardiopulmonary in nature. The cardiopulmonary complication rate was 68.8% in the study by Guggino et al.<sup>[6]</sup> that was comprised of 55 cases, and Karamustafaoglu et al.<sup>[7]</sup> identified a pulmonary complication rate of 28%, and a cardiac complication rate of 12% in their study.

In our study, the average 30-day morbidity rate was 56%, and cardiopulmonary complications made up 82.1% of all complications. Moreover, 33% of the cardiopulmonary complications were pulmonary

and 13% were cardiac in nature. We also determined that the average 30-day mortality rate was 14% and identified the causes of mortality as being respiratory failure in eight cases, postoperative bleeding in five, and MI in one. The mortality rate was statistically significant in the patients with postoperative pulmonary complications who underwent a pneumonectomy in the study by Algar et al.<sup>[3]</sup> In addition, they noted that the pulmonary morbidity rate increased with the age of the patients, the presence of COPD and/or heart disease, and prolonged anesthesia. Licker et al.<sup>[8]</sup> reported that the risk factors that affected the 30-day mortality were male gender, CAD, and patients 70 years of age or older, but they found that smoking status, hypertension, high ASA scores (III and IV) and tumor grade had no effect on morbidity and mortality. Furthermore, in their study of 323 cases, Mansour et al.<sup>[9]</sup> reported that patients who were 70 years of age or older and male gender significantly affected cardiac morbidity, but these two factors played no role in respiratory morbidity and mortality. Moreover, the authors determined that smoking status, hypertension, and DM also had no influence on cardiopulmonary morbidity and mortality. In another study by Stolz et al.,<sup>[10]</sup> there was a correlation between an increase in 30-day mortality and CAD and respiratory failure; however, no statistically significant relationship existed between smoking status or COPD and morbidity and mortality. Karamustafaoglu et al.<sup>[7]</sup> identified the risk factors for increasing cardiopulmonary morbidity rate as being age ( $\geq 60$ ) and BPFs. They also reported that right pneumonectomies had a statistically significant effect on cardiopulmonary morbidity and mortality, but tumor grade did not play a significant role. In a retrospective analysis of 100 cases, Doddoli et al.<sup>[11]</sup> found that mortality was significantly affected by postoperative cardiovascular and respiratory events, whereas gender, age, right-sided resection, and clinical cancer stage had no effect. Chataigner et al.<sup>[12]</sup> also reported that age, CAD, right-sided pneumonectomies, and renal failure did not increase mortality in the 69 cases in their retrospective study, and Alloubi et al.<sup>[13]</sup> identified that age ( $\geq 70$ ), COPD, CAD, and a high ASA physical status were risk factors for the increased morbidity rate in their patients. However, they did not find any relationship between increased morbidity and male gender, a history of smoking, clinical cancer stage, neoadjuvant therapy, or right pneumonectomies. Furthermore, Thomas et al.<sup>[14]</sup> reported that the risk factors for increased 30-day mortality rates were age, CAD, right pneumonectomies, and respiratory failure. In another study,<sup>[13]</sup> age ( $\geq 70$ ), COPD, high ASA physical status (III and IV), and CAD were found to

increase mortality. In the study by Darling et al.<sup>[15]</sup> that was composed of 187 cases, they found that smoking status and BPFs were the risk factors that affected mortality. In our study, the complication rate (23%) was significantly high in the COPD patients ( $n=38$ ), but age, male gender, smoking status, hypertension, DM, CAD, ASA score, and tumor grade did not influence cardiopulmonary morbidity and mortality.

There are different opinions regarding the impact of the histological type of cancer on survival. The mortality rate for SCC is higher than for other types of cancer.<sup>[7,16]</sup> However, Jazieh et al.<sup>[17]</sup> found no relationship between cell type and survival in their study that involved 551 cases. In our study, increased mortality rates were statistically significant for adenocarcinoma ( $p=0.048$ ).

Extended resection increases the rate of mortality.<sup>[5,8]</sup> However, Doddoli et al.<sup>[11]</sup> determined that the 30-day mortality and morbidity rates were not statistically significant for the 13 patients who underwent an extended resection in their study. We operated on 80 cases via a standard pneumonectomy and 20 via an extended resection and found that extended resection did not affect morbidity (45%;  $p=0.92$ ) or mortality (11.1%;  $p=0.56$ ). Additionally, prolonged operation times have been reported to be a high risk factor for pulmonary complications.<sup>[3]</sup> In a study by Haraguchi et al.,<sup>[18]</sup> the average operation time was  $398\pm 166$  minutes, and a prolongation of this period was identified with a significant increase in pulmonary morbidity. In our study, the average operation time was  $220\pm 85$  (range 105-625) minutes, and even when the surgery lasted three hours, this had no effect on pulmonary (23.4%;  $p=0.52$ ) or cardiovascular (3%;  $p=0.25$ ) complications or mortality (10.9%;  $p=0.23$ ).

Patients with pulmonary complications have longer hospital stays.<sup>[8]</sup> In the study by Algar et al.<sup>[3]</sup> the length of ICU stay was  $53\pm 39$  hours while the length of hospital stay was  $18\pm 11$  days. As in our study, the ICU ( $40.56\pm 70.79$  hours  $p=0.031$ ) and hospital ( $14.78\pm 10.57$  days;  $p=0.0001$ ) stays were significantly longer for patients with pulmonary morbidity. They also found that the development of cardiovascular complications was related to extended ICU stays (83.2 hours;  $p=0.0001$ ), but this did not affect time spent in the hospital (nine days;  $p=0.84$ ). Furthermore, Semik et al.<sup>[19]</sup> noted that in some of their cases, the patients who received preoperative neoadjuvant chemotherapy had increased interoperative bleeding and mortality as a result of hilar and intrapericardial adhesions.

Pneumonectomies are associated with significantly higher death rates and are primarily responsible for acute respiratory distress syndrome, BPFs, and other respiratory causes, especially in cases involving right-sided tumors.<sup>[20]</sup> Albain et al.<sup>[21]</sup> showed that previous chemotherapy treatments in combination with radiotherapy could be beneficial if a complete resection with a lobectomy was performed or if mortality from a pneumonectomy could be avoided. In addition, Van Meerbeeck et al.<sup>[22]</sup> noted that a pneumonectomy, as such, is also a known independent negative prognostic factor, and they observed significantly better outcomes in patients after a bilobectomy. Bernard et al.<sup>[5]</sup> reported an increase in the 30-day mortality rates with preoperative neoadjuvant chemotherapy, and Leo et al.<sup>[23]</sup> reported that neoadjuvant therapy had a significant effect on morbidity and mortality on the 202 patients in their study. However, in other studies, neoadjuvant chemotherapy had no significant effect on morbidity and mortality.<sup>[9,11]</sup> Similar to other reports in the literature, the incidents of bleeding were significantly high in our study for the 11 patients who received neoadjuvant chemotherapy (40%;  $p=0.002$ ), but this bleeding did not influence mortality (20%;  $p=0.56$ ). The bleeding also extended the length of ICU stays by 15 hours ( $38.84\pm 35.87$  hours;  $p=0.18$ ) and hospital stays by one day ( $10\pm 4.91$  days;  $p=0.83$ ).

The development of BPFs was higher in patients who underwent a right pneumonectomy.<sup>[3,9,16]</sup> Despite this, Licker et al.<sup>[8]</sup> and Bernard et al.<sup>[15]</sup> found an insignificant correlation between pneumonectomy side and BPFs, but Karamustafaoğlu<sup>[7]</sup> determined that the development of BPFs was statistically significant for 14% of the patients in their study who underwent a right pneumonectomy and 5% who had a left pneumonectomy. Furthermore, Stolz et al.<sup>[10]</sup> found that the risk factors that affected the development of BPFs were male gender and COPD, and Guggino et al.<sup>[6]</sup> determined that the average BPF ratio (12.7%) increased with neoadjuvant chemotherapy (23.8%).

In our study, we identified that COPD (18.4%;  $p=0.01$ ), neoadjuvant therapy (27.2%;  $p=0.025$ ), right pneumonectomies (16.6%;  $p=0.023$ ), and respiratory failure (28.5%;  $p=0.006$ ) were the risk factors that affected the development of BPFs. Mansour et al.<sup>[9]</sup> found that hospital stays for 14 patients with BPFs were 10 days longer ( $22.5\pm 13.45$  days) than for those without BPFs ( $12.19\pm 5.92$  days), but this did not play a role in cardiac morbidity. In the literature, patients with prolonged ICU and hospital stays because of

BPFs show significant overlap. Miller et al.<sup>[4]</sup> reported that intraoperative blood transfusions had no marked influence on mortality, and Karamustafaoğlu et al.<sup>[7]</sup> also demonstrated an insignificant relationship between blood transfusions and morbidity.<sup>[7]</sup> In our study, when the intraoperative and early postoperative periods were considered together, the increase in the morbidity ( $p=0.108$ ) and mortality rates ( $p=0.56$ ) due to blood transfusions was not statistically significant in 80% of the cases. However, when only the intraoperative period was taken into account, the increase in morbidity due to blood transfusions was statistically significant ( $p=0.049$ ), but this was not true for mortality ( $p=0.88$ ). Alloubi et al.<sup>[13]</sup> reported a post-pneumonectomy edema ratio of 2.4% in 168 cases in their retrospective analysis while in our study, this occurred in 1% of the cases. We believe that this complication might have been associated with the perioperative administration of high numbers of crystalloid and blood transfusions.

### Conclusion

The risk factors that affect mortality and morbidity after a pneumonectomy for NSCLC are multifactorial. We found that age, male gender, smoking status, CAD, ASA scores, and tumor grade did not significantly affect morbidity and mortality. However, we determined that the BPF incidence was significantly high in the patients who underwent a right pneumonectomy and those who had neoadjuvant therapy. Therefore, we believe that with careful preoperative evaluations, rigorous anesthesia, and surgical intervention, the risks for patients with NSCLC who undergo a pneumonectomy can be reduced.

### Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

### Funding

The authors received no financial support for the research and/or authorship of this article.

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