

Relationship between survival and erythrocyte sedimentation rate in patients operated for lung cancer

Akciğer kanseri nedeniyle ameliyat edilen hastalarda sağkalım ve eritrosit sedimentasyon hızı arasındaki ilişki

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ABSTRACT

Background: This study aims to investigate the relationship between preoperative erythrocyte sedimentation rate and survival in patients undergoing pulmonary resection due to lung cancer.

Methods: Between January 2011 and July 2017, a total of 575 patients (433 males, 142 females; mean age: 61.2±9.9 years; range, 29 to 82 years) who were operated due to primary lung cancer in our clinic were retrospectively analyzed. The patients were grouped according to erythrocyte sedimentation rate to analyze the relationship between erythrocyte sedimentation rate and survival.

Results: The mean overall survival time was 61.8±1.7 months in 393 patients with an erythrocyte sedimentation rate of ≤24 mm/h and 48.9±2.9 months in 182 patients with an erythrocyte sedimentation rate of ≥25 mm/h (p<0.001). Among the patients with Stage 1-2 disease, the mean survival time was 66.2±1.9 in patients with an erythrocyte sedimentation rate of ≤24 mm/h and 53.8±3.2 in patients with an erythrocyte sedimentation rate of ≥25 mm/h (p=0.008). The mean survival time in patients with adenocarcinoma was 62.4±2.4 months in patients with ≤24 mm/h erythrocyte sedimentation rate and 46.1±4.6 months in patients with ≥25 mm/h erythrocyte sedimentation rate (p=0.003).

Conclusion: The relationship between elevated erythrocyte sedimentation rate and poor prognosis in patients with the same stage of the disease is promising for the use of erythrocyte sedimentation rate as a prognostic marker.

Keywords: Erythrocyte sedimentation rate, lung cancer, postoperative survival.

ÖZ

Amaç: Bu çalışmada akciğer kanseri nedeniyle pulmoner rezeksiyon uygulanan hastalarda ameliyat öncesi eritrosit sedimentasyon hızı ve sağkalım arasındaki ilişki incelendi.

Çalışma planı: Kliniğimizde Ocak 2011 - Temmuz 2017 tarihleri arasında primer akciğer kanseri nedeniyle ameliyat edilen 575 hasta (433 erkek, 142 kadın; ort. yaş: 61.2±9.9 yıl; dağılım, 29-82 yıl) retrospektif olarak incelendi. Hastalar eritrosit sedimentasyon hızı ve sağkalım arasındaki ilişkiyi incelemek için eritrosit sedimentasyon hızına göre sınıflandırıldı.

Bulgular: Eritrosit sedimentasyon hızı ≤24 mm/saat olan 393 hastanın ortalama sağkalım süresi 61.8±1.7 ay iken, eritrosit sedimentasyon hızı ≥25 mm/saat olan 182 hastada 48.9±2.9 ay idi (p<0.001). Evre 1-2 hastalar arasında eritrosit sedimentasyon hızı ≤24 mm/saat olan hastalarda sağkalım süresi 66.2±1.9 ay iken, eritrosit sedimentasyon hızı ≥25 mm/saat olanlarda 53.8±3.2 ay idi (p=0.008). Adenokarsinomlu hastalarda eritrosit sedimentasyon hızı ≤24 mm/saat olanlarda sağkalım süresi 62.4±2.4 ay iken, eritrosit sedimentasyon hızı ≥25 mm/saat olanlarda 46.1±4.6 ay idi (p=0.003).

Sonuç: Hastalığın aynı evresinde olan hastalarda, yüksek eritrosit sedimentasyon hızı ve kötü prognoz arasındaki ilişki, eritrosit sedimentasyon hızının prognostik bir belirteç olarak kullanılması açısından ümit vericidir.

Anahtar sözcükler: Eritrosit sedimentasyon hızı, akciğer kanseri, ameliyat sonrası sağkalım.

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Lung cancer (LC) is the most common cancer type worldwide and the leading cause of cancer-related mortality.^[1,2] In this cancer type, various tumor-related factors including tumor stage and histopathological type and patient-related factors including age, sex, and smoking have been identified that affect the prognosis.^[3-5] Several studies have suggested that the albumin and hemoglobin levels and the platelet count can be used as prognostic factors.^[6,7] The erythrocyte sedimentation rate (ESR) is a simple and inexpensive laboratory test that is used to evaluate the inflammatory or acute phase response.^[8] The ESR may be elevated in non-oncological conditions such as infections, anemia, coronary artery disease, and cerebrovascular disease, in addition to malignancies such as prostate and colon cancer, and it can even be used as a prognostic factor in these particular types of cancer.^[8,9]

The prognostic role of ESR in LC has not been elucidated yet. In the present study, we aimed to investigate the relationship between preoperative ESR and survival in patients undergoing pulmonary resection due to LC.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Ege University School of Medicine, Department of Thoracic Surgery between January 2011 and July 2017. Patients who were applied to lung resection and standard mediastinal lymph node dissection due to primary LC were reviewed. The patients who received neoadjuvant chemotherapy and radiotherapy were excluded from the study. Patients with comorbid conditions that may cause an increase in ESR (rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus; endocrine diseases such as de Quervain thyroiditis; hematological disorders such as anemia and multiple myeloma; signs of an infection such as fever, leukocytosis, etc.; dialysis treatment due to chronic renal failure, and a history of another malignancy) were also excluded. Also, patients with a history of medication use that is known to cause changes in ESR were excluded. Finally, a total of 575 patients (433 males, 142 females; mean age: 61.2±9.9 years; range, 29 to 82 years) who met the study inclusion criteria were evaluated.

Demographic characteristics such as age and sex, comorbid conditions, surgical procedures, peri- and postoperative complications, length of hospital stay, results of histopathological staging, stage of malignancy, ESR, and survival data were recorded.

Comorbid conditions were classified into four categories: cardiac diseases, endocrine disorders, chronic obstructive pulmonary disease (COPD), and “other comorbidities” which were previously diagnosed.

The normal value of ESR differs in the literature and between health institutions. In our institution, the normal value of ESR was determined by the biochemistry laboratory as ≤ 20 mm/h, regardless of age and sex of the patient. The cut-off value of ESR, which is usually used for diagnosis and follow-up, may differ according to diseases.^[8,10] Therefore, a new cut-off value of 24.5 ± 24.0 (range, 1 to 131) mm/h, which is the mean of ESR values of all patients, was determined for LC. When the cut-off value of ESR was accepted as 24.5 mm/h, its sensitivity was 100% and specificity was 90.3%, compared to the reference range of 20 mm/h.

In the first stage of the study, the patients were grouped according to their ESR. The patients with an ESR of ≤ 24 mm/h were defined as normal ESR group (NESRG) and patients with an ESR of ≥ 25 mm/h were defined as high ESR group (HESRG). The two groups were evaluated for their survival data.

In the second stage of the study, the patients were re-grouped according to the histopathological disease stage. The 8th Edition of the Staging System of the International Association for the Study of Lung Cancer (IASLC) was used for disease staging. According to the results of histopathological staging, the patients with Stage 1-2 disease were defined as low-stage group (LSG) and patients with Stage 3-4 disease were defined as high-stage group (HSG). This stage involved evaluation of the change in ESR according to the disease stage.

In the third stage of the study, the patients were grouped according to the histopathological diagnoses. The patients diagnosed with adenocarcinoma (AC) after surgery were defined as Groupac, patients diagnosed with squamous cell carcinoma (SCC) were defined as Groupsc, patients diagnosed with carcinoid tumor were defined as Groupcarcinoid, and patients diagnosed with small cell lung carcinoma (SCLC) were defined as Groupsc. The patients diagnosed with other cancer types were defined as Groupother. The relationship between histopathological diagnosis, ESR, and survival was evaluated among the five groups.

In the fourth step of the study, multimodal analyses were performed to investigate the effect of histopathological diagnosis, stage, comorbidity and

ESR values on survival. The relationships between histopathological diagnosis, stage, comorbidity, and ESR values and survival were examined and the hazard ratios were determined.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean \pm standard deviation (SD), median (min-max) or number and frequency, where applicable. Survival data were analyzed using the Kaplan-Meier method. If a significant difference was detected between the groups

in the Kaplan-Meier method, paired groups were compared using the log-rank (Mantel-Cox) test. Cox regression analyses were performed and hazard ratios were determined. A *p* value of <0.05 was considered statistically significant.

RESULTS

Of the patients, 232 (40.3%) were below 60 years of age and 343 (59.7%) were aged 60 years and older. Regarding comorbid conditions, 278 (48.3%) had cardiac diseases, 173 (30.1%) had endocrine disorders, and 95 (16.6%) had COPD. A total of 207

Table 1. Demographic and clinical features of patients (n=575)

Variables	n	%	Mean \pm SD	Range
Age (years)				
<60	232	40.3		
\geq 60	343	59.7		
Average			61.2 \pm 9.9	29-82
Sex				
Male	433	75.3		
Female	142	24.7		
Comorbidities				
Cardiac	278	48.3		
Endocrinologic	173	30.1		
COPD	95	16.6		
Others	207	36		
Surgical procedures				
RUL	116	20.2		
RML	18	3.1		
RLL	80	13.9		
RUBL	16	2.8		
RLBL	14	2.4		
LUL	60	10.4		
LLL	63	11		
RP	7	1.2		
LP	23	4		
Sublobar resection	178	31		
Histopathologic diagnosis				
Adenocarcinoma	280	48.7		
Squamous cell carcinoma	182	31.7		
Carcinoid tumor	19	3.3		
Small cell carcinoma	10	1.7		
Others	84	14.6		
Histopathologic stage				
1-2	425	73.9		
3-4	150	27.1		
Average length of in-hospital stay (day)			6.9 \pm 4.7	

SD: Standard deviation; COPD: Chronic Obstructive Pulmonary Disease; RUL: Right upper lobectomy; RML: Right middle lobectomy; RLL: Right lower lobectomy; RUBL: Right upper bilobectomy; RLBL: Right lower bilobectomy; LUL: Left upper lobectomy; LLL: Left lower lobectomy; RP, Right pneumonectomy; LP: Left pneumonectomy.

Table 2. Statistical analysis results

Relative factors	n	%	Mean survival time (months)		p
			Mean±SD	Range	
ESR values					
≤24 mm/h	393	68.3	61.8±1.7	1-84	<0.001
≥25 mm/h	182	31.7	48.9±2.9	1-83	-
Clinical stages					
1-2	425	73.9	63.7±1.7	1-84	<0.001
3-4	150	26.1	43.3±2.9	1-83	-
ESR in clinical stage 1-2					
≤24 mm/h	302	71.1	66.2±1.9	1-84	0.008
≥25 mm/h	123	28.9	53.8±3.2	1-78	-
ESR in clinical stage 3-4					
≤24 mm/h	91	60.7	46.4±3.5	1-79	0.057
≥25 mm/h	59	39.3	37±4.6	1-83	-
ESR in adenocarcinoma					
≤24 mm/h	215	76.8	62.4±2.44	1-84	0.003
≥25 mm/h	65	23.2	46.1±4.6	1-78	-
ESR in squamous cell carcinoma					
≤24 mm/h	103	56.6	59.6±3.1	1-80	0.257
≥25 mm/h	79	43.4	54.5±4.3	1-83	-

SD: Standard deviation; ESR: Erythrocyte sedimentation date.

(36%) patients had one or more of the other comorbid diseases (e.g., urological, neurological).

A total of 397 (69%) patients underwent lobectomy or more extensive resections, whereas 178 (31%) patients underwent sublobar resections. The most commonly used anatomical resection type was right upper lobectomy that was performed in 116 (20.2%) patients (Table 1).

According to the results of histopathological examination, 280 (48.8%) patients were in Groupac, 182 (31.8%) patients were in Groupsc, 19 (3.3%) patients were in Groupcarcinoid, 10 (1.7%) patients were in Groupsclc, and 82 (14.5%) patients were in Groupother.

According to the 8th Edition of the IASLC Staging System, 287 (49.9%) patients had Stage 1, 138 (24%) had Stage 2, 137 (23.8%) had Stage 3, and 13 (2.3%) had Stage 4 disease. A total of 425 patients (73.9%) with Stage 1-2 disease were classified in LSG and 150 (26.1%) patients with Stage 2-4 disease were classified in HSG (Table 1).

The ESR was ≤24 mm/h in 393 (68.3%) patients in the NESRG and ≥25 mm/h in 182 (31.7%) patients in the HESRG. The mean survival time was 61.8±1.7 (range, 1 to 84) months in the NESRG and 48.9±2.9 (range, 1 to 83) months in the HESRG. The mean

survival was significantly higher in the NESRG than in the other group (p<0.001) (Table 2) (Figure 1).

When the patients were compared according to their disease stage, the mean survival time was 63.7±1.7 (range, 1 to 84) months in 425 patients (73.9%)

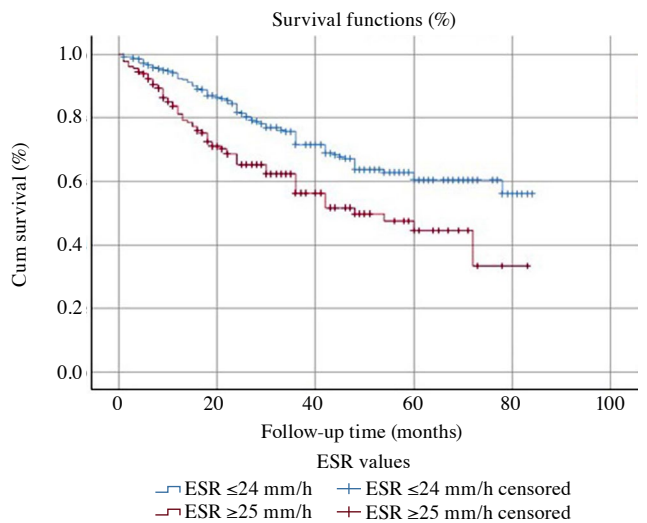


Figure 1. Overall survival curves of only ESR, independent of variables such as stage, tumor type, etc.

ESR: Erythrocyte sedimentation rate; Normal ESR (ESR ≤24 mm/h). High ESR (≥25 mm/h).

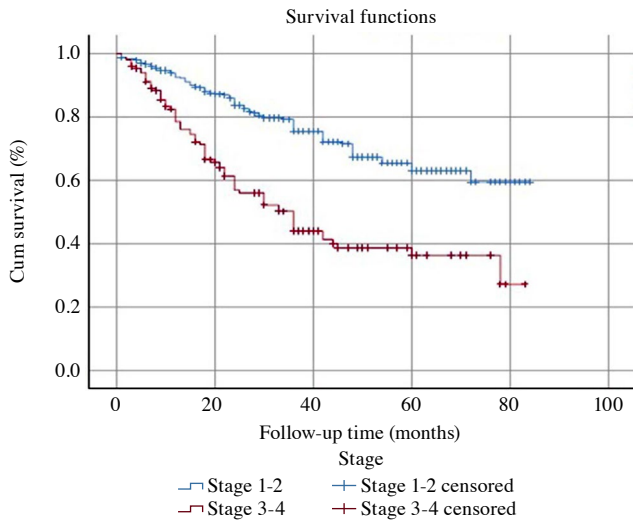


Figure 2. Overall survival curves of patients according to their stages.

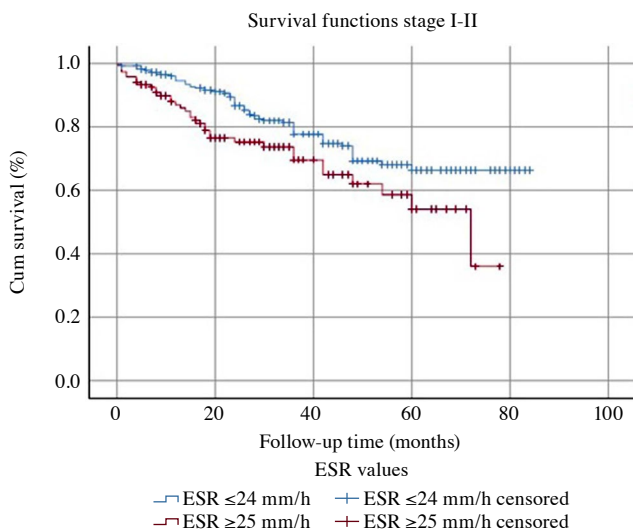


Figure 3. Comparison of overall survival rates of patients with stage I-II according to preoperative sedimentation values.

ESR: Erythrocyte sedimentation rate; Normal ESR (ESR ≤ 24 mm/h). High ESR (≥ 25 mm/h)

with Stage 1-2 disease and 43.3 ± 2.9 (range, 1 to 83) months in patients with Stage 3-4 disease, and the mean survival was significantly longer in patients with early-stage disease ($p < 0.001$) (Figure 2). At this stage, the survival time was compared within each group according to the ESR. The mean survival time was 66.2 ± 1.9 (range, 1 to 84) months in 302 patients (71.1%) in the LSG with an ESR of ≤ 24 mm/h, whereas it was 53.8 ± 3.2 (range, 1 to 78) months in 123 (28.9%) patients in the same group who had

Table 3. Evaluation of factors affecting survival by Cox regression analysis

Patient groups	HR	<i>p</i>
Histopathological stage 3-4	2.4	<0.001
With histopathologically SCLC	2.3	0.043
The presence of COPD	1.5	0.013
ESR ≥ 25 mm/h	1.7	0.001

HR: Hazard ratio; SCLC: Small cell lung cancer; COPD: Chronic obstructive pulmonary disease; ESR: Erythrocyte sedimentation rate.

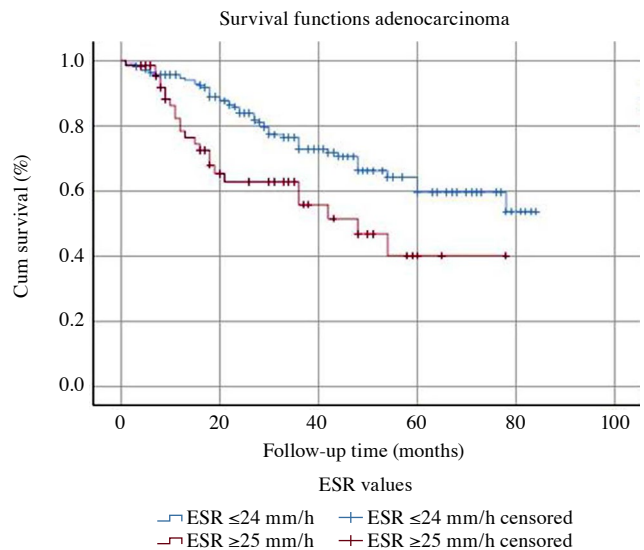


Figure 4. Comparison of overall survival rates of patients with adenocarcinoma according to preoperative sedimentation values.

ESR: Erythrocyte sedimentation rate; Normal ESR (ESR ≤ 24 mm/h). High ESR (≥ 25 mm/h).

an ESR of ≥ 25 mm/h, indicating a statistically significant difference ($p = 0.008$) (Figure 3). The mean survival time was 46.4 ± 3.5 (range, 1 to 79) months in patients with an ESR of ≤ 24 mm/h and 37 ± 4.6 (range, 1 to 83) months in patients with an ESR of ≥ 25 mm/h; however, it did not reach statistical significance ($p = 0.057$) (Table 2).

The ESR was ≤ 24 mm/h in 215 of 280 (76.8%) patients in Groupac and ≥ 25 mm/h in the remaining 65 (23.2%) patients. The ESR was ≤ 24 mm/h in 103 of 182 (56.6%) patients in Groupsc and ≥ 25 mm/h in the remaining 79 (44.4%) patients. The ESR was ≤ 24 mm/h in 18 of 19 (94.7%) patients in Groupcarcinoid and ≥ 25 mm/h in the other two (5.3%) patients. The ESR was ≤ 24 mm/h in two of 10 (20%) patients in Groupsc and ≥ 25 mm/h in the remaining eight (80%) patients. The ESR was

≤ 24 mm/h in 55 (65.5%) of 84 patients in Groupother and ≥ 25 mm/h in the remaining 29 (35.5%) patients in this group.

When the survival data of the groups was examined, the longest survival time was noted in Groupac with a mean survival time of 59.2 ± 2.3 (range, 1 to 84) months. However, it was not significantly longer than those of the other groups (Groupsc, Groupsc, Groupcarcinoid, and Groupother). Among the patients in Groupac, the mean survival time was 62.4 ± 2.4 (range, 1 to 84) months in patients with an ESR of ≤ 24 mm/h and 46.1 ± 4.6 (range, 1 to 78) months in patients with an ESR of ≥ 25 mm/h, indicating a statistically significant difference ($p=0.003$) (Table 2) (Figure 4).

The mean survival time was 57.7 ± 2.9 (range, 1 to 83) months in Groupsc. Among this group of patients, the mean survival time was 59.6 ± 3.1 (range, 1 to 80) months in patients with an ESR ≤ 24 mm/h and 54.5 ± 4.3 (range, 1 to 83) months in patients with an ESR ≥ 25 mm/h, indicating no statistically significant difference ($p=0.257$) (Table 2).

The mean survival time was 53.1 ± 6.2 (range, 5 to 70) months in Groupcarcinoid, 20.4 ± 3.0 (range, 5 to 32) in Groupsc, and 55.8 ± 3.9 (range, 1 to 83) months in Groupother. Statistical analysis could not be performed in these three groups due to insufficient number of patients for the analysis.

Multimodal analyses were performed to investigate the effect of histopathological diagnosis, stage, comorbidity and ESR values on survival. Accordingly, the risk of mortality due to LC was 2.4 times higher in patients with Stage 3-4, 2.3 times higher in patients with small cell LC, and 1.5 times more in those with a diagnosis of COPD. In the patient group with high ESR values, it was found to be 1.7 times higher (Table 3).

DISCUSSION

Several studies have attempted to identify prognostic factors for LC, which ranks the first among the cancer-related deaths worldwide.^[1,2] Although many prognostic factors such as tumor type, stage, mutation type, and patient age have been identified for LC, the prognostic value of ESR has not been clearly established yet.^[3-7]

The ESR is an inexpensive, simple, and easily reproducible laboratory test that is used effectively in the diagnosis and follow-up of many diseases.^[8] Along with its use in determining the risk for non-oncological

conditions such as coronary artery disease and cerebrovascular disease, several studies have also shown that it can be used as a prognostic marker in colon and prostate cancer.^[8-12] A study conducted in patients with prostate cancer found a 29% significantly increased risk of mortality among patients with an ESR of higher than 20 mm/h.^[11] The findings of another study suggested that elevated ESR in patients with cutaneous melanoma was associated with metastatic disease.^[13] Another study evaluating the relationship between breast cancer and elevated ESR reported higher ESR in patients with breast cancer than in the control group.^[14] Although many studies have investigated the relationship between malignancies and ESR, little is known about its value in LC.^[15] A study investigating the association of CRP and ESR values with the risk of LC reported that ESR was elevated in patients with LC, while elevated CRP values did not point to an increased risk of LC.^[16] In the present study, the data of patients who underwent surgery were used while evaluating the relationship between ESR and LC; therefore, patients who had clear data regarding tumor type and stage and extensiveness of disease were analyzed to concretely establish the relationship between ESR and prognosis.

When the patients were grouped according to the ESR independent from stage and tumor type, it was obvious that patients with an ESR of ≤ 24 mm/h exhibited better prognosis than patients with an ESR ≥ 25 mm/h. This surprising and exciting result may not seem to be reliable due to the fact that other factors determining prognosis have been overlooked. This problem was overcome by grouping the patients according to tumor type and stage. When the patients were grouped primarily according to tumor type and ESR, among the patients with AC (Groupac) and SCC (Groupsc), those with an ESR of ≤ 24 mm/h had better prognosis than patients with an ESR of ≥ 25 mm/h (Groupac ($p=0.003$) and Groupsc ($p=0.257$)). A comparison was made with the literature to check the reliability of these results in our patient groups. The mean survival time was 59.2 ± 2.3 months in patients with AC and 57.7 ± 2.9 months in patients with SCC, both of which are pathological subtypes of non-small cell lung carcinoma, consistent with those reported for non-small cell lung carcinoma in the literature (50 months on average).^[17] The reported five-year survival rate after surgical therapy between 58 to 73% in patients with Stage 1 disease, between 36 to 46% in patients with Stage 2 disease, and 24% in patients with Stage 3A disease.^[18,19] In line with these reports, the five-year survival rate in the present study was

63.4% in patients with Stage 1-2 disease and 36.8% in patients with Stage 3-4 disease.

Several studies in the literature indicate tumor stage as the main factor predicting the prognosis. Consistent with the literature, the group of patients with Stage 1-2 disease had better prognosis than patients with Stage 3-4 disease in the present study. In addition to this expected finding, comparison of the ESR within the patient groups showed surprising findings. Among the patients in the LSG, the mean survival time was longer in patients with a preoperative ESR of ≤ 24 mm/h than those with an ESR of ≥ 25 mm/h. This significant difference in the mean survival time despite being at the same disease stage and having undergone surgical therapy may guide future studies. As a result of the multi-module analysis, we found that the risk of mortality due to LC was 2.4 times higher in patients with Stage 3-4 and 1.7 times higher in the patient group with high ESR values. Therefore, we believe that ESR may be an important prognostic factor at least as much as the stage.

Nonetheless, there are some limitations to this study. First, this is a retrospective and single-center study and, therefore, the methodology used cannot be generalized to other centers. Second, sublobar resection, which includes surgical procedures such as wedge resection and segmentectomy, is usually performed on early-stage patients. Although it has less mortality and morbidity compared to anatomical resection, the oncological adequacy of the operation is not as clear as anatomical resection.^[20] Thus, it is more difficult to evaluate survival in the patient group undergoing sublobar resection. In our study, 178 (31%) patients underwent sublobar resection and constitute an important part of the study group. It can be thought that this situation may affect the statistics on survival. However, when patients were grouped according to their ESR values, sublobar resection was applied at similar rates to both groups. The bias that may occur due to this reason can be ignored.

In conclusion, the ESR is an acute phase reactant which increases as a result of rheumatic diseases, hematological disorders, infections, trauma, surgical interventions, hypoxia, burns, and immunological and allergic reactions. Our study results indicate that the mean survival time is longer in lung cancer patients with an ESR of ≤ 24 mm/h. Among the patients with adenocarcinoma and those in the low-stage group, the mean survival time seems to be longer, when the ESR is ≤ 24 mm/h. It may be possible to speculate on the survival of patients according to their preoperative ESR.

Ethics Committee Approval: The study protocol was approved by the Ege University Faculty of Medicine Ethics Committee (Date/no: 08.07.2021/21-7T/31). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All authors contributed equally to the article.

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