Cerrahpaşa Med J 2024; 48(2): 152-158 ORIGINAL ARTICLE

Is Preoperative Anemia a Prognostic Marker in Patients Who Underwent Pneumonectomy for Non-Small Cell Lung Cancer?

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Abstract

Objective: Pneumonectomy is infrequently selected for lung resections due to the high rate of postoperative complications. Thus, identifying risk factors for complications and predicting potential prognostic factors in patients undergoing pneumonectomy is of great importance. We have already described anemia in preoperative patients as a risk factor for postoperative complications. Our objective was to investigate the impact of anemia on pneumonectomy patients' postoperative course and reveal any potential prognostic effects.

Methods: In total, 118 patients who underwent pneumonectomy between 2001 and 2022 were retrospectively assessed. Clinical data, laboratory data, pulmonary function values, pathological data, and survival data were retrospectively recorded, and this data was divided into 2 groups: preoperative hemoglobin values (group 1 anemic: 51 patients) and normal hemogram values (group 2 normal: 67 patients). Univariate and multivariate analyses were conducted.

Results: The evaluation of the development of complications in patients who underwent pneumonectomy did not reveal any clinical condition to be a risk factor, apart from anemia. The Charlson comorbidity risk index, pulmonary risk index, and cardiac risk index were not risk factors for complications in pneumonectomy patients ($P = .324$, $P = .192$, $P = .727$, respectively). A significant difference in survival rates was observed between the groups with and without anemia ($P = .028$).

Conclusion: Anaemia was identified as the only prognostic factor in patients who underwent pneumonectomy. Clinical significance must be taken into account to ensure survival benefits.

Keywords: Anemia, lung cancer, pneumonectomy

Introduction

Surgery is considered to be the standard option in the treatment of early-stage and selected locally advanced-stage non-small cell lung cancer (NSCLC).[1] In surgical excision, anatomical resection procedures include segmentectomy, lobectomy, bilobectomy, and pneumonectomy.[3]

Lobectomy is the most commonly selected surgical resection, whereas parenchyma-preserving surgeries and segmentectomy are performed in selected cases.[4] Although not commonly favored, pneumonectomy is still necessary in some cases,[5] particularly for centrally located, large, and fissure-invading tumors.[6] The pneumonectomy procedure has a higher rate of postoperative complications,[6] resulting in higher mortality and morbidity in the postoperative period.[7] Identifying risk factors for complications and predicting potential prognostic factors in patients undergoing pneumonectomy is of great importance.[8]

Identification of predictive factors in pneumonectomy patients in the postoperative period is significant for overall survival and success.[9] This would aid in detecting underlying and existing clinical conditions, thus enabling the identification of negative predictive factors.[10]

Anemia is recognized as a risk factor for postoperative complications. These complications are respiratory and infectious, and associated with nutritional deficiencies that were not detected during the preoperative evaluation.[11] Anemia is also a significant prognostic factor for thoracic surgery patients.[12] Treating anemia may reduce postoperative complications.[13]

We aimed to investigate the effect of anemia on pneumonectomy patients' postoperative course and to reveal the potential prognostic effect.

Methods

The study included 856 patients who underwent surgery for non-small cell lung carcinoma between September 2001 and April 2022. We excluded patients who underwent lobectomy, bilobectomy, sleeve lobectomy, segmentectomy, and wedge resection (Figure 1). In addition, having had a preoperative blood transfusion was an exclusion criterion. A total of 118 patients (13.7%) who had a pneumonectomy fit the inclusion criteria. Informed consent was obtained from all patients. Their medical records were evaluated retrospectively. This study received approval from the İstanbul University-Cerrahpaşa Clinical Research Ethics Committee (Approval no: 83045809-604.01.01-854397, Date: December 6, 2023).

In accordance with the World Health Organization's criteria, a hemoglobin value of less than 13 g/dL in men and a hemoglobin value of less than 12 g/dL in women were defined as a state of anemia. Thus, we divided patients into 2 groups: preoperative

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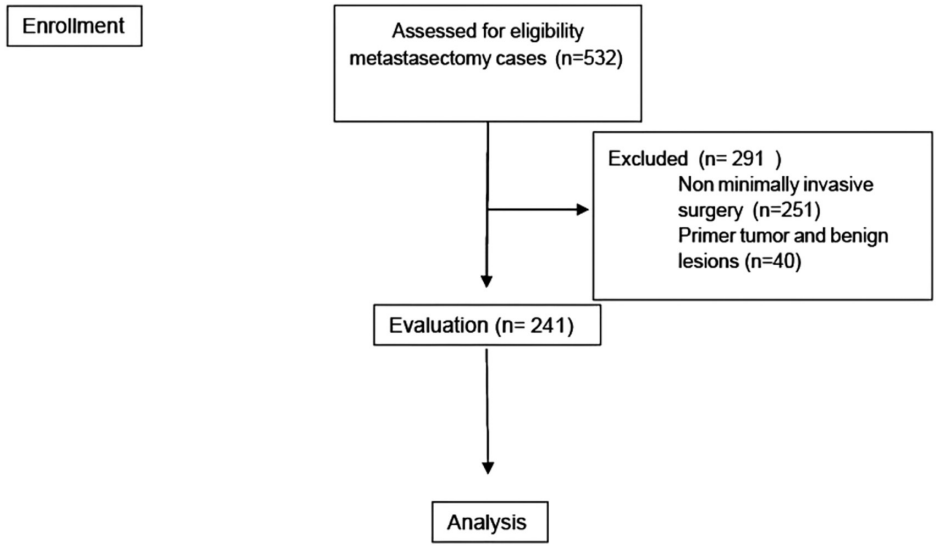

Figure 1. Consort Diagram

hemoglobin values (group 1 anemic: 51 patients) and normal hemogram values (group 2 normal: 67 patients). During surgery, we observed no major bleeding in the patients that required a blood transfusion. None of the patients had a clinical need for blood transfusions during the postoperative period.

We retrospectively recorded the following: clinical data (age, gender, comorbidity, cardiac risk index, pulmonary risk index, hypertension, diabetes, smoking history, neoadjuvant treatment history, complication status); laboratory data (hemoglobin, albumin, C-reactive protein, lactate dehydrogenase enzyme, leukocytes, lymphocytes, monocytes, neutrophil value); pulmonary function values (FVC, FVC%, FEV1, FEV1%, FEV1/FVC, DLCO, DLCO%, preoperative O_2, preoperative CO_2); pathological data (tumor diameter, N status, perineural invasion, lymphatic invasion, vascular invasion). We staged all patients using the 8th TNM staging method. In our clinical practice, we used the Charlson comorbidity risk index, the pulmonary risk index, and the cardiac risk index. The Charlson comorbidity risk index encompasses comorbid conditions that assess the risk of morbidity. The pulmonary risk index is a clinical evaluation that assesses factors including cough, active smoking, respiratory function tests, body mass index, and respiratory sounds. The cardiac risk index is a clinical evaluation that includes age, myocardial infarction history, and physical examination findings. The complications of 118 patients who underwent pneumonectomy were also analyzed separately to determine the clinical factors that facilitate complications.

We employed SPSS 25.00 for statistical analysis. Two groups (anemic and normal) were compared using univariate and multivariate analyses. A student-t testStudent's *t*-test was used to evaluate parametric data in the univariate analysis. A chi-square test was used to analyze non-parametric data. The Kaplan–Meier test was used for survival analysis. We used both linear regression and logistic regression tests in our multivariate analysis. A value of $P < .05$ was considered statistically significant.

Results

Demographic characteristics (age, sex, etc.) of the 2 groups were statistically similar (Table 1) ($P = .123$ and $P = .616$). The mean age was 61.8 ± 7.5 years in the group with anemia. The mean age was 56.4 ± 9.6 years in the group with normal hemogram values. There were 49 male [96%] and 2 female (4%) patients in the group with anemia. In the group with normal hemogram values, there were 63 male (94%) and 4 female [6%] patients (Table 1).

The hemoglobin values of all patients were between a minimum of 8.9 g/dL and a maximum of 16.7 g/dL. In the anemia group, the hemoglobin value varied between 8.9 g/dL and 12 g/dL. In the group without anemia, the hemoglobin value was between 12.5 g/dL and 16.7 g/dL.

The preoperative CO_2 value was significantly lower in the anemia group (Group 1) (group 1 PCO_2: 36.2 ± 7.2, group 2 $PCO_{2:}$ 36.8 ± 1.7 ($P = .008$). The albumin value was significantly lower in the anemia group, while CRP and leukocyte values were significantly higher in the anemia group ($P = .05$, $P < .001$, $P = .026$, respectively). Tumor diameter and distance to the surgical margin were significantly higher in the anemia group ($P = .001$, $P = .028$, respectively) (Table 2).

Table 1. Table Showing the Demographic Data of the 2 Groups

	Group 1 (Group with Anemia) *n* = 51	Group 2 (Group with Normal Hemogram Values) *n* = 67	*P*
Age	61.8 ± 7.5	56.4 ± 9.6	.123
Gender Male Female	 49 (96%) 2 (4%)	 63 (94%) 4 (6%)	.616
Additional diseases	66.6%	55.2%	.208
COPD	13.7%	13.4%	.963
Hypertension	29.4%	19.4%	.206
Diabetes	17.6%	710.5%	.258
Neoadjuvant Treatment	15.7%	10.5%	.397
VATS	5.9%	3.0%	.439
Right Left	29.4% 70.6%	46.3% 53.7%	.063

Chi-square and Student's *t*-test were used. Mean values, SD, and percentage values are given.

Table 2. Evaluation of the 2 Groups in Terms of Parametric Data

	Group 1 (Group with Anemia) *n* = 51	Group 2 (Group with Normal Hemogram Values) *n* = 67	*P*
Preoperative CO_2 (mm Hg)	36.2 ± 7.2	36.8 ± 1.7	.008
Albumin (g/dL)	3.6 ± 1.4	4 ± 0.5	.05
CRP (mg/dL)	32.2 ± 35.4	13.6 ± 15.5	< .001
Leukocyte (µL)	9.7 ± 4.6	8.8 ± 2.9	.026
Surgical margin distance (cm)	1.3 ± 1.5	1.1 ± 1.1	.028
Tumor Diameter (cm)	5.3 ± 3	4.1 ± 1.8	.001

Student's *t*-test was used. Mean values and SD are given.

Table 3. Evaluation of Clinical Risk Factors for Postoperative Complications After Pneumonectomy

	P
Charlson Comorbidity Risk Index	.324
Pulmonary Risk Index	.192
Cardiac Risk Index	.727

Chi-square test was used.

The evaluation of the development of complications in patients who underwent pneumonectomy did not reveal any clinical condition to be a risk factor, apart from anemia. The Charlson comorbidity risk index, pulmonary risk index, and cardiac risk index were not risk factors for complications in pneumonectomy patients (*P* = .324, *P* = .192, *P* = .727, respectively) (Table 3). There was no statistically significant difference in survival rate data between the groups with and without postoperative complications after pneumonectomy (*P* = .385) (Figure 2, Table 4).

The mean 5-year survival in group 1 was 63.6 ± 10 months (95% CI: 43.9-83.4 months) (Table 5). In the group with normal hemogram values, the mean 5-year survival was 95.4 ± 9.8 months (95% CI: 76.1-114.7 months) (Table 5). The 5-year survival rate in the anemia group was 23.5%. The 5-year survival rate in the group without anemia was 35.8%. The group with anemia had significantly worse outcomes in terms of survival data (*P* = .028) (Figure 2). There was no survival difference between the groups in terms of 90-day mortality (*P* = .728) (Figure 3). Cardiac issues were evaluated as complications. For example, the presence of tachycardia and arrhythmia were considered complications. A total of 12 patients showed signs of cardiac complications. We observed no survival difference between the anemia and non-anemia groups in the 90-day mortality evaluation (*P* = .728) (Figure 4). We observed atrial tachycardia in 9 patients. Three patients experienced supraventricular tachycardia. No statistically significant difference was observed in terms of complications between the 2 groups with and without anemia ([*P* = .466) (Table 6). There was no difference in pathological diagnosis, TNM stage, positive surgical margin, perineural invasion, lymphatic invasion, or vascular invasion between the 2 groups with anemia and normal hemogram values (*P* = .194, *P* = .457, *P* = .918, *P* = .891, *P* = .674, *P* = .737) (Table 6). Therefore, it was discovered that anemia was the sole prognostic factor in patients who underwent pneumonectomy.

In multivariate analysis, the albumin value was independently low in patients with anemia (*P* = .011) (Table 7). No correlation was observed between the side of pneumonectomy and anemia (*P* = .163) (Table 8). No statistically significant difference was observed among neoadjuvant history, COPD history, diabetes, and hypertension history between the groups with and without anemia (Table 1).

Discussion

Non-small cell lung cancer comprises approximately 80% of all lung cancers.[14] The most important criterion in determining

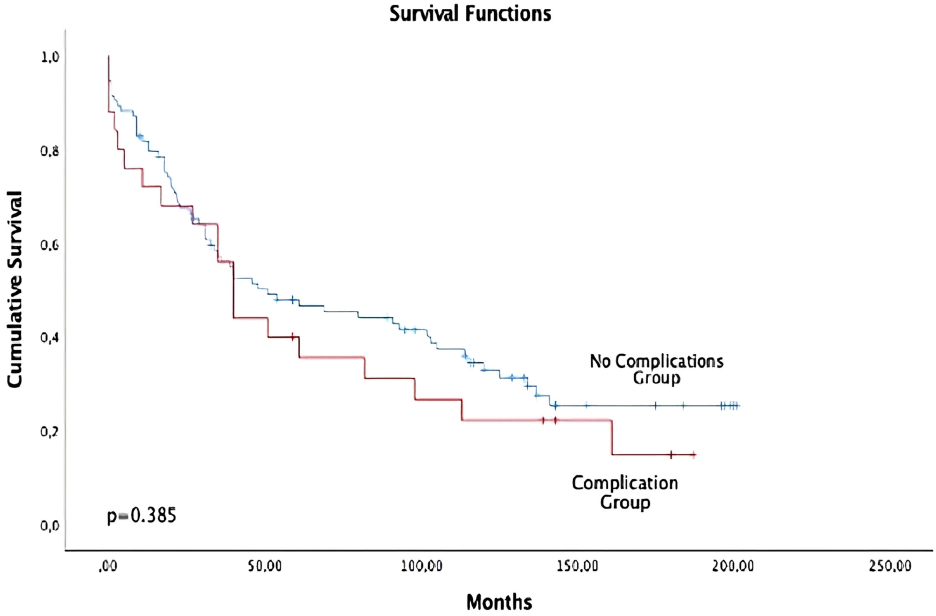

Figure 2. Evaluation of 2 groups with and without complications in terms of survival data. No statistically significant difference was observed between the 2 groups. Kaplan–Meier test was used. *P* = .385.

Table 4. Evaluation of the 2 Groups With and Without Postoperative Complications in Terms of Survival Data

Complication group *n* = 25	67.6 ± 13.4 months (95% CI: 41.1-94.0 months)
No complications group *n* = 93	86.3 ± 8.3 months (95% CI: 69.9-102.8 months)
Total	82.5 ± 7.2 months (95% CI: 68.2-96.8 months)

Kaplan–Meier analysis was used.

Table 5. Evaluation of 2 Groups With and Without Preoperative Anemia in Terms of Survival data

Group 1 (group with anemia)	63.6 ± 10 months (95% CI 43.9-83.4 months)
Group 2 (Group with normal hemogram values)	95.4 ± 9.8 months (95% CI 76.1-114.7 months)
Total	82.5 ± 7.2 months (95% CI 68.2-96.8 months)

Kaplan–Meier analysis was used.

the treatment method for lung cancer is determining the patient's stage of cancer.[15] There are surgical, chemotherapy, and radiotherapy treatment options for non-small cell lung cancer.[15] However, at the time of diagnosis, only 25% of these patients are at an appropriate stage for surgical treatment.[16] Some of these operable patients require pneumonectomy due to various reasons.[6,17] Pneumonectomy has the highest risk compared to other types of resection, OR (odds ratio), 1.42, 95% CI (conŞdence interval) 0.40-5.05.[6] When the causes of morbidity and mortality in patients who underwent pneumonectomy were investigated, clinical data such as right pneumonectomy, neoadjuvant treatment, smoking, and anemia habits were identified.[13,18] In a meta-analysis study evaluating pneumonectomy, right pneumonectomy was approximately 2 times more likely to have postoperative complications than left side procedures.[19] Blanc et al. also added chronic heart disease and a high Charlson comorbidity risk index as risk factors for morbidity after pneumonectomy.[20] Brunelli et al., in contrast to the literature, found that there was no difference in 30-day mortality and morbidity after pneumonectomy in patients receiving neoadjuvant therapy.[29] Chamogeorgakis et al. showed that hemoglobin levels increase the postoperative complication rate regardless of the surgical resection performed and that the complication rate is higher following pneumonectomy.[12]

Carter et al. reviewed 9 studies that cited blood hemoglobin concentration as a potential prognostic factor. Five of these 9 studies showed that higher hemoglobin levels were associated with better outcomes.[22] Chamogeorgakis et al. demonstrated that preoperative hemoglobin concentration and pneumonectomy (HR = 3.58, 95% CI 1.26-10.16, *P* = .017) were the sole predictors of all-cause mortality. When only lung cancer-related death was considered (HR = 6.89, 95% CI 2.29-20.73, *P* = .001), preoperative hemoglobin (HR = 1.81, 95% CI 1.17-2.78, *P* = .007) and pneumonectomy were independent predictors. The study revealed that age, gender, pulmonary function test results, tumor stage, and histology did not affect survival, while anemia was a risk factor for survival and lung cancer-specific mortality in patients who underwent lobectomy or pneumonectomy.[12] We have encountered various complications, morbidity, and mortality in anemic patients after pneumonectomy. For this reason, we aimed to evaluate the effect of anemia on complications and mortality in pneumonectomy patients.

Similar to the results of Chamogeorgakis et al., our series showed that although the TNM stage and pathological features were similar, a significantly worse survival rate was observed in the anemia group (*P* = .028) (Figure 2). Conversely, there are opposing ideas as well. Anile et al. showed that preoperative anemia is not a risk factor for postoperative complications after lung cancer surgery.[23] Our results show that preoperative anemia is a significant prognostic factor.

Liao et al. showed that elevated CRP was associated with a poor prognosis in patients with advanced non-small cell lung carcinoma.[24] In our series, the significantly higher CRP (group 1 CRP: 32.2 ± 35.4; group 2 CRP: 13.6 ± 15.5, *P* < .001) elevation in the anemia group reveals the characteristics of the advanced-stage non-small cell lung carcinoma patient group. Dingxiu et al. emphasized the prognostic importance of high CRP and

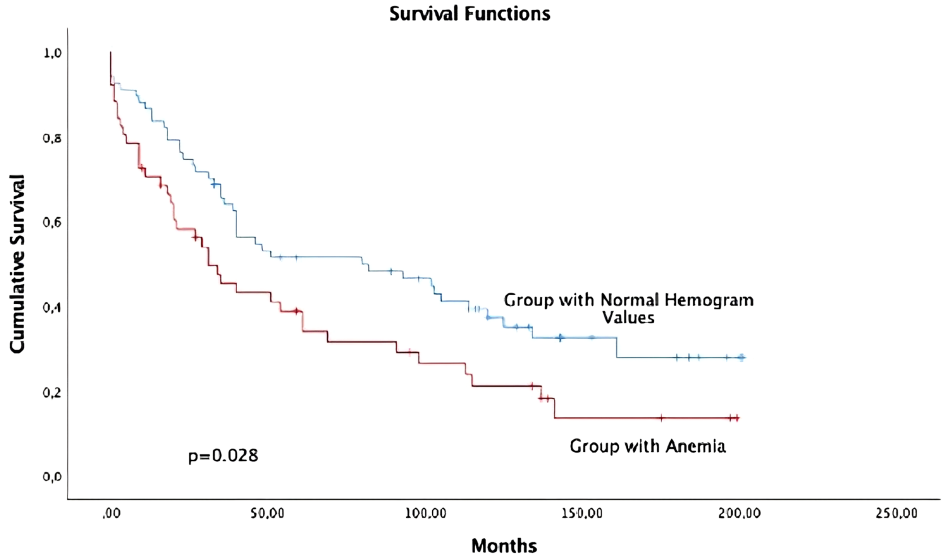

Figure 3. Evaluation of 2 groups with and without preoperative anemia in terms of survival data. A statistically significant difference was observed between the 2 groups. Kaplan– Meier test was used. *P* = .028.

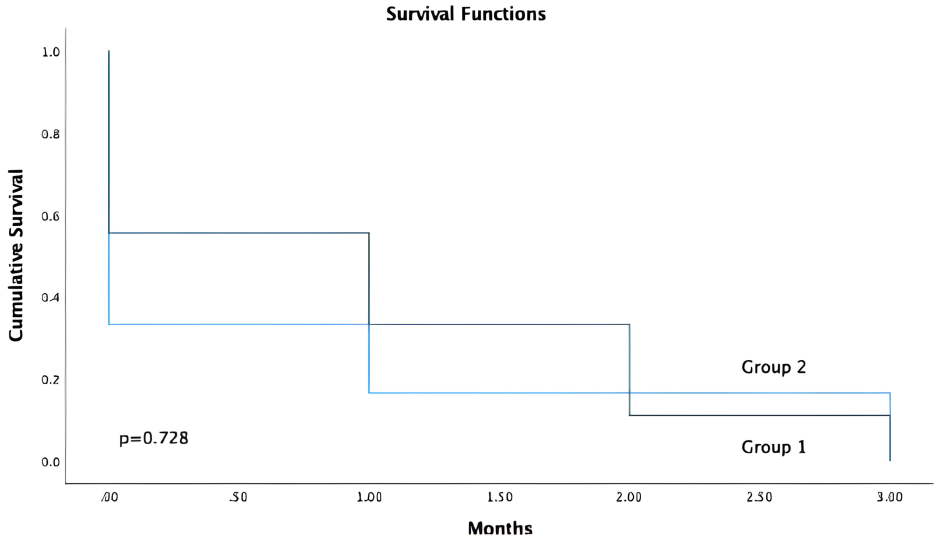

Figure 4. Evaluation of 2 groups with and without preoperative anemia in terms of 90- day survival data. No statistically significant difference was observed between the 2 groups. Kaplan–Meier test was used. *P* = .728.

low albumin levels in patients with non-small cell lung carcinoma.[25] Zhang et al. emphasized the prognostic importance of inflammatory markers in patients with non-small cell lung cancer.[26] Similarly, in our study, statistically high leukocyte values in patients with anemia indicate an advanced-stage lung cancer patient group. Albumin, a biomarker, reduces the level of pro-inflammatory cytokines in cases of inflammation.[26] CRP, a typical acute-phase reactant, decreases inflammation.[26] According to the tumor microenvironment,[26] CRP/albumin levels are an effective prognostic value in non-small cell lung carcinoma. Neutrophil and lymphocyte values, which are white blood cells in the tumor microenvironment, indicate active systemic inflammation.[26,27] The hemoglobin, albumin, lymphocyte, and platelet (HALP) score shows the degree of both nutrition and immunity, and holds prognostic significance in non-small cell lung carcinoma. In line with this information, an important advance can be made in predicting prognosis by evaluating inflammatory biomarkers together.[26,27] The HALP score is calculated via the formula: [hemoglobin (g/L) × albumin (g/L) × lymphocytes (/L)]/platelets (/L) lymphocyte ()]/ platelet ().[26,27]

Table 6. Evaluation of 2 Groups With and Without Preoperative Anemia in Terms of Tumor Characteristics

	P
Pathological diagnosis	.194
TNM stage	.457
Positive surgical margin	.918
Perineural invasion	.891
Lymphatic invasion	.674
Vascular invasion	.737
Complications	.466
Chi-square test was used.	

Table 8. Evaluation of 2 Groups With and Without Preoperative Anemia by Multivariate Analysis

	P
Side of pneumonectomy	.153
Pulmonary risk ındex	.404
Pathological diagnosis	.774
Logistic regression analysis was used.	

As mentioned in several meta-analyses, anemia is involved in the etiology of respiratory alkalosis.[28] Respiratory alkalosis, or primary hypocapnia, occurs when alveolar ventilation exceeds the level required to remove the ventilator. The simultaneous decrease in Paco2, increase in pH, and compensatory decrease in the blood's HCO_3 level are associated with respiratory alkalosis. Due to the decrease in the hemoglobin value, oxygen delivery to tissues decreases and carbon dioxide levels increase.[28] In our series, the high preoperative CO2 value (group 2 CO_2 value: 36.8 ± 1.7) in the anemia group is consistent with the literature (*P* = .008).

Weber et al. classified the causes of anemia in patients undergoing cancer surgery as preoperative, perioperative, and postoperative.[29] They reported that caution should be exercised when blood transfusions are required.[29] In patients with low hemoglobin, a hemoglobin value of < 6 g/dL is stated to be an absolute indication for blood transfusion.[30] Patients with hemoglobin values between 6 and 8 g/dL are in the relative indication group.[26] Blood transfusions are recommended for patients with a history of additional cardiovascular and cerebrovascular disease and for patients with hypoxia.[26] We evaluated the patients in our study based on their preoperative anemia. No major bleeding occurred, and no blood transfusion was performed.

In our study, there was no difference in the incidence of complications after pneumonectomy between the anemia group and the normal patient group. The groups with and without complications were similar in terms of risk indices (Charlson comorbidity risk index, pulmonary risk index, and cardiac risk index) and patient characteristics (Table 3). Although the groups with and without anemia were similar in terms of pathological features and staging, the group with anemia was in a worse state in terms of prognosis (Table 6, Figure 2). This highlights the impact of anemia on the inflammation process and overall survival.

In a review article evaluating the prognosis in advanced non-small cell lung cancer patients, Carter et al. pointed out that a large tumor diameter and low hemoglobin levels were poor prognostic factors.[22] In our series, the larger tumor diameter in patients with preoperative anemia is consistent with the literature.

Arrhythmias are the most common complications following pneumonectomy, as demonstrated by Kalathiya et al.[13] Advanced age, right pneumonectomy, and a history of neoadjuvant therapy have been associated with increased mortality.[13] In our series, no difference was found in terms of cardiac risk index, pulmonary risk index, or the Charlson comorbidity risk index (P = .727, P = .192, P = .324). In light of these data, similar to the literature, we assert that pneumonectomy should be performed in cases where it is necessary due to oncologic principles.[13]

Prognosis prediction is crucial for pneumonectomy patients, and it is in the patient's best interest to identify negative predictive factors in order to then eliminate these factors.[10] The identification of anemia as a negative predictive factor emphasizes the significance of correcting anemia in the preoperative period.[13]

Limitations

The study was subject to various limitations. First, the study employed a convenience sample that was small in size, within a single institution, making a comprehensive conclusion on documentation extremely difficult. One of our study's limitations is that it cannot reveal the prognostic effect of anemia severity. Due to the limited number of patients, subgroup evaluations for complications could not be made.

Conclusion

As a result, it is known that pneumonectomy is associated with worse outcomes in terms of patients' quality of life, morbidity, and mortality compared to other types of resection. Patients who underwent pneumonectomy at older ages and those who had a right pneumonectomy had a high morbidity rate, indicating a need for more careful monitoring. Despite an increase in sublobar resections and sleeve lobectomies, some patients still prefer pneumonectomy. Our results reveal that preoperative anemia affected survival in patients who underwent pneumonectomy. We recommend evaluating patients undergoing pneumonectomy for preoperative anemia before surgery. We recommend blood transfusions or iron replacements for patients with anemia. It is critical to identify perioperative risk factors in lung surgery patients with appropriate preoperative treatment, including anemia treatment. We believe that anemia can be detected in these patients during staging, and if they have an iron deficiency, they can be treated with supplementary treatments during the preoperative period. We advise considering treatment options like intravenous iron therapy, which can yield immediate results, to avoid postponing surgery, particularly for patients who are at risk of anemia.

In summary, addressing preoperative anemia is vital for successful pneumonectomy outcomes. Early detection, appropriate treatment, and close monitoring contribute to better results. Prospective studies that include patients who have received treatment for anemia would help us determine strategies to reduce the risks of pneumonectomy complications. Nevertheless, the current data strongly supports the need for transfusions or iron replacement to raise hemoglobin levels before surgery, surpassing the threshold of what is considered anemia.

Ethics Committee Approval: Ethics committee approval was received for this study from the clinical reserachs ethics committee of İstanbul University-Cerrahpaşa (Approval no: 83045809-604.01.01-854397, Date: December 6, 2023).

Informed Consent: Written informed consent was obtained from all patients who participated in this study.

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