Original Article

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Prognostic Effects of Red Blood Cell Transfusion in Lung Cancer Patients Receiving Chemotherapy

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Abstract

Aim: Few studies have followed the effects of red blood cell (RBC) transfusion on patient outcomes throughout the disease course in lung cancer. The aim of our study was to evaluate the relationship between blood transfusion frequency and disease prognosis in lung cancer patients receiving chemotherapy, to review the complications experienced and our clinical practices.

Methods: This study was conducted as an observational study between 01.07.2021 and 31.12.2021. Patients diagnosed with small-cell lung cancer were included in the study. Patient data were collected retrospectively. During the follow-up period, patients who received and did not receive blood transfusions were compared in terms of various clinical conditions.

Results: A total of 405 patients were included. Blood transfusion was performed in 96 (23.7%) patients. While the rate of infection development was 68.8% in the transfused group, this rate was statistically significantly lower at 35.3% in the non-transfused group ($p<0.001$). The median progression rate was statistically significantly higher in the group with infection ($p=0.001$). It was determined that 21 (38.2%) patients who resulted in exitus were transfused with an average of 3.1±3.0 units, and an average of 2.81±2.24 units of blood was transfused to 75 (21.4%) of the 350 (86.4%) surviving patients. A statistically significant difference was found between whether blood transfusion was performed in surviving and non-survived patients ($p=0.011$).

Conclusions: It was determined that RBC transfusions during the disease in patients with lung cancer patients who underwent chemotherapy may adversely affect survival and disease progression.

Keywords: Erythrocyte transfusion, prognosis, lung neoplasms, disease progression

Introduction

Lung cancer is a cancer type with a high incidence of cancer-related mortality and morbidity. During the follow-up of lung cancer patients, blood transfusion is often needed for reasons such as cancer-induced anemia, blood loss during surgery, or bone marrow suppression caused by chemoradiation (1,2). Although red blood cell (RBC) transfusion is a common practice in cancer patients, its effects on patient outcomes and possible complications are still not clearly explained, and there are considerable variations among physicians and institutions. The hypothesis that blood transfusions in various types of cancer may be harmful due to the possible immunosuppression effect has been investigated. This makes us think that in addition to the damage caused by cancer to the body, it may also lead to transfusion-related mortality and morbidity. Additionally, transfusion-related infectious conditions and transfusion-related febrile/non-febrile reactions can be included among other conditions that cause concern in these patients. NCCN guidelines provide recommendations on the management of chemotherapy-induced anemia in lung cancer patients (3).

Although it has been studied in a large number of cancer types, few studies have followed the effects of RBC transfusion throughout the disease course on patient outcomes in lung cancer. The aim of our study, specifically designed out of this curiosity, was to evaluate the relationship between blood transfusion frequency

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and disease prognosis in lung cancer patients receiving chemotherapy and to review our clinical practices.

Materials and Methods

Compliance with Ethical Standards Patients

Our study is an observational study and was conducted between 01.07.2021 and 31.12.2021 after the approval of the Karadeniz Technical University's Clinical Research Ethics Committee with the protocol number 2019/263.

Patients

Patients diagnosed with small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) and given chemotherapy between 01/01/2014-31/12/2018 in the Department of Chest Diseases of Karadeniz Technical University Faculty of Medicine were included in the study. Patient data were collected retrospectively using file records and a hospital automation system (clinical course, blood bank data, consultation records, etc.). Staging of the patients was performed according to the results of fluorine-18-fluorodeoxy glucose positron emission tomography/computed tomography, computed tomography, and brain magnetic resonance imaging. All patients who received adjuvant and neoadjuvant chemotherapy were included in the study.

The following parameters were defined as the exclusion criteria. Patients with known hematological malignancies other than lung cancer, patients of ages <18 years, patients with a second primary malignancy, patients who were treated with the diagnosis of anemia before the diagnosis of lung cancer, patients who were diagnosed with lung cancer in our clinic but did not continue their treatment in our clinic, and patients who were thought to compromise data integrity due to missing data were excluded from the study. Patient data were followed until the patients were exitus or for a maximum of 24 months.

The primary outcome of the study was survival at 24 months, and the secondary outcome was the total number of progression.

Data Collection

Demographic characteristics, comorbid diseases, cancer type, and stage, how long he/she was followed with this diagnosis, hemoglobin (Hb) value before starting chemotherapy, whether RBC transfusion was performed during the follow-up period, if so at which Hb value blood transfusion was applied, how many units of RBC or other blood product replacements they received during the total follow-up period, how many chemotherapy cycles they received in total, which chemotherapy drugs they received, whether there was a delay in treatment due to treatment-related anemia, the most common transfusion indications, and complications (frequency of allergic reaction, febrile reaction, infection, and thromboembolic complications) whether they received additional radiotherapy, whether they received granulocyte-macrophage colony-stimulating factor for anemia, blood types, survival times, how many cancer progressions under treatment occurred, and if there was distant metastasis, metastasis sites were reported.

The definition of anemia was made according to the definition of the World Health Organization and the Turkish Society of Hematology, and the lower limit of Hb was 13 g/dL in men over 15 years of age, 12 g/dL in women over 15 years of age and in nonpregnant, and pregnant women it was taken as below 11 g/dL.

In our clinic, patients on a chemotherapy plan are hospitalized the day before, and blood parameters including hemoglobin are studied, and all patients are evaluated in detail before each cycle in terms of clinical and radiological suitability for chemotherapy, even if it is time for chemotherapy. In patients with active infection, the treatment regimen is delayed until after antibiotics. Likewise, the chemotherapy regimens of the patients whose blood transfusion decision is taken are also carried out in the post-transfusion period.

Statistical Analysis

In the analysis of data, the conformity of the data to the normal distribution was examined using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Kruskall-Wallis, Mann-Whitney U, Student's t-test, and chi-square tests were used for comparisons between groups. General linear models and Wilcoxon and Friedman tests, were used in serialized data. Data were given as percentages, mean (standard deviation), and median (minimum-maximum). The chi-square test was used to compare the qualitative data. Categorical data are presented as frequencies and percentages.

Results

A total of 405 patients were included in the study. Of these patients, 380 (93.8%) were male and 25 (6.2%) were female. The median age was 63 (IQR: 57-70) years. Anemia was present in 184 (45.4%) patients It was observed that 96 (23.7%) of all study patients received a blood transfusion. Demographic and clinical information are given in Table 1.

It was determined that each patient received an average of 2.87±2.42 transfusions (Table 2). Evaluation of transfusion needs according to cancer type and stage is given in Table 3.

There was no difference in mortality and disease progression rates between the groups with and without treatment delay due to anemia (Table 4).

While the rate of infection development was 68.8% in the transfused group, this rate was significantly lower at

Table 1. Baseline demographic and clinical characteristics			
	Transfused patients	**Non-transfused patients**	**p-value**
	n=96 (23.7%)	**n=309 (76.3%)**	
Gender			
Female	5 (5.2%)	20 (6.7%)	0.647
Male	91 (94.8%)	289 (93.5%)	
Age (Median±SD)	63.51±8.768	62.84±9.63	0.590
Female	57.40±15.662	61.30±12.26	0.737
Male	63.85±8.250	62.94±9.44	0.432
Comorbidities			
Cardiac	42 (43.8%)	107 (34.6%)	0.105
Respiratory	20 (20.8%)	67 (21.7%)	0.859
Neurologic	6 (6.3%)	12 (3.9%)	0.393
Other	28 (29.2%)	63 (20.4%)	0.078
Type of cancer			
Squamous	32 (33.3%)	112 (36.2%)	0.603
Adeno	32 (33.3%)	112 (36.2%)	0.603
Adenosquamous	1 (1.0%)	2 (0.6%)	0.557
Small cell	23 (24.0%)	41 (13.3%)	0.024
Large cell	0 (0.0%)	16 (5.2%)	0.016
Carcinoid	0 (0.0%)	1(0.3%)	1.000
Anaplastic	0 (0.0%)	1 (0.3%)	1.000
Mesothelioma	0 (0.0%)	3 (1.0%)	1.000
Untyped	9 (9.4%)	27 (8.7%)	1.000
Stages of cancer			
Stage I	4 (4.2%)	14 (4.5%)	1.000
Stage II	10 (10.4%)	55 (17.8%)	0.073
Stage III	36 (37.5%)	134 (43.4%)	0.309
Stage IV	46 (47.9%)	106 (34.3%)	0.022
Chemotherapeutics			
Cisplatin	81 (84.4%)	272 (88.0%)	0.360
Carboplatin	37 (38.5%)	90 (29.1%)	0.101
Gemcitabin	47 (49.0%)	110 (35.6%)	0.023
Vincristine	11 (11.5%)	12 (3.9%)	0.022
Vinorelbine	29 (30.2%)	108 (35.0%)	0.459
Paclitaxel	0 (0.0%)	5 (1.6%)	0.596
Docetaxel	44 (45.8%)	129 (41.7%)	0.555
Etoposide	25 (26.0%)	55 (17.8%)	0.106
Cyclophosphamide	11 (11.5%)	12 (3.9%)	0.022
Topotecan	12 (12.5%)	20 (6.5%)	0.080
Pemetrexed	9 (9.4%)	30 (9.7%)	1.000
Doxorubicin	10 (10.4%)	11(3.6%)	0.015
Radiotherapy	60 (62.5%)	165 (53.4%)	0.127
Progressive disease	67 (69.8%)	159 (51.5%)	0.002
Exitus	21 (21.9%)	34 (11.0%)	0.010
Survey (Month)	19.52±15.012	19.36±15.75	0.235

35.3% in the non-transfused group (p<0.001). Infection requiring antibiotics was detected in 175 (43.2%) patients. The progression rate was 67.4% in the infected group, whereas this rate was 47% in the non-infected group (p<0.001). While the rate of infection development was 68.8% in the transfused group, this rate was statistically significantly lower at 35.3% in the non-transfused group (p<0.001). A statistically significant positive weak correlation was found between the administration of transfusion to the patients and the development of infection (r=0.287, p<0.001).

While progression was observed in 67 (69.8%) of transfused patients, this rate was 51.5% in non-transfused patients (p=0.002). There was also a significant difference in the number of progressions between the two groups (p=0.001) (Table 5). Neutropenia developed in 78 (81.3%) of 96 transfused patients and 149 (48.2%) of non-transfused patients (p<0.001). In connection with this, GM-CSF treatment was also higher in the transfused group (p<0.001). GM-CSF was administered to 49 (12.1%) of 405 patients included in the study. While the rate of infection development was 77.6% in the GM-CSF-administered group, this rate was statistically significantly lower than 38.5% in the non-administered group (p<0.001).

It was observed that 55 (13.6%) of the 405 patients included in the study died within 24 months. The majority of the patients with exitus (30-54.5%) consisted of Stage IV patients, and there was a significant difference between them and the other stages (p=0.042). It was determined that 21 (38.2%) patients who resulted in exitus were transfused with 3.1±3.0 units to the mean, and an average of 2.81±2.24 units of blood was transfused to 75 (21.4%) of the 350 (86.4%) surviving patients. While there is a statistically significant difference in terms of whether a blood transfusion is performed in surviving and non-survived patients (p=0.011), no significant difference was found in the average blood transfusion amounts per person (p=0.640). No significant correlations were found between the amount of transfusion and mortality with univariate logistic regression analysis (p=0.665, B=1.043 (confidence interval 95% 0.861-1.263).

Discussion

Anemia is a common condition in the treatment process of cancer patients. The aim of this study was to detect lung cancer cases who received RBC transfusion due to anemia and to evaluate the results of transfusion-related patients.

Table 2. Characteristics of transfusion patients by gender

	Anemic patients	Hemoglobin value before first transfusion (g/dL)	Number of patients transfused	Number of transfusion
	No, %*	Mean±SD		
Female	5 (20 %)	8.36±0.47	5	2.6 ±1.81
Male	179 (47.1%)	8.78±0.79	91	2.89±2.45
Total	184 (45.2%)	8.76±0.78	96	2.87±2.42

*Refers to the ratios in female, maleand total patient groups

Table 3. Evaluation of transfusion need according to cancer types

	Untyped n=36	Skuamus n=144	Adeno n=141	Largecell n=13	AS n=3	Carcinoid n=1	Small cell n=63	Anaplastic n=1	Mesothelioma n=3	p-value
Transfusion no (%)	9 (25)	32 (22.2)	31 (22)	0 (0)	1 (33.3)	0 (0)	23 (36.5)	0 (0)	0 (0)	0.156
		Stage I n=18		**Stage 2 n=65**		**Stage 3 n=170**		**Stage 4 n=152**		**p-value**
Transfusion no. (%)		4 (22.2)		10 (15.4)		36 (21.2)		46 (30.3)		0.081
Transfusion count-unit, mean ± SD		2.5±1.73		1.78±0.83		2.92±2.05		3.13±2.9		0.490

T: Transfusion, AS: Adenoskuamous, SD: Standard deviation

Table 4. Relationship between anemia and treatment delay

	Delayed therapy due to anemia		
	Yes n=18	**No** n=387	**p-value**
Exitus no. (%)	4 (22.2)	51 (13.2)	0.286
Progression no. (%)	11 (61.1)	215 (55.6)	0.825

Tumorassociated anemia may occur in lung cancer patients due to tumoral factors and tumor treatment-related factors. Chemotherapy-induced anemia (CIA) often develops in patients with cancer who are treated with myelosuppressive chemotherapy (4-6). On the other hand, it has been shown that when diagnosed with cancer, patients already have a significant risk of anemia, almost five times that of healthy people.

In our study, the data of 405 patients were scanned and 184 of these patients were detected with anemia (45.4%), and 96 (23.7%) of all patients with transfused erythrocytes (RBC). In the latest current guidelines, it is reported that RBC transfusion should not be performed according to a certain "threshold value" or "trigger point". The NCCN panel view draws attention to 3 important points: 1. Observation and periodic reassessment should be performed in asymptomatic patients without serious comorbidities. 2. Transfusion may be considered in patients receiving high-risk intensive chemotherapy and radiotherapy if there is a progressive decrease in Hb level, or asymptomatic patients with comorbidities (cardiac disease, chronic pulmonary disease, cerebral vascular disease). 3. Transfusion should be applied in symptomatic patients (such as tachycardia, tachypnea, chest pain, exercise dyspnea, and syncope). The onset, severity, and duration of anemia, as well as other factors affecting tissue oxygen delivery, are related to the clinical manifestations of anemia. Adaptation to the process in chronic anemia depends on heightened cardiac output, increased coronary flow, altered blood viscosity, oxygen consumption, and extraction. The decision to correct anemia mainly depends on the individual characteristics of the patients, the severity of the anemia, the severity of comorbidities, and the clinical judgment of the physician (3).

In newly diagnosed cancer patients, Kenar et al. (7) evaluated that metastatic diseases, factors such as iron, B12, and folate deficiencies, gastrointestinal cancer, and a history of previous tumor surgery are possible risk factors. Direct infiltration of the bone marrow by cancer cells, a reduction of RBC production by causing iron sequestration of cancer cells and shortening its life, chronic blood loss from tumoral areas, deterioration in oral intake, and deterioration in the coagulation system can be evaluated as the causes of anemia seen in patients with cancer. All these reasons are mechanisms that increase proportionally with cancer weight (8-10).

The main purpose of RBC transfusion is to increase the oxygen-carrying capacity to provide tissue oxygenation. In 2016, the American Association of Blood Banks made several recommendations suggesting that the threshold values of 7 g/dL Hb in hospitalized and hemodynamically stable patients, and 8 g/dL Hb levels in patients with orthopedic, cardiac surgery, or known cardiovascular disease require transfusions (10). However, this recommendation excluded cancer patients. NCCN panelists state that a single value cannot be determined for all patients in the transfusion decision and that this decision should be made according to the individual risk/benefit ratios for the patient. In our study, the patients with an average value of 8.76±0.78 Hb received transfusions based on not only the clinical assessment but also the finding that cardiac disease (36.8 %) was the most common comorbidity.

In several reports, the mean Hb level was 9 g/dL, 9.5 g/dL, and 9.7 g/dL before starting iron supplementation, transfusion, or Erythropoietin Stimulating Agent (ESA) use in cancer patients (11-13). Rather than a specific absolute value, studies have identified anemia symptoms as an

Table 5. Relationship between transfusion and ınfection development and disease progession

	Infection requiring antibiotic treatment		
	Yes n=175	No n=230	**p-value**
Progression no. (%)	118 (67.4)	108 (47)	<0.001
Progression count-median (IQR)	1 (1-2)	0 (1-2)	0.001
Transfusion need-no (%)	66 (37.7)	30 (13)	<0.001
Transfusion count-unit,median (IQR)	2 (1-4)	2 (1-3.25)	0.372
	Transfusion		
	Yes n=96	**No** n=309	**p-value**
Infection requiring antibiotic treatment no (%)	66 (68.8)	109 (35.3)	<0.001
Pneumonia no. (%)	22 (22.9)	91 (29.5)	0.206
Upper respiratory tract infection no (%)	5 (5.2)	22 (7.1)	0.668
Progression no (%)	67 (69.8)	159 (51.5)	0.002
Progression count-median (IQR)	1 (1-2)	1 (0-2)	0.001

*The sum of the percentages are not be 100 because of they are rounded. Some patients have more than one infection

important clinical indicator in the decision to perform transfusion, in contrast to non-cancer anemia states (14). Generally, fatigue is not a major indication for transfusion other than cancer. In cancer patients, particularly in patients with a hemoglobin value of 8 g/dL and below, a blood transfusion may provide a short-term improvement in the symptoms associated with anemia. In a study by Mercadante et al. (15), they found improvement in the complaints of fatigue and dyspnea associated with anemia in various types of cancer patients hospitalized in a palliative care center and receiving a blood transfusion, but it was observed that this improvement in symptoms tended to decrease within 15 days, even if the hemoglobin value did not decrease in the follow-up of the patients. The result was interpreted by the researchers as factors other than anemia may play a role in the development of these symptoms (15).

In our study, 55 (13.6%) of 405 patients diagnosed with lung cancer died within 24 months. It is determined that while 38.2% of these patients (median 3.1±3.0 units) were transfused, 21.4% (mean 2.81±2.24 units) of 350 surviving patients were blood transfused (p=0.011). It was observed that 24-month mortality increased with blood transfusion. However, there was not a dose-dependent association between the number of blood transfusions and survival outcomes of patients with lung cancer.

Although the effect of blood transfusions performed in the perioperative period in many cancer types has been examined, there are not many studies on this subject in patients with advanced cancer. Watering et al. conducted a randomized study involving 697 patients with colorectal carcinoma and evaluated the perioperative group of patients who received a packaged red blood transfusion, a group of patients who received a blood transfusion with reduced leukocyte content, and a group of patients who were not transfused in terms of five-year survival and cancer recurrence rates. They did not observe any difference in terms of recurrence and survival rates among the transfused patient groups. However, although there was no difference in terms of cancer recurrence between the transfused and non-transfused patient groups, they found that mortality rates were higher in the transfused group, similar to our study (17). A meta-analysis by Wang et al. (16) showed that blood transfusion significantly increased the rates of all-cause death and cancer-related death and cancer risk in bladder cancer patients undergoing radical cystectomy.

In a study by Tai et al. (18), of 1803 patients, 209 of whom received a perioperative blood transfusion, the results showed that transfusion was associated with an increase in postoperative cancer recurrence, an increased risk of death from all causes in transfused patients, and mortality increased with the number of units transfused.

There are few studies examining transfusion outcomes during routine chemotherapy in patients with lung cancer patients. In a meta-analysis including 12,175 patients with lung cancer and 23 studies, it was found that blood transfusions were associated with decreased survival. However, only 1 of these studies evaluated transfusions during chemotherapy, and perioperative transfusion results were evaluated in other patients (19). In the study by Sakin et al. (20), similar to our results in this study, RBC transfusion was significantly associated with earlier progression and shorter survival. This study is important because it is the first study that evaluates transfusion outcomes in patients with metastatic NSCLC patients. In this study, 87 patients who received blood transfusions were included and patients with small cell lung cancer and non-metastatic were not included (20). In our study, there were 96 patients in the transfusion group, and the results of all patients who received chemotherapy with the diagnosis of lung cancer were evaluated. Aoe et al. (21) reported that regardless of the need for transfusion, survival was significantly shorter in 298 patients with anemia [median survival time (MST): 7.5 months] compared with 313 patients without anemia (MST: 11.8 months, p<0.0001). As found in our study, there may be several possible reasons for more frequent blood transfusions in non-surviving patients; one of these can be explained as the fact that many chemotherapy agents cause myelosuppression and lead to anemia, and severe cancer patients are exposed to a longer and high-dose chemotherapy burden. Additionally, the initial stages of non-survival patients in our study were more advanced and this may increase the need for blood transfusions in accordance with the anemia hypothesis. Another reason is the higher incidence of infectious complications, as determined in our study with frequent blood transfusions. In our study, the rate of infection requiring antibiotic use was 68.8% in the transfused group, while this rate was 35.3% in the non-transfused group (p<0.001). Additionally, the primary disease progression rate was found to be significantly higher in the infected group (67.4%) and this may have contributed to the increased mortality rates in the high group with transfusion frequency. The incidence of sepsis due to bacterial infections, which is one of the undesirable transfusion-related complications, is reported to be less than 10 per year (22). In a randomized controlled trial with 31 RCTs and 12587 patients, a restrictive transfusion strategy was suggested, and for nosocomial infections, there was a significantly higher risk of infection among patients receiving fresher RBCs (23). On the other hand, the recognition of the immunosuppression caused

by frequent transfusions in cancer patients has raised concerns that blood transfusions may increase the risk of cancer recurrence, particularly after curative surgery (24). Over the past four decades, it has been estimated that blood transfusions cause cancer progression by reducing the immunity of patients (25). Primer disease progression, which is an important prognostic indicator in lung cancer patients, was observed more frequently in patients who underwent transplantation in our study. Our results are important because they are one of the latest and rare data on transfusion in patients with lung cancer receiving chemotherapy. Although the life-threatening risk is lower, the most common non-hemolytic transfusion reactions associated with RBC transfusion are expected. Hemolytic reactions, febrile reactions, lung damage, and transfusion-associated circulatory overload can be counted as other possible complications, but since our study was retrospective, these data could not be collected in our patients.

One of our interests in our study was whether there was a delay in treatment in patients due to anemia. The chemotherapy of a few our patients (18 patients 4.4%) was delayed until after replacement or anemia treatment was arranged due to anemia, but this did not cause any difference in disease progression or mortality.

Tiotiu et al. (26) rated the frequency of CIA in lung cancer and emphasized the impact on patients' quality of life. They stated that maintaining a normal Hb level is important in improving the quality of life of these patients and recommended reducing the number of blood transfusions and initiating treatment with ESAs in symptomatic patients. They recommended that it should be used at the lowest effective dose and sharing the results with patients to avoid increased risk of thromboembolism, accelerated tumor progression, decreased survival, and major cardiovascular adverse reactions and blood transfusion (26). Erythropoietin Stimulating Agents stimulate erythropoiesis in patients with low Hb levels, but their effects appear weeks later, and a Hb increase of 1 g/dL was observed in only 65% of patients (27). The current guidelines recommend that ESAs should not be used in cancer patients who are not receiving myelosuppressive therapy. Except for the patients requiring blood transfusion andthose in palliative care, the NCCN panelists do not recommend routine ESA treatment to increase Hb levels (3). Erythropoietin Stimulating Agent was not applied to any patient in our study. According to the data of our study, in parallel with the data of our country, the most common cancer type was determined as SCC (22.2%), and no difference was observed in the need for blood transfusion according to cancer types and stages.

Study Limitations

The limitations of our study can be listed as follows: 1. Since our study was planned retrospectively, patients who received immunotherapy were not included. 2. The effects of radiotherapy applied to patients have not been examined. 3. While detecting infections requiring antibiotics, data loss may happen because the focus of infection in some patients cannot be fully retrieved from retrospective records. Only pneumonia and upper respiratory tract infection data were included. 4. The assessments of iron stores or iron treatments were not recorded. 5. Complications associated with transfusion therapy were not recorded. The strengths of our study are that it examines a large patient group, focuses on a subject for which there is not much data, and contributes to the literature.

Conclusion

It was determined that RBC transfusions during the disease in lung cancer patients who underwent chemotherapy may adversely affect survival and disease progression. Although the exact mechanism is not known, it is thought that transfusion-related immunomodulatory effects are effective in this result. We intend that our study will contribute to the literature as one of the few studies in the literature concerning this isolated patient group. Studies with a large number of homogeneous patient groups are needed for more reliable results.

Ethics

Ethics Committee Approval: The ethical approval was obtained from the Karadeniz Technical University's Clinical Research Ethics Committee with the protocol number 2019/263.

Informed Consent: Our study is an observational study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: O.A., M.P.K., Design: O.A., A.O.K., M.P.K., M.O.A., A.P., F.O., Data Collection or Processing: O.A., A.O.K., M.P.K., M.O.A., A.P., F.O., Analysis or Interpretation: O.A., A.O.K., M.P.K., M.O.A., A.P., F.O., Literature Search: O.A., A.O.K., M.P.K., M.O.A., A.P., F.O., Writing: O.A., M.P.K.

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